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# Influence of vigorous physical activity on myocardial structure and function in young competitive athletes

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I ABBREVIATIONS

| | |
|---|---|
| 2DE | 2-dimensional echocardiography |
| 3DE | 3-dimensional echocardiography |
| A | Peak late LV diastolic filling velocity |
| AEPC | Association for European Paediatric and Congenital Cardiology |
| AHA/ ACC | American Heart Association/ American College of Cardiology |
| AMSSM | American Medical Society for Sports Medicine |
| ASHT | American Society of Hand Therapists |
| BSA | Body surface area |
| cMRI | Cardiac magnetic resonance imaging |
| CPET | Cardiopulmonary exercise testing |
| cSBP | Central systolic blood pressure |
| DBP | Diastolic blood pressure |
| E | Peak early LV diastolic filling velocity |
| ECG | Electrocardiogram |
| EF | Ejection fraction |
| ESC | European Society of Cardiology |
| FAC | Fractional area change |
| FIFA | Fédération International de Football |
| FS | Fractional shortening |
| HCM | Hypertrophic cardiomyopathy |
| HGS | Handgrip strength |
| HR | Heart rate |
| IGF-1 | Insulin like growth factor 1 |
| IOC | International Olympic Committee |
| IVSd | Interventricular septal thickness in diastole |
| LA | Left atrium |
| LVEDV | Left ventricular end-diastolic volume |
| LVH | Left ventricular hypertrophy |
| LVIDd | Left ventricular internal diameter in diastole |
| LVM | Left ventricular mass |
| LVPWd | Left ventricular posterior wall thickness in diastole |
| MET | Metabolic equivalent |
| mRNA | Micro ribonucleic acid |
| MoMo-AFB | Motorik Modul physical activity questionnaire |
| MRI | Magnetic resonance imaging |
| MuCAYA-Study | Munich Cardiovascular Adaptations in Young Athletes Study |
| MVC | Maximum voluntary contraction |
| NO | Nitric oxide |
| PI3K | Phosphoinositide 3-kinase |

| | |
|---|---|
| PPCS | Pre-participation cardiovascular screening |
| $PGI_2$ | Prostacyclin |
| PWV | Pulse wave velocity |
| RA | Right atrium |
| SBP | Systolic blood pressure |
| SCD | Sudden cardiac death |
| STE | Speckle Tracking Echocardiography |
| TAPSE | Tricuspid annular plane systolic excursion |
| TTE | Transthoracic echocardiography |
| TUM | Technical University of Munich |
| $VO_{2max}$ | Maximum aerobic capacity |
| $VO_{2peak}$ | Peak aerobic capacity |
| WHO | World Health Organization |
| WHR | Waist-to-hip ratio |
| WHtR | Waist-to-height ratio |

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# 1 ABSTRACT

Physical exercise leads to cardiac adaptations. What has been studied extensively in the adult population is now being investigated more and more in young competitive athletes. This work entails a systematic review, to give an introduction and overview of cardiac adaptations in young competitive athletes, and results of the Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA-Study), conducted in a sample of 404 athletes (97 females, 14.11±2.04 years; 397 males, 14.27±1.99 years), participating in various types of sports. The results reported within the systematic review, such as significantly increased left ventricular diameters, left ventricular wall thickness, and left ventricular mass are in line with the MuCAYA-Study. Main results of this cross-sectional sample were left ventricular eccentric hypertrophy in the majority of young competitive athletes, independent of the underlying training stimulus. We found significantly increased z-scores for left ventricular internal diameter in systole, interventricular septal thickness and posterior wall thickness. Training intensity significantly influenced left ventricular internal diameters, and left ventricular mass. Peak oxygen uptake significantly influenced interventricular septal thickness and left ventricular mass. When endurance athletes were compared to strength athletes, the former had a better diastolic function. The analysis of a longitudinal sub-sample of 85 young competitive athletes over a study period of two years revealed significantly increased left ventricular dimensions, a significant reduction in diastolic function, and an improved exercise performance.

In summary, cardiac adaptations do occur in young competitive athletes already, independent of the underlying training stimulus but being influenced by training intensity and peak oxygen uptake. Within the longitudinal sample, altered cardiac parameters were considered as physiologic response to exercise training as cardiac adaptations resulted in an improved exercise performance. To better understand these adaptations and their consequences further studies will be needed, especially in a longitudinal setting.

# 2 INTRODUCTION

## 2.1 GENERAL INTRODUCTION AND STUDY PURPOSE

The term ‘athlete’s heart’ defines cardiac hypertrophy in response to exercise in trained athletes. In adults, features of the ‘athlete’s heart’ have been studied extensively [2-11]. The Swedish physician Salomon Eberhard Henschen was the first to describe cardiac adaptations in 1899. He and his colleagues reported differences in cardiac size in 24 cross-country skiers [12]. A century later, Morganroth et al. [13], reported an increase in left ventricular mass in athletes relative to the underlying training stimulus. The authors observed an increase in cardiac chamber diameters in endurance athletes, defined as eccentric hypertrophy, and an increase in left ventricular wall thickness in strength athletes, defined as concentric hypertrophy. What was known as the ‘Morganroth hypothesis’ has since been discussed controversially [14-18]. Most studies in adult athletes reported an increase in left ventricular wall thickness and cardiac diameter as well as an improved diastolic and systolic function [2]. On the contrary, adverse adaptations have been observed, too, like ventricular arrhythmias, atrial dilatation, and tricuspid regurgitation [6-11].

Cardiac adaptations found in athletes are not an exclusive feature of the adult athlete’s heart but do also occur in young competitive athletes. Especially as training loads and training intensity, the level of competitiveness and specialization in young competitive athletes increased extensively over the past years, reaching up to levels of professional adult athletes [19]. In this regard, studies investigating cardiac adaptations in young competitive athletes become more and more important, to better understand cardiac adaptations in response to exercise training in this population. Results will help to differentiate better between physiologic benign adaptations and adverse adaptations, leading to rhythm disorders, or structural or functional limitations. Therefore, this work will provide an overview on the literature, investigating cardiac adaptations in young competitive athletes and present results of a study performed in 404 young competitive athletes over a period of two years.

## 2.2 CHARACTERISTICS OF YOUNG COMPETITIVE ATHLETES

When talking about young competitive athletes, it is necessary to define this term and to name criteria that need to be fulfilled to call somebody an ‘athlete’ or a ‘young competitive athlete’, respectively. In scientific literature, only one publication provides a precise definition of the term ‘athlete’ [20]. Araujo and Scharhag [20] emphasize this deficit and the misleading classification of athletes within the current literature. People who perform sport are being classified as athletes, with a wide range of attributes regarding their performance and competitiveness or regarding the time and intensity they spend exercising. In research, this will lead to difficulties, when comparing athletes with athletes, as the former might have taken part in the Olympics three times in a row and the latter in one regional competition, only. Therefore, Araujo and Scharhag [20] propose to name somebody an athlete, if four criteria apply to her or him: (1) the person is training in order to improve her/ his performance or results; (2) the person is actively participating in sports competitions; (3) the person is formally registered in a local/ regional/ national sports federation; (4) the person is mainly engaged in sports training, spending most of her/ his time on it.

Regarding children and adolescents, the authors suggest an age classification, where adolescents aged 12 - 17 years who meet the above-mentioned criteria should be called ‘young athletes’. For children younger than 12 years, no definition exists. However, in current literature, dealing with echocardiographic findings in exercising children and adolescents, different terms appear, for example ‘paediatric athletes’ [21, 22], ‘pre-adolescent athletes’ [23], or ‘young competitive athletes’ and ‘young elite athletes’, respectively [24]. However, none of the authors named the rationale for defining their participants as being an athlete.

When searching PubMed/ MEDLINE database from the years 2000 to 2022 for the terms ‘young athlete’, ‘junior athlete’ or ‘paediatric athlete’ over 76 000 publications can be found (April 12$^{th}$ 2022), bearing these terms within the studies’ title. In a random sample of 15 studies [19, 21-34] out of these results, only one publication did define young athletes [19], according to the definition proposed by Araujo and Scharhag [20]. Searching PubMed/ MEDLINE further for

publications that define young athletes other than the one by Araujo and Scharhag [20] no study can be found.

Within the present work, the definition by Araujo and Scharhag [20] was chosen to define participants as ‘young competitive athletes’, but applied to a larger age range from 7 - 18 years. In this context, Pieles and Stuart [35], report that ambitious sports with regular exercise training does start in children aged six years. Furthermore, the definition was completed by the condition that only those participants were enrolled in the study who exercised three hours and more per week, as this amount of exercise has been shown to be associated with cardiac adaptations [36].

Besides the scientific definition of a young competitive athlete, specific characteristics go along with being an athlete. Bergeron et al. [37] emphasize an increase in specialization, competitiveness, and professionalization at a young age already. According to Jayanthi et al. [38], a high degree in specialization is reached if (1) the athlete is engaged in > 8 months of training within one year; (2) the focus is placed on one single main sport; (3) other sports are quit to follow the main sport. Within this comprehensive study 28.1% of n = 1190 female and male athletes, 13.7±2.3 years, fulfilled all criteria, thereby being defined as highly specialized young athletes. 33.7% fulfilled two and 38.1% one criteria, corresponding with moderate and low specialization, respectively [38].

D’Ascenzi as well as Pieles and Stuart [21, 35] reported a trend for more intensive training loads in children and adolescents, that can reach the level of professional adult athletes as stated by Pieles and Oberhoffer [19]. Whereas general recommendations by the World Health Organization (WHO) or governmental institutions (Australia, Canada, UK, USA) on daily activity levels in children and adolescents agree on 60 minutes of moderate to vigorous physical activity per day [19, 39]. The German Ministry of Health suggests 90 minutes of moderate to vigorous physical activity per day to maintain a healthy lifestyle [40]. Young competitive athletes however, exceed these recommendations. Jayanthi et al. [38] observed an average training time of 19.0±9.1 hours/ week. Cavarretta et al. [41] reported 7.2±1.1 hours/ week at an intensity of at least 75% of maximal heart rate in n = 2111 soccer players (12.4±1.4 years).

Given the nature of exercise training with intensive workloads, performed to improve one's exercise capacity and results, the amount of weekly exercise training exceeds general recommendations by far.

To summarize, a young competitive athlete trains in organized sport club settings to improve her/ his performance. A young competitive athlete participates in competitions regularly and dedicates a considerable amount of time per week to practice her/ his main type of sport. Accompanied by a trend of more intensive training loads and professionalization, sports performed by children and adolescents take on features of adult sports.

## 2.3 CHARACTERISTICS OF DIFFERENT TYPES OF EXERCISE

It is accepted that cardiac adaptations to exercise depend on the kind of the underlying stimulus, in other words, on the characteristics of the disciplines performed, the training intensity, training volume, and training history [42]. Sports disciplines can be characterized according to the type of muscular work, being either of isotonic or dynamic character or isometric or static character, respectively. However, there is always a varying degree of overlap between disciplines with dynamic and static components and within training regimes [17, 42, 43]. Therefore, concepts to classify different sports disciplines have been introduced.

The Mitchell Classification groups disciplines into one of nine categories according to an increasing static component, rated as low, which corresponds with < 20 % of maximum voluntary contraction (MVC), as moderate, corresponding with 20 - 50 % of MVC, or as high, corresponding with > 50 % of MVC. Furthermore, disciplines are grouped according to an increasing dynamic component, rated as low, corresponding with < 40 % of maximum aerobic capacity ($VO_{2max}$), moderate (40 - 70 % $VO_{2max}$), and high (> 70 % $VO_{2max}$) [43]. A more practical approach was published by Pelliccia et al. [42]. The authors suggested to group various sports disciplines into four categories, according to the predominant component, being either skill, power, endurance, or mixed. This approach was applied within the following work as this classification also considers the degree of cardiac remodelling as a function of the underlying training stimulus (Figure 1).

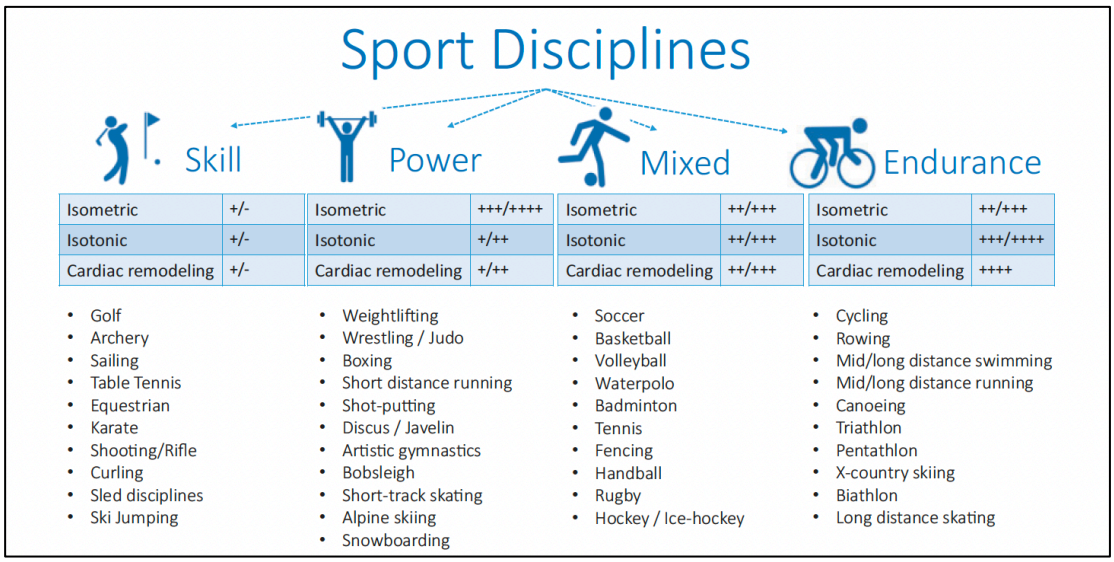


**Figure 1** Sport disciplines grouped into four categories according to their predominant characteristics as being either isometric or isotonic and according to the level of cardiac remodelling [42].

## 2.4 CARDIAC ADAPTATIONS TO EXERCISE

As any other muscle, the cardiac muscle is able to adapt to physical stress to keep up with the body's requirements imposed on the heart. This cardiac adaptation is reflected by structural alterations like a hypertrophic increase in wall thickness, defined as ventricular hypertrophy, affecting both, the left and the right ventricle, and by cardiac chamber enlargement [2, 14, 44-46]. Both mechanisms – the hypertrophic increase in wall thickness and cardiac enlargement – fulfill the function to normalize ventricular wall stress [14]. Furthermore, functional adaptations can be observed, for example a lower heart rate that is accompanied by an increased stroke volume, an increased cardiac output, and an increased oxygen supply of working muscles during exercise [2, 14].

It was Salomon Eberhard Henschen, a Swedish physician, who first discovered cardiac adaptations to exercise, over a century ago in 1899 [12]. He and his colleagues examined the hearts of 24 cross-country skiers (12 - 18 years) by percussion. They discovered differences in cardiac size, that corresponded well with exercise performance observed in these athletes. In 1968, Gott et al. [47] published an article about cardiac changes, observed over five years in a highly trained rower. The authors called this phenomenon the 'athlete's heart syndrome'. A couple of years later, the 'Morganroth Hypothesis' was published

by Morganroth et al. [13] – it was a fundamental publication, that has influenced the field of research in exercise physiology until today.

The following paragraphs will introduce the mechanisms of cardiac adaptation and highlight the work by Morganroth et al. [13]. Recent publications will be presented that look at the 'Morganroth Hypothesis' from different angles. Furthermore, an overview of the current state of research regarding cardiac adaptations to exercise in young competitive athletes will be given.

### 2.4.1 Mechanisms of cardiac adaptation

Cardiac adaptations to exercise can be assigned to acute and chronic adaptations. Acute adaptations are dynamic, occur rapidly during intensive exercise and are reversible when athletes stop exercising [48]. Acute adaptations are an increased cardiac output, stroke volume, systolic blood pressure (SBP), and a decreased peripheral vascular resistance. Chronic changes result in an increased peak oxygen uptake ($VO_{2peak}$) and an arterio-venous oxygen difference [49]. The mechanisms that lead to cardiac adaptations are complex and can be explained at a biochemical, molecular, and mechanical level [50-52].

On the biochemical level, insulin-like growth factor 1 (IGF-1) and neuregulin 1 are the most important paracrine factors that act on cardiomyocytes in response to exercise training [51, 52]. These factors lead to a growth in cardiac sarcomeres [53] and an increase in ventricular volume, which is considered a physiological adaptation [52]. This entails a proportional growth in length and width of the heart with a balanced enlargement of all cardiac chambers [51]. IGF-1 is released in response to exercise [54, 55] and is related to physiologic growth of the heart as observed by Neri Serneri et al. [56] in professional soccer players. Aerobic and strength training can increase serum levels of IGF-1 in humans [57, 58]. IGF-1 is able to mediate exercise induced physiological cardiac hypertrophy and the proliferation of cardiomyocytes via a complex cascade of intracellular signalling pathways [59, 60]. The primary signalling pathway is the IGF-1/ phosphoinositide 3-kinase (PI3K)/ Akt pathway which leads to the proliferation of cardiomyocytes, protein synthesis, and ribosomal biogenesis [52, 61]. Neuregulin 1 acts via ErbB2/ ErbB4 signalling pathways and PI3K, leading to cardiomyocyte proliferation and cell differentiation [62]. Furthermore, micro ribonucleic acids

(miRNAs), with miR-222 being the most important miRNA, contribute as regulatory factors of the cell cycle, thereby inducing cell proliferation [63, 64]. Figure 2 illustrates the mediators and pathways mentioned in this paragraph.

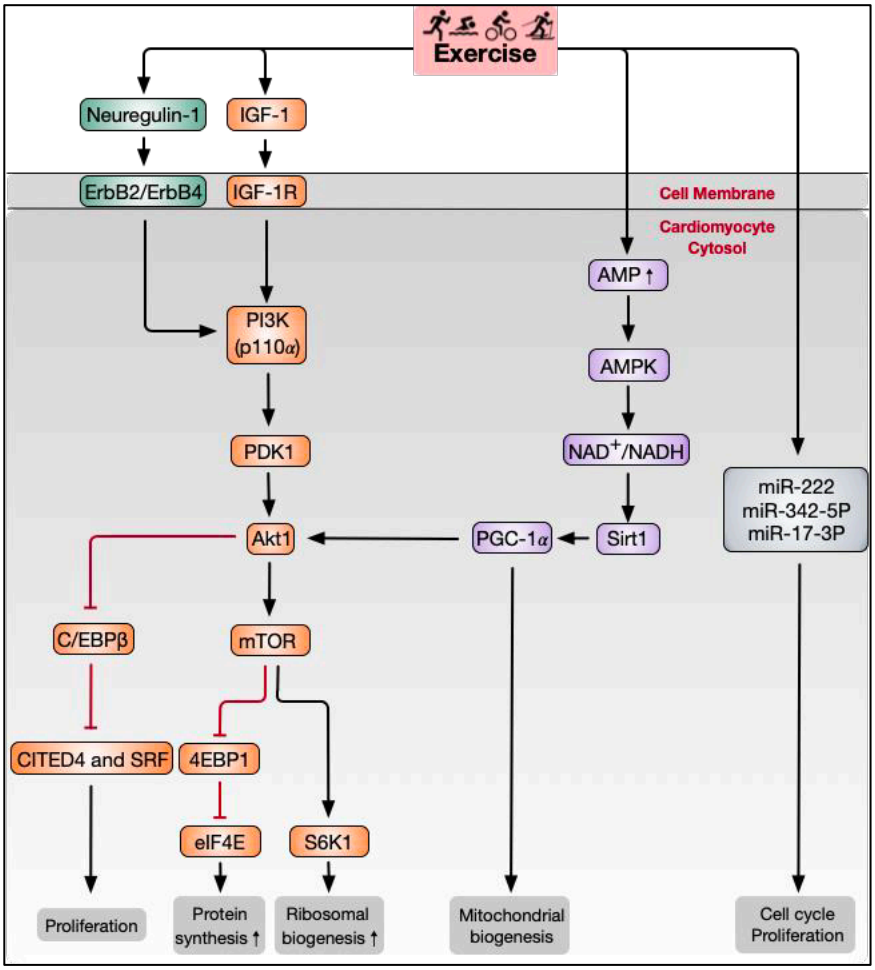


**Figure 2** Overview of signalling pathways showing the main mediators that are involved in cardiac remodelling [52].

On the mechanical level, hemodynamic changes during exercise are the central stimulus for cardiac remodelling [50]. Exercise causes an acute hypervolemia, triggered via the renin-angiotensin-aldosterone cascade which leads to sodium retention and increases plasma volume [65-67]. As a chronic effect of exercise, there's an increase in erythrocyte volume leading to a higher oxygen capacity of erythrocytes [65]. The acute increase in plasma volume stabilizes at a constand level after around 10 - 14 days of training and the chronic increase in erythrocyte volume can be noted after around 30 days of training. In summary, an 8 - 10 % higher blood volume can be observed in athletes compared to sedentary controls [65]. This hemodynamic stimulus, leading to cardiac adaptations via a volume overload is accompanied by a pressure stimulus, mediated through the entire

cardiovascular system, hence the heart and the vessels [50]. Endurance training lowers blood pressure post-exercise and in general at rest [68, 69], mediated by the release of vasoactive substances like nitric oxide (NO) and prostacyclin ($PGI_2$). Strength training, on the contrary, leads to an acute increase in peripheral vascular resistance, thereby acting as hypertrophic stimulus on the cardiac muscle [50]. The extent to which the cardiac muscle adapts to exercise is relative to the underlying training stimulus, to training intensity and training loads, and furthermore there's a genetic component, too, which plays an important role [17, 70, 71]. The interaction of all systems working together in cardiac adaptation to exercise is complex and not completely understood. However, IGF-1 and neuregulin 1 as well as mechanical influences are revealed as major components contributing to cardiac adaptation to exercise that help to better understand this process [50, 51].

### 2.4.2 DEFINING THE ATHLETE'S HEART: THE MORGANROTH HYPOTHESIS

In 1975, Morganroth et al. [13] examined 42 male athletes (15 swimmers, 15 runners, 12 wrestlers), 18 - 24 years old, via M-mode echocardiography. Results were compared to 16 age- and sex-matched controls. In all athletes, left ventricular hypertrophy (LVH) was observed, defined by a significantly increased left ventricular mass (LVM) compared to control subjects. In swimmers and runners, classified as athletes who performed isotonic or dynamic exercise, the increased LVM was caused by a significantly increased left ventricular internal diameter in diastole (LVIDd) and left ventricular end-diastolic volume (LVEDV) compared to wrestlers and controls. Whereas in wrestlers, classified as athletes who perform isometric or static exercise, left ventricular posterior wall thickness in diastole (LVPWd) and interventricular septal thickness in diastole (IVSd) were significantly increased compared with swimmers and runners. Alterations observed in swimmers and runners, thus a proportional increase in LV wall thickness and diameter is defined as eccentric LVH. In contrast, the sole increase in LV wall thickness with no accompanying increase in LV diameter is known as concentric hypertrophy (Figure 3) [13, 14, 72].

In this regard, Morganroth et al. [13] hypothesized that cardiac adaptations are a function of the underlying stimulus, thus, the corresponding type of exercise, with

being either dynamic or static. The rationale behind this hypothesis is a chronic volume overload in dynamic types of sports. Working muscles require large amounts of blood flow to supply the body with oxygen. Thereby, the heart's preload is increased which is the adequate stimulus for a proportional increase in LVIDd and LVPWd. In predominantly static types of sports, cardiac adaptation is triggered by increased intravascular pressures and an increased afterload. Subsequently, this leads to an increase in LV wall thickness without proportional chamber dilatation, which is defined as concentric hypertrophy [17, 42, 70].

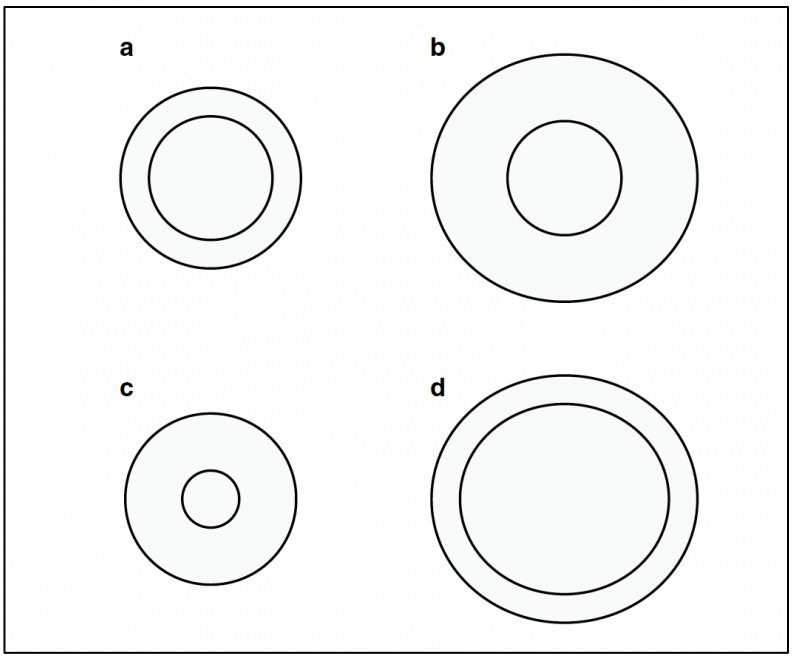


**Figure 3** Left ventricular cavity dimensions in adaptation to exercise: (a) normal LV geometry, (b) concentric hypertrophy, (c) concentric remodelling, (d) eccentric hypertrophy [1].

The 'Morganroth hypothesis' has been questioned numerous times so far [14-18]. First, it has to be mentioned, that sport disciplines cannot be regarded as being exclusively dynamic or static. There is a varying degree of overlap between disciplines with dynamic and static components [42, 49]. Second, Morganroth et al. [13] compared absolute values of cardiac parameters, which are dependent on the subject's body size and should therefore be reported relative to body surface area (BSA) [4, 46, 73, 74]. And third, the 'Morganroth hypothesis' has been built upon a cross-sectional study, where athletes were compared to controls but without accounting for inter-individual differences in exercise intensity, exercise volume and exercise duration [17]. Methodologically, there is to criticize that the original work was performed with 2-dimensional

echocardiography (2DE) in M-mode technique. According to Dickhuth et al. [75], the minimum change in LVM that can be detected on a 95% confidence interval (95% CI) by 2DE is 60 g. Compared with cardiac magnetic resonance imaging (cMRI), M-mode overestimates cardiac dimensions by 30% whereas B-mode echocardiography provides an underestimation of results by 11% [76]. Furthermore 3-dimensional echocardiography (3DE) correlates better with cMRI than 2DE [77].

In an extensive review, Naylor et al. [17], confirmed LVH in athletes vs. controls. Most studies reported a significantly increased LVM and LVIDd in endurance athletes vs. strength athletes, which is in line with the original 'Morganroth Hypothesis'. However, there were also studies reporting the opposite [78] or no significantly different results [79, 80]. Haykowski et al. [1] observed concentric LVH and normal ventricular dimensions in strength athletes to the same percentage (37.5%) and eccentric hypertrophy in 25.0% of strength athletes. In another publication, the authors reported no association between resistance training and increased LVPWd, LVIDd, and LVM [15]. Spence et al. [18] observed increased LVM, LVEDV, and IVSd via cMRI in untrained men after six months of endurance training vs. strength training.

As often, presented results are studied exclusively in male cohorts, whereas female athletes are underrepresented in studies regarding the 'athlete's heart'. Only one publication could be identified by Kooreman et al. [16] that reported a proportional increase in LVM and LVEDV in response to exercise in female college athletes, irrespective of the type of exercise performed.

To summarize, there is evidence in the work, initiated over a century ago [12, 13, 47], which became well-known as the 'Morganroth hypothesis'. However, above mentioned studies challenge the dogma of Morganroth et al. [13] when reporting balanced LVH in endurance and strength athletes vs. controls and a lack of concentric remodelling in strength athletes.

### 2.4.3 Structural adaptations of the left heart

The left ventricle is the part of the heart that was investigated most in studies regarding cardiac adaptation to exercise. The left ventricle's muscular structure is stronger compared to the right ventricle. It supplies the body with blood, oxygen

and nutrients, and thus, working muscles during exercise. In athletes, eccentric and concentric LVH is reported. In children and adolescents, eccentric LVH is defined as relative wall thickness (RWT) $\leq$ 0.42 and LVM/ BSA > $95^{th}$ percentile and concentric LVH as RWT > 0.42 and LVM/ BSA > $95^{th}$ percentile [81]. Characteristics of studies in young competitive athletes mentioned in this paragraph are displayed in table 1.

Results by Simsek et al. [82] support the traditional view of concentric hypertrophy in wrestlers, presenting with increased LVPWd and LVM. In comparison, eccentric hypertrophy was reported in marathon runners who had increased LVPWd and LVM but also an increased LVIDd. The same is for results by Sulovic et al. [83] in 100 dynamic training athletes, where eccentric hypertrophy was observed in 79.4% athletes. In 100 athletes of the static group, eccentric and concentric hypertrophy was present almost to the same extent (49.95% and 54.05%). Compared to the dynamic group and to controls, LVM/ BSA and LVPWd were significantly higher in static training athletes ($p < .001$). In a study by Binnetoglu et al. [84], LVM/ BSA was highest in wrestlers. Compared to controls, it was significantly increased ($p < .005$), but not compared to dynamic athletes or mixed athletes. The authors reported concentric hypertrophy in only one (4.3%) but eccentric hypertrophy in 9 (39.1%) wrestlers, out of 23 wrestlers in total. In soccer players and swimmers, eccentric and concentric hypertrophy was present almost to the same extent (soccer players: 16.1% and 19.4%; swimmers: 28.9% and 35.6%). Zdravkovic et al. [85] compared 94 soccer players to 47 controls. In this study, athletes had significantly higher LVM/ BSA, IVSd/ $BSA^{0.5}$, LVPWd/ $BSA^{0.5}$ and LVIDd/ $BSA^{0.5}$ compared to controls ($p < .0001$). Results are in accordance with a study by Rundqvist et al. [86] in 27 endurance athletes. Kayali et al. [87] also reported the same for IVSd and LVPWd ($p < .001$) but not for LVIDd ($p = .077$). Compared with reference values, one in five tennis players and one in three swimmers in a study by Rodriguez-Lopez et al. [88] had an IVSd z-score of > 2. Within this study, a longer training time, older age, and longer training history were associated with a higher IVSd. Contrary to the results presented, Beaumont et al. [89] did not observe significantly different structural parameters in 22 athletes vs. 22 controls. Only LVEDV/ $BSA^{1.5}$ was significantly increased in athletes, LVM/ BSA and LVIDd however, showed the tendency to be increased in controls.

**Table 1** Studies reporting adaptations of the left heart in young competitive athletes.

| Author | Athletes (females) | Sports-Classification | Age (years) | Athletes' training profile | Controls (females) | Age (years) | Controls' profile |
|---|---|---|---|---|---|---|---|
| Beaumont et al. [89] | n = 22 (0)<br>soccer players | Mixed | 12.0±0.3 | 4.5±1.5 years of Soccer training<br>11±1 months of training / year<br>4±1 training sessions / week<br>9.4±2.4 h of training / week<br>1 match / week | n = 22 (0) | 11.7±0.3 | 1.53±1.77 h of recreational physical activity / week |
| Binnetoglu et al. [84] | n = 25 (0)<br>basketball players | Mixed | 16.2±1.1 | Minimum: 2 years of training<br>Minimum: 3h of training / week | n = 25 (7) | 14.7±1.5 | Sedentary |
| | n = 31 (0)<br>soccer players | Mixed | 15.1±1.1 | | | | |
| | n = 45 (26)<br>swimmers | Endurance | 12.9±1.6 | | | | |
| | n = 16 (7)<br>tennis players | Mixed | 15.5±1.5 | | | | |
| | n = 23 (0)<br>wrestlers | Power | 12.2±0.8 | | | | |
| D'Ascenzi et al. [23] | n = 57 (0)<br>swimmers | Mixed | 10.8±0.2 | 5 -6 training sessions / week<br>105 - 135 min / session | n = 37 (0) | 10.2±0.2 | Recreational activity < 2 h/ day |
| Kayali et al. [87] | n = 126 (NR) | Endurance | 13.5±2.6 | Group Low<br>< 8h training / week<br>Group High<br>> 8h training / week | n = 62 (NR) | 13.5±2.6 | Not actively engaged in sports |
| Pelliccia et al. [11] | n = 1777 (479) | Various Sports | 24±6 | 2 - 28 years of training (mean 6 years) | – | – | – |

**Table 1 (continued)** Studies reporting adaptations of the left heart in young competitive athletes.

| Author | Athletes (females) | Sports-Classification | Age (years) | Athletes' training profile | Controls (females) | Age (years) | Controls' profile |
|---|---|---|---|---|---|---|---|
| Rodriguez-Lopez et al. [88] | n = 331 (86) | Various Sports | 11.9±3.2 | Minimum: 3h training / week | – | – | – |
| Rundqvist et al. [86] | n = 27 endurance athletes | Endurance | 15.5 (13 - 19) | Minimum: 2 years of training ≥ 5x30 min training / week | n = 27 (11) | 15.4 (13 -19) | Not engaged in regular exercise |
| Simsek et al. [82] | n = 24 wrestlers<br>n = 22 marathon runners | Power<br>Endurance | 16.8±1.9<br>17.5±2.2 | Minimum: 2 years of training > 15 hours training / week | n = 20 (0) | 16.4±1.8 | Sedentary lifestyle/ not engaged in any sports |
| Sulovic et al. [83] | n = 100 dynamic athletes<br>n = 100 static athletes | Endurance<br>Power | 15.0±1.0<br>15.4±1.6 | Minimum: 2 years of training 5-7 training sessions / week Dynamic: 4.1±1.2 years of training Static: 3.9±1.0 years of training | n = 100 (0) | 15.2±1.6 | Not engaged in competitive sports |
| Zdravkovic et al. [85] | n = 94 soccer players | Endurance | 12.85±0.84 | 4.6±1.2 years of training | n = 47 (0) | 12.85±0.86 | Exercise ≤ 2 h/ week |

NR – not reported

Pelliccia et al. [11] quantified the association of an adaptation of the left ventricle and left atrium (LA) in 1777 elite athletes, 11 - 56 years. An increase of 1 mm in LV cavity diameter was accompanied by an increase in LA diameter by 0.4 mm. As the heart's chambers do not work independently of each other, it seems as a logic consequence, that cardiac adaptations occur relative to each other.

In young athletes, five studies have been identified that investigated LA structure [23, 82, 83, 85, 86]. Three studies out of four reported a significantly increased LA diameter in athletes vs. controls. However, only Rundqvist et al. [86] and Zdravkovic et al. [85] calculated indexed LA diameter, relative to BSA and may therefore provide a more reliable result than studies that reported absolute values. Controversial results regarding indexed LA volumes were observed in two studies [23, 90]. D'Ascenzi et al. [23] noted no significant difference between 57 swimmers vs. 37 controls ($p = .14$) opposite to 27 endurance athletes vs. 27 controls in the study by Rundqvist et al. [86]. It is to mention that the difference in indexed LA volumes between the two studies was 10 mm with 17.2±3.3 mm in 57 swimmers by D'Ascenzi et al. [23] and 27 (21 - 36) mm in 27 endurance athletes by Rundqvist et al. [86]. This difference could be explained by the age difference. Athletes by Rundqvist et al. [86] were 5 years older (15.5 (13 - 19) years vs. 10.8±0.2 years) but also by the different training stimulus (dynamic exercise vs. mixed exercise). The latter is in line with findings by Pelliccia et al. [11] who stated that LA cavity enlargement is dependent on the type of exercise.

### 2.4.4 Structural adaptations of the right heart

The assessment of the right ventricle is more challenging than the left ventricle. Its structure is of a more complex 3D shape and its form of contraction is not concentric but rather longitudinal [90]. Due to these difficulties, there is a lack of studies investigating the right ventricle's response to exercise in young competitive athletes [70]. In adults, there's evidence for an influence of intense endurance exercise on RV structure. According to La Gerche et al. [9, 45] the hemodynamic overload of maximal work might affect the RV even more than the LV. Kovacs et al. [70] reported balanced biventricular stress caused by isotonic exercise that results in RV dilatation. Isometric training, however, is supposed to result in less RV remodelling, due to the mitral valve's protective mechanism, that

limits high intravascular pressures, created during isometric work, from being transmitted to the RV.

In young competitive athletes, two studies assessed RV structure [34, 86]. D'Ascenzi et al. [34] performed a more comprehensive analysis that compared RV basal and mid-cavity diameter as well as RV end-diastolic and end-systolic area. While absolute values were significantly higher in 57 swimmers vs. 37 controls, indexed parameters failed to reach significance, except for RV end-systolic area/ BSA (6.6±1.5 $cm^2$/ $m^2$ vs. 5.5±1.6 $cm^2$/ $m^2$, p = .003). Rundqvist et al. [86] reported significantly higher values for indexed RV basal diameter/ BSA (23 (19 - 28) mm/ $m^2$ vs. 20 (17 - 28) mm/ $m^2$, p < .001) and RV end-diastolic area/ BSA (15 (11 - 21) $cm^2$/ $m^2$ vs. 13 (9 - 17) $cm^2$/ $m^2$, p < .001) in 27 endurance athletes vs. 27 controls.

Within the same studies, right atrial (RA) structure was investigated with both authors, reporting significantly increased values in athletes vs. controls. Swimmers in the study by D'Ascenzi et al. [34] had a significantly increased RA area (10.0 ± 2.2 $cm^2$ vs. 9.0 ± 1.4 $cm^2$, p = .022) and RA volume/ BSA (17.6 ± 3.9 ml/ $m^2$ vs. 15.4 ± 2.9 ml/ $m^2$, p = .007). Rundqvist et al. [86] also assessed right atrial structure and reported a significantly increased RA area/ BSA (9.1 (6.6 – 11.4) mm/ $m^2$ vs. (7.2 (5.1 – 8.7) mm/ $m^2$, p < .001) and RA diameter/ BSA (23 (17 – 28) mm/ $m^2$ vs. (20 (15 – 27) mm/ $m^2$, p = .008) in 27 endurance athletes vs. 27 controls.

### 2.4.5 Functional adaptations of the left heart

Regarding the left heart's function, studies in young athletes assessed left ventricular systolic and diastolic function. Controversial results are reported regarding LV ejection fraction (EF) which represents the heart's systolic function. Compared to controls, in a study by De Luca et al. [24], soccer players and basketball players had a significantly higher LV EF. Rundqvist et al. [86] reported higher values in endurance athletes vs. controls (p = .036) and Sulovic et al. [83] in dynamic exercising athletes vs. static exercising athletes (p < .001) and controls (p = .036). No differences between athletes and controls and between different types of athletes were reported in other studies [82, 84, 85].

LV diastolic function, represented by the peak early LV diastolic filling velocity (E) and peak late LV diastolic filling velocity (A) was investigated in seven studies [24, 82-84, 86, 91, 92]. Unnithan et al. [91] compared 22 soccer players with 15 controls. The authors observed a significantly higher E in soccer players at rest and during submaximal exercise. E was significantly lower in cyclists compared to the other groups ($p < .001$) in the study by De Luca et al. [24]. Rundqvist et al. and Sulovic et al. [83, 86] reported a significantly higher E for endurance athletes and Binnetoglu et al. [84] for swimmers vs. other groups ($p = .026$). Furthermore, in static exercising athletes, E was significantly lower compared to controls in the study by Sulovic et al. [83]. The same is for A compared to controls ($p < .05$) in the study by Sulovic et al. [83] and Binnetoglu et al. [84]. De Luca et al. [24] reported a significantly lower A compared to controls and basketball players ($p < .001$). The ratio of both parameters (E/A) was significantly higher in young athletes compared to controls in two studies [86, 92].

### 2.4.6 Functional adaptations of the right heart

Three studies assessed right ventricular function in young athletes [31, 34, 86]. Bjerring et al. [31] observed no significantly different RV fractional area change (FAC) or tricuspid annular plane systolic excursion (TAPSE) in athletes vs. controls. Even more, athletes in the study by D'Ascenzi et al. [34] had a significantly reduced RV FAC ($p = .007$). The authors did not report a significantly different systolic function, contrary to Rundqvist et al. [86] who observed a significantly higher TAPSE relative to BSA, in athletes vs. controls ($p = .008$).

### 2.4.7 ECG-characteristics in athletes: the Seattle-criteria

The interpretation of an athlete's electrocardiogram (ECG) is not part of this work. However, sport-specific ECG alterations in athletes will be presented in the following paragraph, in order to provide a comprehensive picture of sports cardiology.

Sudden cardiac death (SCD) is the leading cause of death in athletes during exercise [49, 93, 94] – most underlying pathologies, such as cardiomyopathies and primary electrical diseases can be identified on a resting 12-lead ECG [95]. In 2012, an international group of experts defined the 'Seattle Criteria' as expert consensus on the interpretation of an ECG in athletes [96]. In 2015, the 'Seattle

Criteria' have been revised to its current version [95]. Table 2 presents normal ECG findings in athletes, that are associated with physiologic adaptations to exercise, as well as borderline and abnormal findings in athletes. The latter present a pathological status.

**Table 2** International criteria for the interpretation of electrocardiographic findings in athletes, with results divided into normal, borderline, and abnormal ECG findings [95].

| Normal ECG findings | Borderline ECG findings | Abnormal ECG findings |
|---|---|---|
| Increased QRS voltage for LVH or RVH | Left axis deviation | T wave inversion |
| Incomplete RBBB | Left atrial enlargement | ST segment depression |
| Early repolarization/ ST segment elevation | Right axis deviation | Pathologic Q waves |
| ST elevation followed by T wave inversion in V1-V4 in black athletes | Right atrial enlargement | Complete LBBB |
| T wave inversion in V1-V3 $\leq$ age 16 years old | Complete RBBB | QRS $\geq$ 140 ms duration |
| Sinus bradycardia or arrhythmia | | Epsilon wave |
| Ectopic atrial or junctional rhythm | | Ventricular pre-excitation |
| 1° AV block | | Prolonged QT interval |
| Mobitz Type I 2° AV block | | Brugada Type 1 pattern |
| | | Profound sinus bradycardia < 30 bpm |
| | | PR interval $\geq$ 400 ms |
| | | Mobitz Type II 2° AV block |
| | | 3° AV block |
| | | $\geq$ 2 PVCs |
| | | Atrial tachyarrhythmias |
| | | Ventricular arrhythmias |

AV - atrioventricular, LBBB - left bundle branch block, LVH - left ventricular hypertrophy, PVC - premature ventricular contraction, RBBB - right bundle branch block, RVH - right ventricular hypertrophy.

## 2.5 PRE-PARTICIPATION CARDIOVASCULAR SCREENING IN ATHLETES

Pre-participation cardiovascular screening (PPCS) in athletes is recommended by major sports associations, like the International Olympic Committee (IOC) or the Fédération International de Football (FIFA), as well as the European Society of Cardiology (ESC), American Heart Association/ American College of Cardiology (AHA/ ACC), American Medical Society for Sports Medicine (AMSSM), and Association for European Paediatric and Congenital Cardiology (AEPC) [97-103]. Its use is to screen young athletes for cardiac pathologies that go along with an increased risk for SCD during exercise. Fortunately, such an event is very rare. Every single incident, however, is a tragedy.

The annual SCD incidence varies within different studies from to 1 : 417 000 [104] to 1 : 43 770 [105] or an annual incidence of 1 : 53 000 in college athletes, within the entire study population, and 1 : 38 000 in male athletes but 1 : 122 000 in female athletes [106]. The risk in males is about ten times higher than in females [107]. Furthermore, the incidence differs with ethnicity, as black athletes have a higher risk than white athletes (1 : 21 000 in black athletes vs. 1 : 68 000 in white athletes) [106]. Compared to the general population, athletes have a 2.5-fold increased SCD risk. In this regard, exercise is not the cause for SCD but a potent trigger in combination with underlying cardiac disorders [98]. These underlying disorders are, according to results by Harmon et al. [106] in about 25 % of cases unexplained autopsy-negative SCDs, followed by congenital anomalies of the coronary arteries (11 %), myocarditis (9 %) and coronary atherosclerosis (9 %). Hypertrophic cardiomyopathy (HCM), believed to be the main cause for SCD for many years, was found in 8 % of autopsied bodies.

Different PPCS recommendations agree on the assessment of an athlete's personal and family medical history and a physical examination. Opposite to European recommendations and the FIFA, the AHA/ ACC does not include a general ECG screening. It is only supported in athletes aged 12 - 25 years if on-site expertise and resources are available [103]. In the English Football Association, a mandatory screening with ECG and echocardiography is performed in youth academy players of 15 - 17 years [108].

An ECG is an objective method to assess cardiac electrical activity and increases the sensitivity of screening programs for cardiovascular disorders that are

associated with SCD [98]. Approximately 60 - 80 % of all cardiac pathologies that are associated with an increased risk of SCD may be detectable via ECG [99, 109, 110]. In Italy, the first PPCS program has been established by law in 1971 and revised in 1982. Due to PPCS the SCD incidence in Italian athletes could be reduced by 89 % [98] which is one of the best reasons in favour of including an ECG within a PPCS. Furthermore, it is objective and can be done in less than five minutes, in almost any location [111]. Arguments against the inclusion of an ECG within a PPCS are additional costs and a high rate of false-positive results, that lead to further diagnostic procedures and restriction from sport [101]. False-positive results have initially been reported to be around 16 % but could be dropped to 9 % with recommendations on the interpretation of an ECG in athletes [112, 113].

Pelliccia et al. [109] evaluated the efficacy of the Italian PPCS over nine years from 1990 - 1998 in 4485 elite athletes (24±6 years, 9 - 56 years) competing at a national and international level who had been cleared via PPCS. In 98.8 % no HCM could be diagnosed via echocardiography. In 37 out of 41 male athletes, LVH was identified with eccentric remodelling. Out of four athletes with LVH that were considered to be in the grey zone between HCM and having an ‘athlete’s heart’, three had an abnormal ECG. In this case of having an abnormal ECG, a secondary work up is recommended via TTE as non-invasive gold standard of cardiac imaging [98, 114].

In 2005, Corrado et al. [98] published costs for performing a PPSC of around 20 Euros per screening with history taking and physical examination, and 30 Euros per screening with an additional ECG. Halkin et al. [115] estimated the costs for a 20-year PPCS program to be approximately 51 - 69 billion $ in total. The costs per one life saved on the contrary were about 10.6 - 14.4 million $. In this regard, however, it is priceless to protect one’s life. This cannot be counterbalanced with costs that have been saved instead.

## 2.6 RECOMMENDATIONS ON CARDIAC IMAGING IN ATHLETES

Data on cardiac assessment in young competitive athletes are inconsistent with no strict recommendations on how to screen young athletes, to which extent, in which intervals, and which imaging modalities to apply [19]. The AEPC recommends a cardiovascular screening in young athletes before they start their competitive career that includes the athlete's personal and family history and a 12-lead ECG as mentioned in the paragraph above. The screening should be repeated every second year [102]. A TTE examination is recommended to be used as primary diagnostic screening tool but should be performed by experienced paediatric cardiologists [116] following current standards and guidelines [19, 117]. The parameters assessed should be indexed to BSA, and existing z-scores should be applied [21].

Cardiac Magnetic resonance imaging (cMRI) is recommended as a secondary screening tool in athletes who had suspicious findings within the primary screening [118]. It should be performed as routine examination in athletes who bear a high-risk for cardiovascular pathologies or SCD [119]. Additionally, Speckle Tracking Echocardiography (STE) can be performed as a very potent diagnostic tool to detect subtle changes in myocardial function [116].

# 3 METHODOLOGY

## 3.1 MUNICH CARDIOVASCULAR ADAPTATIONS IN YOUNG ATHLETES STUDY: THE 'MUCAYA-STUDY'

This work is part of the MuCAYA-Study, which was conducted from September 2018 to September 2020 at the Chair of Preventive Pediatrics, TUM Department of Sport and Health Sciences, Technical University of Munich (TUM). The study was approved by the local ethics committee (301/18S) and is in line with the Declaration of Helsinki (2013). Funding was provided by 'Deutsche Stiftung für Herzforschung e.V.', grant number F06/18. The detailed study protocol can be found elsewhere [120]. Additionally, a systematic literature review has been performed to provide a comprehensive overview on the current state of research regarding cardiac adaptations in young competitive athletes [121].

## 3.2 STUDY PARTICIPANTS

Study participants were competitive active boys and girls, 7 - 18 years old, who visited our department for a PPCS. Participation was voluntary and only allowed after informed consent from participants' legal guardians and/ or from participants themselves, for age groups 14 - 18 years. Inclusion criteria were: no acute infection or orthopaedic injury, no cardiac disorders detected by auscultation, ECG or 2-dimensional TTE, and medical clearance for maximum cardiopulmonary exercise testing (CPET). Only participants who practiced sports in an organized sports club setting, who trained regularly for at least three hours per week, and participated in competitions were enrolled in the data analysis. Participants were recruited through cooperation with the Bavarian State Sports Physicians Association, the Bavarian State Sports Club, and local sports clubs.

Regarding their major type of sports, participants were grouped into four categories (endurance, power, mixed, skill), defined by Pelliccia et al. [42]. For example, cycling, running or rowing were assigned to the endurance category with higher isometric than isotonic components, leading to pronounced cardiac remodelling. Wrestling or alpine skiing were assigned to the power category with higher isotonic than isometric components, leading to less pronounced cardiac remodelling. The mixed category includes soccer or basketball, for example, with

balanced isometric and isotonic components, leading to moderate cardiac remodelling. And last, the skill category, including sports like golf or sailing, with low isometric and isotonic components and minor cardiac remodelling.

### 3.3 PHYSICAL ACTIVITY QUESTIONNAIRE

Participants' main type of sports as well as further types of sports that they performed, their training history in years, training time per week and training intensity for each type of sports was assessed with the self-reported Motorik Modul (MoMo-AFB) physical activity questionnaire [122]. In detail, participants reported how much time they exercised per week (min/ week) and at which intensity they exercised, rated on a three-item scale (low, moderate, intense). According to this information, training time in h/ week was calculated and adjusted for a factor depending on how many months the sport is performed per year as the MoMo-AFB is calculated over the time span of one year. For example, if participants do alpine skiing for five months during winter, the exercise time is multiplied by the factor 5/ 12. Last, participants' overall exercise time in hours per week is calculated for the combination of different types of sports.

An intensity-index is derived, based on the calculation of metabolic equivalents (METs) and depending on participants' rating of the intensity level of their training sessions. One MET refers to the body's oxygen consumption of 3.5 ml $O_2$/ min/ kg when sitting at rest. In comparison, the body consumes 6.6 ml and 8.8 ml $O_2$/ min/ kg playing soccer at low or moderate intensity, respectively. A soccer game of 90 minutes at moderate intensity refers to an intensity of 792 MET-minutes or 13.2 MET-hours, respectively. MET-values for the different types of sports were derived from Schmidt et al., Ridley et al., and Ainsworth et al. [122-124]. MET-minutes were calculated for all indicated types of sports and added to an overall intensity index in MET-minutes and MET-hours per week, respectively. The questionnaire's Kappa-Coefficient is 0.66, its intraclass correlation coefficient is 0.68 [125].

## 3.4 ANTHROPOMETRIC MEASUREMENTS

Participants' anthropometry was assessed following standardized instructions by trained staff [126]. Body height and body mass were measured without shoes, wearing light sports clothes, and standing upright. Body height was registered to the next 0.1 cm, body mass to the next 0.1 kg (seca 799, seca GmbH&Co.KG, Hamburg, DEU). Waist circumference was measured by placing the measuring tape at the approximate midpoint between the lower margin of the lowest palpable rip and the top of the superior iliac spine. To measure hip circumference, the measuring tape was placed around the widest points of the hip. Body mass index (BMI) was further calculated as body mass/ (body height)$^2$, with body mass in kg and body height in meters. Waist-to-hip ratio (WHR) was calculated as waist circumference/ hip circumference, and waist-to-height ratio (WHtR) as waist circumference/ body height with waist circumference, hip circumference and body height in cm. Standardized z-scores for body height, BMI, WHR, and WHtR were further calculated as recommended by Neuhauser et al. [127] according to the formula below and compared to German reference values [127, 128].

$$z - Score = \frac{\left[\left(\frac{x}{M}\right)^{L} - 1\right]}{S\ x\ L}\ for\ L\ \neq 0$$

and

$$z - Score = \frac{1}{S}\ x \ln\left(\frac{x}{M}\right)\ for\ L\ = 0$$

BSA was calculated according to Du Bois and Du Bois [129] applying the following formula:

$$BSA = (body\ mass^{0.425}\ x\ body\ height^{0.725})\ x\ 0.007184$$

## 3.5 HEART RATE, BLOOD PRESSURE AND PULSE WAVE ANALYSIS

Resting heart rate (HR) and peripheral SBP and diastolic blood pressure (DBP) were measured oscillometrically once, with participants lying in a supine position on an examination bench, after 10 minutes of rest (Mobil-O-Graph®, I.E.M., Stolberg, DEU). An appropriate cuff, available in four sizes (XS, S, M, L) according to the participant's upper arm circumference in cm, was placed on the participant's left arm. Central SBP (cSBP) and pulse wave velocity (PWV) were

determined with the ARCSolver pulse wave analysis algorithm (AIT, Austrian Institute of Technology GmbH, Vienna, AUT) [130]. The ARCSolver pulse wave analysis algorithm was validated with invasive cardiac catheter measurements of cSBP ($r^2$ = 0.899, p<.0001, [131], and $r^2$ = 0.97, p<.001, [132]) and PWV ($r^2$ = 0.81, p<.001, [133]). Furthermore, the method is validated with non-invasive measurements with the SphygmoCor device ($r^2$ = 0.532, p<.05 [134]). Standardized z-scores were calculated and compared to German reference values [127, 135].

## 3.6 TWO-DIMENSIONAL ECHOCARDIOGRAPHIC MEASUREMENTS

2DE measurements were performed to assess the left ventricle's dimensions, such as LVIDd and left ventricular internal diameter in systole (LVIDs), IVSd, and LVPWd. RWT was calculated according to Lang et al. [72] as (2 x LVPWd) / (LVIDd).

Standardized z-scores for LVIDd, LVIDs, IVSd, and LVPWd were further calculated according to reference values published by Pettersen et al. [136]. LVM was calculated according to Devereux and Reicheck [137] and presented relative to BSA (LVM/ BSA) and body height in meters (LVM/ height). For the distinction between eccentric LVH (RWT $\leq$ 0.42 and LVM/ $m^{2.7}$ > $95^{th}$ percentile) and concentric LVH (RWT > 0.42 and LVM/ $m^{2.7}$ > $95^{th}$ percentile) reference intervals for indexed LVM/ $BSA^{2.7}$ (LVM/ $m^{2.7}$) were calculated according to Khoury et al. [81].

The left ventricle's systolic function was assessed by EF, measured in B-mode with the biplane method of disks (modified Simpson's rule), thereby assessing left ventricular volumes in end-diastole (LVEDV) and end-systole (LVESV). EF was further calculated as EF = (LVEDV - LVESV)/ LVEDV, and fractional shortening (FS), which was measured in M-mode according to Lang et al [72].
Left ventricular diastolic function was assessed by the ratio of mitral E- and A-wave (E/A), measured via pulsed-wave Doppler. Hereby, the E-wave represents the early inflow via the mitral valve and is a surrogate marker to assess the heart's diastolic function. The A-wave represents the late inflow via the mitral valve, and is a surrogate marker for the left atria's contribution to diastolic filling [138].

Two experienced cardiologists performed all echocardiographic measurements and off-line analyses. Measurements were performed with a GE VIVID 7 Dimension ultrasound system (GE Healthcare, Horten, NOR). All off-line analyses were done with dedicated software (ECHOPAD Software, GE Healthcare, Horten, NOR).

## 3.7 HANDGRIP STRENGTH TEST

Handgrip strength (HGS) was applied as surrogate marker for participants' overall muscular strength [139]. Participants' HGS was assessed, following standardized recommendations by the American Society of Hand Therapists (ASHT) with the participant sitting on a chair, the upper body upright and shoulders abducted at 10˚. Both elbows were flexed at 90˚, holding the forearm in a neutral position between pronation and supination [140].

The testing procedure was explained to each participant following a standardized description, encouraging the participant to push the handgrip dynamometer (SAEHAN Hydraulic Hand Dynamometer SH5001, SAEHAN Corporation, Masan, KOR) at maximum strength, alternately three times with the right hand and three times with the left hand. For further calculations the maximum attempt out of the six attempts was applied, relative to participants' body mass [141]. In one study in children, HGS showed a high association with the one-repetition maximum bench press test ($r = .79$, $p < .01$; $R^2 = 0.621$) [142].

## 3.8 CARDIOPULMONARY EXERCISE TEST

To assess maximum exercise performance, each participant performed a CPET to exhaustion after medical clearance. The test was performed on an ergobike (Lode Corival, Lode B.V., Groningen, NLD) wearing a breathing mask for the spirometric measurement of $VO_{2peak}$ (Ergostik, Geratherm Respiratory GmbH, Bad Bissingen, DEU). Participants' cardiac function was monitored during the test with a 12-lead ECG (CARDIOVIT CS-200 Office, SCHILLER AG, Baar, CHE). CPET was done following a modified Godfrey protocol [143]. After 2 minutes of rest participants started cycling with an initial load of 50 % of their body mass. The incline was chosen to reach 4 - 5 Watt/ kg body mass within 6 - 12 minutes at a cadence between 60 - 80 revolutions per minute (rpm) [144, 145]. Maximum HR (1/ min), maximum workload (Watt), relative maximum workload (Watt/ kg),

and relative $VO_{2peak}$ (ml/ min/ kg) were assessed. CPET was conducted by trained sports scientists with a cardiologist aside. The test was terminated, if the participant was not able to keep the cadence > 60 rpm or if participants stopped the test themselves when reaching the individual maximum performance or if they showed signs of dyspnoea or muscular fatigue, respectively. In case of pathological ECG changes, for example arrhythmia like atrial flutter or atrial fibrillation, ventricular tachycardia, ST-segment alterations or any signs indicating that participants didn't feel well, testing would have been terminated. No such events have been observed within the study.

## 3.9 RESEARCH QUESTIONS

One purpose of this work was to provide an overview of current studies investigating echocardiographic parameters in young competitive athletes. Inconsistent findings in these studies, summarized in a systematic review, with most of the studies investigating echocardiographic parameters in small study samples and in a cross-sectional setting only, resulted in the MuCAYA study protocol to answer the following research questions:

(1) is there an association between structural cardiac parameters and exercise training, defined by training intensity and duration, in young competitive athletes?

(2) is there an association between functional cardiac parameters and exercise training, defined by training intensity and duration, in young competitive athletes?

(3) are cardiac adaptations in young competitive athletes dependent on the underlying training stimulus, being either endurance training or strength training?

(4) can cardiac adaptations in young competitive athletes be detected in a longitudinal setting over the time span of two years?

## 3.10 DATA MANAGEMENT AND DATA PROCESSING

Study data was stored in an online database pseudonymously with participants' and legal guardians' informed consent. Participants and legal guardians could withdraw their consent at any time during the study without naming any reasons for their decision. Data will be stored for scientific purpose for a period of ten years. Access to the database was limited to the study members involved. Data

was further processed using Microsoft Excel (Microsoft® Excel for MAC, Version 16.57, Redmond, Seattle, USA). The statistical analyses were performed with SPSS statistical software (version 25 for MAC, IBM, Chicago, IL, USA).

# 4 PUBLICATIONS

## 4.1 SUMMARY: CARDIAC STRUCTURE AND FUNCTION IN JUNIOR ATHLETES: A SYSTEMATIC REVIEW OF ECHOCARDIOGRAPHIC STUDIES

In young athletes, the level of competitiveness in sports is increasing, as well as frequency and intensity of exercise training. Adaptations of the cardiac system to this increased workload imposed by exercise has not yet been studied sufficiently. In adults, studies point towards a shift from the functional athlete's heart towards pathological cardiac remodelling, with ventricular arrythmia and impaired cardiac function, that is exercise-related. This systematic review investigates cardiac adaptations to exercise in junior athletes compared to inactive controls. Three electronic databases (PubMed/ Medline, ScienceDirect and Web of Science) were searched for studies assessing 2-dimensional transthoracic and speckle tracking echocardiography (2D TTE and 2D STE) parameters in junior athletes, aged 7-19 years, compared to inactive controls. Data was screened and extracted by two reviewers; study quality and risk of bias was assessed by three reviewers. Eight out of 1460 studies met all inclusion criteria, with all studies reporting results on 2D TTE and six studies reporting results on 2D STE parameters in 540 (51 girls) junior athletes and 270 (18 girls) controls. There is evidence for structural cardiac adaptations of the left ventricle and both atria in junior athletes. Results regarding left ventricular function are controversial with a tendency to improved function in dynamic exercising athletes. Left ventricular mass and relative wall thickness point towards higher values in static exercising athletes. Cardiac adaptations to exercise occur in children and adolescents. These adaptations are more pronounced in structural left ventricular parameters. Functional parameters are preserved or slightly improved in junior athletes but not impaired by exercise.

Author's contribution: Heidi Weberruß designed the review study, performed the literature research and screened publications, she performed the data extraction, risk of bias, and quality assessment and wrote the manuscript.

## 4.2 CARDIAC STRUCTURE AND FUNCTION IN JUNIOR ATHLETES: A SYSTEMATIC REVIEW OF ECHOCARDIOGRAPHIC STUDIES

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*Systematic Review*

# Cardiac Structure and Function in Junior Athletes: A Systematic Review of Echocardiographic Studies

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**Abstract**

**Background**: In young athletes, the level of competitiveness in sports is increasing, as well as frequency and intensity of exercise training. Adaptations of the cardiac system to this increased workload imposed by exercise has not yet been studied sufficiently. In adults, studies point towards a shift from the functional athlete's heart towards pathological cardiac remodelling, with ventricular arrythmia and impaired cardiac function, that is exercise-related. This systematic review investigates cardiac adaptations to exercise in junior athletes compared to inactive controls. **Methods**: Three electronic databases (PubMed/Medline, ScienceDirect and Web of Science) were searched for studies assessing 2-dimensional transthoracic echocardiography (2D TTE) and 2-dimensional speckle tracking echocardiography (2D STE) parameters in junior athletes, aged 7–19 years, compared to inactive controls. Data was screened and extracted by two reviewers; study quality and risk of bias was assessed by three reviewers. **Results**: Eight out of 1460 studies met all inclusion criteria, with all studies reporting results on 2D TTE and six studies reporting results on 2D STE parameters in 540 (51 girls) junior athletes and 270 (18 girls) controls. There is evidence for structural cardiac adaptations of the left ventricle and both atria in junior athletes. Results regarding left ventricular function are controversial with a tendency to improved function in dynamic exercising athletes. Left ventricular mass and relative wall thickness point towards higher values in static exercising athletes. **Conclusions**: Cardiac adaptations to exercise occur in children and adolescents. These adaptations are more pronounced in structural left ventricular parameters. Functional parameters are preserved or slightly improved in junior athletes but not impaired by exercise.

**Keywords:** athlete's heart; junior athletes; 2D transthoracic echocardiography; 2D speckle tracking echocardiography; cardiac remodelling

## 1. Introduction

Young athletes performing sports on a competitive level practice between 10–20 hours a week at moderate to high intensities [1]. To keep up with the increased demands imposed on the body by intensive physical exercise, the cardiovascular system has to increase its capacity by a factor of 5–6 compared to moderate exercise [2]. Additionally, the level of competitiveness is increasing as well as training frequency, intensity, and demands that are placed into children's training sessions [3,4]. Several studies have reported cardiac remodelling in children and adolescents [5–8]. Apparently, cardiac adaptation does not require the time span of a long professional training career.

To provide an overview of the current state of research regarding structural and functional cardiac adaptation in junior athletes, and to present results of these studies regarding the influence of exercise on the cardiovascular system, we performed this systematic review, searching electronic databases for studies investigating the cardiac structure and function in male and female junior athletes (7–19 years) compared to a non-active control group by two-dimensional transthoracic echocardiography (2D TTE) or 2D speckle tracking echocardiography (STE).

## 2. Materials and Methods

This review is in line with the PRISMA Statement [9].

**Search strategy and selection criteria**: We searched databases PubMed/Medline, ScienceDirect, and Web of Science. Inclusion criteria were (1) exercising or active children and/or adolescents, aged 7–19 years; (2) comparison of athletes with an inactive control group (CG); (3) performing 2-dimensional transthoracic echocardiography and/or 2-dimensional speckle tracking echocardiography. The exact search term was: ((children OR adolescents) AND (activ* OR trained OR exercise) AND (echocardiography or speckle tracking) AND (control group)). Only articles published in English were included. Review articles and meta-analyses were not considered, as well as articles including animal studies and the use of patients. Further exclusion criteria were: (1) not meeting our age criteria; (2) not exercising regularly/at a competitive level; (3) no inactive control-group; (4) other cardiac imaging methods.

Results were screened by two researchers separately (HW and TE).

**Risk of bias assessment**: The risk of bias assessment for methods was performed according to an 11-item checklist for case-control studies [10]. To assess the risk of bias in study results a 12-item checklist was applied based on a recent review [4]. Three researchers (HW, LB, TE) screened the methods section and checked each study's results. If no agreement could be found a consensual decision was made.

**Data extraction**: A standardized data extraction form was set up (TE) and cross-checked (HW). Where study data was unclear, authors of the corresponding publication were contacted.

**Quality assessment**: Study's quality was assessed with the study quality assessment tool by the NIH National Blood, Heart, and Lung Institute [11]. Criteria were rated by three researchers (HW, LB, TE). If no agreement could be found a consensual decision was made.

## 3. Results

In total, eight of 1460 studies met all inclusion criteria. Most of the studies (1424/97.7%) were excluded after the first screening. The majority of these studies did not deal with the matter of this review (43%), included patients (29%), did not meet our age criteria (16.5%), included animals (7%), or were recommendations or reviews (4%). Results of our search and reasons for excluding studies are shown in Fig. 1.

### *3.1 Risk of Bias Assessment*

Regarding the risk of bias assessment for methods full agreement was met in 44% of cases. Regarding the risk of bias assessment in reporting results, the researchers fully agreed in 93% of cases (see **Supplementary Table 1** and **Supplementary Table 2**).

### *3.2 Quality Assessment*

Five studies were rated to be of good quality [3,12–15], one as fair [16] and two studies as being of poor quality [17,18]. Full agreement between the researchers was met in 60.6% and a majority agreement in 38.3% of the categories. Authors did not agree on 1 point (1.1%) (see **Supplementary Table 3**).

### *3.3 Study Groups Characteristics*

Sample sizes varied from n = 44 to n = 300 participants [3,12–14,17]. Only two studies included female athletes [14,16]. All studies included athletes performing predominantly dynamic (soccer and tennis) or mixed types of sports (basketball, running, cross-country skiing). Three studies included static types of sports [16–18]. A minimum training history of two years was required in four studies [14,16–18]. Athletes in other studies trained for an average 4–6 years [12,15,18]. Training time per week varied from 2.5–3 hours [14,16] up to 15 hours [17]. The control group's activity level was <2 hours in most studies. An overview of the studies is given in **Supplementary Table 4**.

### *3.4 Anthropometry, Heart Rate and Blood Pressure*

Anthropometric characteristics of study participants (age, body height, body mass, body surface area [BSA], body mass index [BMI]) as well as heart rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP] are displayed in **Supplementary Table 5**.

### *3.5 Heart Rate and Blood Pressure*

Four authors reported a significantly lower heart rate in athletes compared to controls ($p < 0.05$) [3,13,14,17,18]. Blood pressure results are inconsistent, with significantly lower results in athletes [3,13], in dynamic-exercising athletes only [18] or only for DBP [15] or no significant differences in athletes vs. controls [12,14,17].

### *3.6 2D Transthoracic Echocardiography*

There was a huge variety of echocardiographic parameters and their methodological approach which made it difficult to compare these studies. Most authors focused on parameters regarding the left heart [12,14–18] and two studies on the right heart's structure and function [3,13]. Results were categorized according to the heart's structure and function.

#### 3.6.1 Left Ventricular Structure

Six studies focused on LV structure [12,14–18]. As structural parameters are largely influenced by BSA [19,20] only indexed parameters were compared: LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), interventricular septal thickness (IVS), LV wall thickness (LVWT), LV posterior wall thickness (LVPWT), mean wall thickness (MWT), relative wall thickness (RWT), LVM, LV length, LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV). LVEDD was significantly higher in athletes in two studies [14,15]. The latter also reported a significantly higher LVEDS. Binnetoglu *et al.* [16] reported similar mean values for LVEDD and LVESD in athletes and controls, except for basketball players. Athletes' IVS was significantly higher in three studies [14–16], LVPWT was significantly increased in five studies [14–18]. Sulovic *et al.* [18] reported a higher RWT in athletes. In addition, static exercising athletes had a significantly higher RWT compared to dynamic exercising athletes. The same for LVM held true in this study and in three other studies [14,15,17,18]. Binnetoglu *et al.* [16] reported the same findings in soccer players vs. tennis players and controls and a significantly increased LVM in wrestlers vs. tennis players. In summary, there is evidence of structural cardiac adaptations in junior athletes. These adaptations cannot be exclusively attributed to either dynamic or static types of sport (see **Supplementary Table 6**).

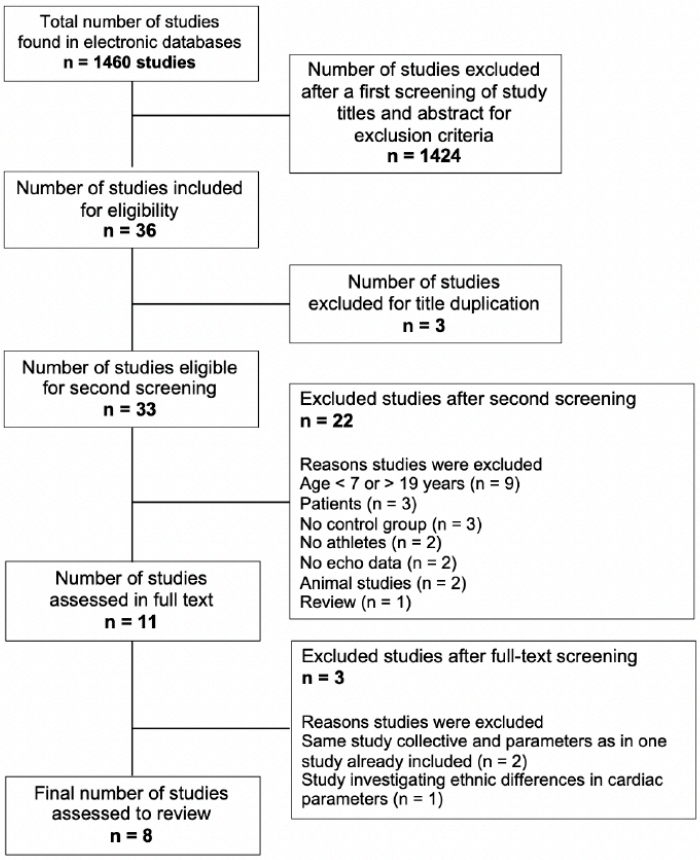


**Fig. 1. Flow chart of the study selection process.**

3.6.2 Left Ventricular Function

LV systolic function is represented by stroke volume (SV), LV ejection fraction (EF), fractional shortening (FS), cardiac output (Q), cardiac index, peak systolic myocardial velocity (S'), LV myocardial performance index (Tei index), concentricity, and sphericity index.

Endurance athlete's EF was significantly increased in the study by Rundqvist *et al.* [14]. Divided into dynamic and static types of sport, Sulovic *et al.* [18] reported a significantly higher EF in dynamic exercising athletes and a significantly reduced EF in static exercising athletes. Contrary to these findings, three studies did not report significant differences [15–17]. The same is reported for FS [15,16].

Diastolic function is represented by eleven parameters: mitral annulus plane systolic excursion (MAPSE), peak early LV diastolic filling velocity (E), peak late LV diastolic filling velocity (A), E/A ratio (E/A), deceleration time of E (DT), early diastolic myocardial velocity (E'), late diastolic myocardial velocity (A'), E/E' ratio (E/E'), and E'/A' ratio (E'/A').

Significant differences for E and A are reported by Binnetoglu *et al.* [16] and Sulovic *et al.* [18]. Swimmers' E was significantly higher than the other athletes and the CG [16]. Sulovic *et al.* [18] reported a significantly higher E in dynamic compared to static exercising athletes, and a significantly reduced E in the latter, compared to controls. Wrestlers [16] had a reduced A compared to controls as well as static exercising athletes compared to dynamic exercising athletes and controls [18]. E/A was significantly higher

in athletes in the study by Rundvqist *et al.* [14]. Summarized, the studies reported contradictory findings regarding LV function (**Supplementary Table 7**).

#### 3.6.3 Right Ventricular Structure

Two studies assessed RV structure [3,14] with the following parameters: right ventricular outflow tract (RVOT) assessed in the parasternal long-axis view (PLAX) and the parasternal short-axis view (PSAX), RVOT distal diameter, RV basal diameter, RV mid-cavity diameter, RV end-diastolic area, and RV end-systolic area. All RV parameters in D'Ascenzi *et al.*'s [3] study failed significance (indexed to BSA) except for RV end-systolic area. RV parameters by Rundqvist *et al.* [14] were significantly higher in athletes compared to controls ($p < 0.01$). In summary, there are conflicting results on the effect of exercise on RV structure (**Supplementary Table 8**).

#### 3.6.4 Right Ventricular Function

Diastolic parameters as tricuspid annular plane systolic excursion (TAPSE), E/A, E', A', E/E', and E'/A' were assessed by two authors [3,14]. RV systolic function was assessed with two parameters: S' and RV fractional area change (FAC). Only TAPSE, indexed to BSA, was significantly higher in athletes whereas RV FAC was significantly reduced [14]. Summarized, there are conflicting results on the effect of exercise on RV function (**Supplementary Table 9**).

#### 3.6.5 Left Atrial Structure

D'Ascenzi *et al.* [13] reported results of biatrial remodelling. Four other authors [14,15,17,18] assessed LA diameter and LA volume. There were no significant differences in the study by D'Ascenzi *et al.* [13] and Sulovic *et al.* [18]. Rundqvist *et al.*'s [14] study showed an increased LA diameter and volume. Soccer players in the study by Zdravkovic *et al.* [15] had an increased diameter compared to controls. Summarized, three out of five studies reported increased left atria dimensions in athletes (**Supplementary Table 10**).

#### 3.6.6 Right Atrial Structure

Two authors reported results of RA structure [13,14]. Parameters assessed were: RA area, RA diameter, and RA volume. Soccer players in the study by D'Ascenzi *et al.* [13] had a significantly larger RA volume compared to controls. Rundqvist *et al.* [14] observed a significantly increased RA area and diameter in endurance athletes. Summarized, there is evidence of the influence of exercise on right atrial structure (**Supplementary Table 11**).

### *3.7 2D Speckle Tracking Echocardiography*

Six of the eight studies assessed myocardial strain by 2D speckle tracking echocardiography [3,12–14,16,17]. Four studies assessed LV function [12,14,16,17], two authors focused on the RV [3,14], and/or function of the atria, respectively [13,14]. This categorization was further followed to compare studies' results. All studies applied the same software for off-line analysis (EchoPAC, GE Healthcare), but used different versions. All performed the analysis from 40 frames/s to 80–100 frames/s and measured myocardial movement selecting the heart cycle with the most defined endocardial border at end-diastole. Authors, however, applied different recommendations on how to perform 2D STE (**Supplementary Table 4**).

#### 3.7.1 Left Ventricular Function

Three studies [12,16,17] reported results on four-chamber longitudinal strain. Whereas Beaumont *et al.* [12] did not observe significant differences between soccer players and controls, basketball players in the study by Binnetoglu *et al.* [16] had a significantly lower strain ($p < 0.0001$) compared to soccer players, swimmers, wrestlers, and controls but not tennis players. Controls in the study by Simsek *et al.* [17] had a significantly lower strain compared to runners and wrestlers. The authors observed the same for the two- and three-chamber view as well, with a significantly lower strain in controls. The global longitudinal strain (GLS) as an overall marker of LV function was assessed in three studies [14,16,17]. Binnetoglu *et al.* and Rundqvist *et al.* [14,16] reported GLS as an average strain of 18 segments (four-, two-, and three-chamber view, two walls each, subdivided into basal, mid, and apical segments). Simsek *et al.* [17] however, reported GLS as an average strain of 15 segments.

Again, basketball players in the study by Binnetoglu *et al.* [16] presented the lowest GLS compared to other study groups ($p < 0.001$). Simsek *et al.* [17] did not observe a significant difference in GLS between runners and wrestlers but a significant difference between the two athlete groups and controls was reported. Rundqvist *et al.* [14] on the contrary did not observe a significant difference in GLS between endurance athletes and controls.

Two studies [12,16] reported results on circumferential and radial strain but for different LV segments. Beaumont *et al.* [12] measured circumferential and radial strain at the mitral valve or basal level, respectively, and mid-ventricular at the mid-papillary muscle level [12]. Circumferential strain differed significantly at both levels between soccer players and controls with higher values in soccer players. They did not observe significant differences regarding radial strain. In contrast, Binnetoglu *et al.* [16] reported global circumferential and radial strain, measured at the anteroseptal, anterior, lateral, posterior, inferior, and septal wall but did not state at which segmental level [16]. The combined group of athletes showed a significantly lower circumferential strain ($p < 0.04$), however, post-hoc analysis did not reveal significant differences between groups. Only Beaumont *et al.* [12] assessed rotational and twist mechanics and found a significant dif-

ference between soccer players and controls in counter-clockwise apical rotation. In summary, three out of four studies reported higher strain values in athletes with results being influenced by the type of sports (**Supplementary Table 12**).

#### 3.7.2 Right Ventricular Function

D'Ascenzi *et al.* [3] and Rundqvist *et al.* [14] reported RV longitudinal strain values assessed at the four-chamber view. Both authors took measurements of the RV free wall only, subdivided into basal, mid, and apical segments, and did not observe significant differences between athletes and controls ($p > 0.05$), see **Supplementary Table 13**.

#### 3.7.3 Left Atrial Function

Two of six studies reported results on 2D STE of the LA, however, D'Ascenzi *et al.* [13] and Rundqvist *et al.* [14] did not investigate the same LA parameters. D'Ascenzi *et al.* [13] reported results on peak atrial longitudinal strain (PALS), which is a measure of LA deformation during the reservoir phase, and peak atrial contraction strain (PACS), which is the myocardial strain during atrial systole [21,22]. They did not report significant differences between athletes and controls. Rundqvist *et al.* [14] assessed LA total strain measured at the four- and two-chamber view with subdividing the LA into six segments each [23] and also did not observe significant differences between athletes and controls either. Summarized, there is no evidence of an influence of exercise on LA strain, (**Supplementary Table 13**).

#### 3.7.4 Right Atrial Function

Only D'Ascenzi *et al.* [13] reported results on 2D STE of the right atrium, assessed at the four-chamber view with subdividing RA into six segments. Analogous to LA function, PALS and PACS of the right atrium were assessed. The authors did not find significant differences between athletes and controls. Summarized, there is no evidence for an influence of exercise on RA strain (**Supplementary Table 13**).

## 4. Discussion

This systematic review compared results of eight studies assessing 2D TTE and 2D STE parameters in junior athletes vs. an inactive CG. The main findings of the study were: (1) Training-induced chamber-remodelling does occur in junior athletes. (2) Results regarding 2D TTE assessed LV and RV function are conflicting and do not provide a clear statement pointing towards an improved function in athletes. (3) LV function assessed by 2D STE was improved in junior athletes in two of three studies. RV and atrial function were not affected by exercise.

### *4.1 2D Transthoracic Echocardiography*

#### 4.1.1 Left Ventricular Structure

Overall, five of six studies observed increased LV dimensions. These results are in line with other authors [4,5,7,8,24–26]. Mc Clean *et al.* [4], reported increased LV morphometry in a meta-analysis involving >14 000 junior athletes. LVEDD, LVDS, IVSD, RWT, LVM ($p \leq 0.001$), and LVPWT ($p \leq 0.01$) differed by 5.6–27.6% from non-athletic controls. Krysztofiak *et al.* [25] observed a significantly increased LVEDD, LVPWT ($p < 0.001$) and IVS ($p < 0.01$) in 791 boys and girls of different types of sports (5–18 years) and Sharma *et al.* [7] significantly higher IVSD, LVPWT, LVWT, LVEDD. Non-significant LV structure in soccer players compared to controls by Beaumont *et al.* [12] were explained by participants maturity status, referring to Nottin *et al.* [27] who concluded that a sufficient maturity status has to be reached to elicit an exercise-induced increase in LV structure. This observation is not in line with results by Mc Clean *et al.* [4] who observed a significant influence of exercise on cardiac dimensions during as well as before puberty. Ayabakan *et al.* [5], reported a significantly increased IVSD, LVPWT, LVMI ($p < 0.001$), and RWT ($p < 0.007$) in 22 pre-pubertal male swimmers (10–12 years). These results, as well as results by D'Ascenzi *et al.* [3], interfere with the hypothesis by Nottin *et al.* [27], leading to the assumption that adaptations do take place before and during puberty – however adaptations might be accelerated by hormonal influences during puberty. Additionally, other factors contribute to cardiac adaptations, such as genetics, training history and intensity.

LV hypertrophy, defined by an LVM >95th percentile can be differentiated into eccentric (RWT ≤0.42) and concentric (RWT >0.42) hypertrophy [28]. Traditionally, it is believed that dynamic stimuli result in eccentric and static stimuli in concentric hypertrophy, respectively [29,30]. Binnetoglu *et al.* [16] observed LV hypertrophy in 45.9% of all athletes with 29% being eccentric and 16.1% concentric. Interestingly, the type of LV hypertrophy was not a function of the underlying training stimulus. More than one third (35.6%) of swimmers (static-dynamic) as well as 39.1% of wrestlers (static) presented eccentric hypertrophy whereas concentric hypertrophy was observed in 28.9% of swimmers and only 4.3% of wrestlers. Sulovic *et al.* [18] reported eccentric hypertrophy in 79.4% of athletes in the dynamic group and 54.05% of the static group. Concentric hypertrophy was prevalent in 20.6% of athletes of the dynamic and 49.95% of the static groups. On the contrary, Simsek *et al.* [17] reported results that support the traditional view. Participants in this study [17] were slightly older compared to Binnetolgu *et al.* [16] and Sulovic *et al.* [18]. Aformentioned influences like hormonal status, genetics and training history could play a role in this adaptive process.

Regarding LV wall dimensions, a LVWT or IVSD >12 mm represents the upper limit in males, and >11 mm the upper limit in females [7]. Binnetoglu *et al.* [16] reported 98.9% of male athletes having IVSD >12 mm. Other authors [14,15,17,18] reported none of the athletes exceeding this cut-off which is in line with Pelliccia *et al.* [6] who reported LVWT >12 mm in only 16 of 947 male elite Olympic athletes (13–49 years) as well as results by Sharma *et al.* [7] who reported LVWT >12 mm in 38 out of 720 male elite athletes (15.7 ± 1.4 years). None of the studies included in this review reported IVSD or LVWT >11 mm for females. During puberty, testosterone levels in males exceed female levels by up to 15 times [31]. That is why structural changes in males may be more pronounced than in females.

In conclusion, exercise does have an impact on LV structure in young athletes. This impact is influenced by athletes' age, hence pubertal and hormonal status and also by training volume and intensity. Most studies observed significantly increased LV diameter, LVWT, and LVM in athletes.

#### 4.1.2 Left Ventricular Function

Results regarding LV function did not clearly state significantly different results between athletes and controls or within the athletic groups. None of the studies reported any adverse results regarding a significantly impaired LV function. Three authors [12,14,18] noticed an improved systolic function by a significantly increased EF in soccer players and dynamic sports, respectively. Rundqvist *et al.* [14] observed a significantly improved diastolic function (E/A) as well as Sulovic *et al.* [18] in endurance-trained athletes (E). This result is in line with other studies [5,24,32,33]. Unnithan *et al.* [33] compared 22 highly trained soccer players (12 ± 0.3 years) and 15 controls (11.7 ± 0.2 years) and noticed a significantly higher E in soccer players at rest as well as during submaximal exercise on the cycle ergometer. The authors concluded that exercise leads to an improved diastolic function in highly trained athletes even at a young age. Ayabakan *et al.* [5] and Rundqvist *et al.* [34] noticed significantly improved diastolic function in pre-pubertal male swimmers (10–12 years) and endurance athletes (13–19 years), respectively. Gajda *et al.* [35] examined 12 swimmers at a ultramarathon-relay with TTE before, during the competition and during recovery, e.g., 48 hours after the competition. During recovery, LV EF and SF were significantly increased compared to baseline measurements and during the competition. On the contrary, Pavlik *et al.* [32] compared male children, adolescents, and adults with a significantly improved diastolic function in adolescents (15–18 years) and adults (19–60 years), only. McClean *et al.* [4] and Sharma *et al.* [7] did not report a significantly improved diastolic function at all, and Sulovic *et al.* [18] noticed a reduced diastolic function compared to controls (E, A) in static training athletes.

In conclusion, results are controversial and do not allow a clear statement. Regarding LV systolic function, there are studies reporting improved results in young athletes but also no significantly different results compared with controls. The same is for LV diastolic function. If significantly increased results were reported, they were reported in endurance athletes but not in strength-trained athletes.

#### 4.1.3 Right Ventricular Structure

Two studies assessed RV structure [3,14] with conflicting results. D'Ascenzi *et al.* [3] only noted a significant increase in RV end-systolic area index in swimmers compared to controls. All other parameters failed statistical significance when indexed to BSA. Rundqvist *et al.* [14] observed a significantly increased RVOT, RV basal diameter index, and RV end-systolic area index. RV adaptation is expected in athletes as the RV works hand-in-hand with the LV [36,37]. Strength training, on the contrary, does not affect the RV to the same extent that endurance exercise does, and pulmonary vasculature is protected by high pressures [30,38]. Current literature does not provide better insight into RV structure in children and adolescents. Only one study could be found that assessed RV structure in this age group [39]. Allen *et al.* [39] reported RVWT and RV cavity in 77 swimmers (32 females), aged 10.8 (5–17) years. All participants exceeded the 95th percentile of reference values for RVWT, and most of the participants for RV cavity. La Gerche *et al.* [38] noticed a significant increase in RV volume right after a competition in 40 adult athletes (37 ± 8 years) and hypothesize a strong impact of endurance exercise on the right heart's structure. Comparisons of RV end-diastolic and end-systolic areas were significantly higher in adult athletes vs. controls [40] and endurance athletes vs. strength-trained athletes [41]. In conclusion, results are controversial. Results in adults point towards an influence of predominantly dynamic but not strength exercise. Further studies are needed to confirm these results in the younger age group.

#### 4.1.4 Right Ventricular Function

Two studies investigated RV function in junior athletes [13,14]. Rundqvist *et al.* [14] found a functional remodelling in endurance-trained athletes whereas D'Ascenzi *et al.* [3] observed no differences between swimmers and controls for most parameters and a significantly reduced RV FAC in swimmers. La Gerche *et al.* [38,42] confirmed these results in adults at rest and immediately after a competition. Thus, the slightly reduced resting function that was preserved during exercise rather bears a contractile reserve but does not represent impaired RV function [42]. Reduced RV function in highly trained athletes immediately after a competition mostly recovered after one week but long-term structural remodelling is likely [38]. The adverse consequence of this is ventricular arrhythmia, which is observed in trained adults, associated with a longer duration of exer-

cise [29,38,43]. To prevent this adverse adaptation in children and adolescents, a closer observation of junior athletes is needed—especially in a longitudinal setting.

#### 4.1.5 Left and Right Atrial Structure

Five studies examined LA structure [13–15,17,18], and two studies assessed RA structure [13,14]. All studies except for two [13,18] reported significantly increased LA and RA dimension and volumes which is in line with studies in adult athletes [44–49]. During exercise, the LA adapts to pressure and volume overload, which leads to LA dilatation [45]. Pelliccia *et al.* [48] observed marked atrial dilatation ($\geq$40 mm) in 20% of n = 1777 adult athletes but defined this as a physiological adaptation to exercise as only 0.8% of athletes presented with supraventricular arrhythmias. LA adaptation was largely associated with the LV as 1 mm in LV dilatation induced a 0.4 mm increase in LA diameter. Furthermore, LVWT, BSA, and age contributed to LA adaptation. For the RA, increased diameter and volume were also regarded as a physiological adaptation [13,49]. Gjerdalen [47], however, noticed significantly more tricuspid regurgitations in adult athletes vs. controls (n = 343/58% vs. 17/36%).

In conclusion, LA diameter and volume, RA volume, area, and diameter were increased in athletes, indicating a significant influence of exercise. As a consequence of LA dilatation, atrial flutter or fibrillation could arise as complication. Therefore, more focus should be placed on atrial examination to detect adverse adaptations as early as possible.

### *4.2 2D Speckle Tracking Echocardiography*

Six of eight studies included in this review performed STE analysis [3,12–14,16,17]. 2D STE is accepted as an early marker for systolic dysfunction as it detects a decrease in contractility when EF is still within normal limits [50,51].

#### 4.2.1 Left Ventricular Function

Two of four studies reported improved LV function in junior athletes. In the study by Simsek *et al.* [17], this difference did not depend on the types of sports, as there were no significant differences between endurance and strength athletes. On the contrary, Binnetoglu *et al.* [16] observed a significantly reduced strain in basketball players compared to other groups and controls whereas Rundqvist *et al.* [14] did not observe significant differences in strain between endurance athletes and controls. The latter is in line with no significant results reported by other authors [33,52,53] who compared 22 soccer players (12.0 $\pm$ 0.3 years) with 15 controls (11.7 $\pm$ 0.2 years) at rest and during submaximal exercise [33], and 76 cross country skiers (12.1 $\pm$ 0.2 years) with 25 controls (12.1 $\pm$ 0.3 years) [52]. No significant differences for GCS and GRS were reported by Charfeddine *et al.* [54] in a cohort of 33 soccer players (13.19 $\pm$ 1.2 years) and 20 controls (12.9 $\pm$ 2.1 years). Furthermore, GLS turned out to be significantly reduced in athletes (20.68 $\pm$ 2.05 vs. 22.99 $\pm$ 2.32, $p < 0.001$). De Luca *et al.* [55] support these results. They recognized reduction in LV strain as an early sign of LV dysfunction in n = 50 athletes (soccer, cycling, basketball, 14–19 years). In conclusion, results are conflicting regarding LV function. Contrary to the majority of studies [14,33,52–54], two studies presented in this review [12,17] reported an improved LV function in junior athletes.

#### 4.2.2 Right Ventricular Function

Two studies assessed RV function in junior athletes [3,14] and did not observe significantly different values in athletes and controls. Furthermore, there was a tendency toward lower strain values in athletes vs. controls. Bjerring *et al.* [52] observed a significantly reduced RV GLS (28 $\pm$ 4 vs. 31 $\pm$ 3, $p < 0.001$) in 76 cross country skiers (12.1 $\pm$ 0.2 years) compared to 25 controls (12.1 $\pm$ 0.3 years) and a negative correlation of RV GLS with $VO_{2max}$ (r = –0.22, $p < 0.06$) and the amount of exercise (r = –0.24, $p < 0.05$). They hypothesize that the RV might be affected by cardiac fatigue through exercise which is explained by a reduced resting cardiac function in athletes after strenuous exercise. This cardiac fatigue might affect the RV earlier than the LV [38,52]. In conclusion, results of this review do not point towards a significant influence of exercise on RV longitudinal strain. However, only two studies out of six reported RV longitudinal strain. There is evidence that the RV is affected by strenuous exercise. As the RV bears the potential to elicit arrhythmogenic cardiomyopathies, the focus of further studies should be placed of the assessment of RV function.

#### 4.2.3 Left and Right Atrial Function

Two studies investigated atrial function by 2D STE [13,14]. D'Ascenzi *et al.* [13] examined biatrial function in swimmers vs. controls and did not report significant differences. Rundqvist *et al.* [14] observed non-significant differences in LA strain between endurance athletes and controls. One study was identified that examined LA function in n = 595 highly trained soccer players (25.1 $\pm$ 4.6 years) and n = 47 controls (26.2 $\pm$ 6.5 years) with no significant differences between groups [47]. Furthermore, in athletes with enlarged atria, LA function was still preserved. In conclusion, results do not point towards a significant influence of exercise on LA strain parameters. However, only two studies of six investigated LA strain. Only one study examined RA function and did not observe a significant influence of exercise. As both atria, are affected by higher blood volume in athletes, and the LA also by an increase in pressure during exercise, assessing atrial function is of importance.

### *4.3 Limitations*

The number of studies investigating cardiac adaptations in young athletes is limited. Comparability of ex-

isting studies is difficult due to differences in age groups, different types of sports, whether male or female athletes are being compared, and, importantly the difference in the parameters assessed by echocardiography itself. The latter calls for a consensual recommendation on how to assess the pediatric athlete's heart by 2D TTE and 2D STE and on how to report these data [56]. If available, sex- and age-dependent z-scores should be reported instead of absolute values [4,56]. In total, 51 parameters have been assessed by 2D TTE in eight studies, regarding the left and right heart structure and function, and 15 different parameters with 2D STE. All parameters have been assessed in different cohorts, with sub-groups of n = 16 to n = 100 participants, predominantly males. The age varied from 10.8 $\pm$ 0.2 to 17.5 $\pm$ 2.2 years, including pre-, peri-, and post-pubertal athletes, respectively. This variation in-between and within studies itself complicates the comparison of echocardiographic parameters, that should be discussed regarding age and pubertal status, respectively. Additionally, sex, ethnicity, and genetic influences contribute to the variability in results [4,29,31,37,57,58]. Regarding sex, females are not represented equally in the literature. Out of >14 000 young athletes in the review by McClean *et al.* [4], only 19% of participants were females. Studies included in this review include Caucasian athletes only. In general, cardiac adaptations are more pronounced in athletes of African ethnicity compared to other ethnicities [59–61]. It is not possible to rule these influences out, especially the role of genetics. Therefore, considerable care should be taken to ensure balanced study groups. In this review, participants took part in 10 different types of sport. As the training stimulus is known to influence physical adaptation, this is a further source of controversial results. Genetic traits, determine the type of sports a child chooses to some extent [33], depending on the ability to perform successfully in the chosen discipline. By comparing adequate samples of different types of sports, this impact could be accounted for. The definition of inactive controls varied considerably within the studies. Authors defined their control groups as either being sedentary [16,17], not engaged in regular exercise or competitive sports [14,18] or not exercising more than 2 hours/week [3,13,15]. Only one study [12] specified the activity of the control group with 1.53 $\pm$ 1.77 hour of recreational physical activity/week. Fagard *et al.* [62] observed cardiac adaptations to happen if subjects exercise $\geq$3 hours/week. This activity level of the control group could have led to non-significant differences between athletes and controls in this study.

Most echocardiographic parameters are indexed to BSA, to account for anthropometric differences in subjects and to enable comparability [19]. However, how parameters were indexed contributed to variation in echo parameters. Diameters were either not indexed to BSA or indexed to BSA or $BSA^{0.5}$, volumes were either not indexed to BSA or indexed to BSA or $BSA^{1.5}$. LVM can be indexed to BSA, $BSA^{1.5}$, or body $height^{2.7}$ ($m^{2.7}$). Additionally, three different methods to calculate BSA are reported in the studies presented: the Mosteller method [63], the Du Bois formula [64], and the Haycock formula [65]. The Mosteller formula was proven to be a reliable estimate of BSA in children [66]. There are studies reporting a good correlation between the Mosteller and Du Bois as well as between the Mosteller and Haycock formula (r = 0.99 for both) [67] however, some studies revealed considerable differences [68,69]. Guidelines, providing a concept on which formula to apply, and on how to report indexed results are needed to overcome this large variability in data.

Overall, as requested by D'Ascenzi [44], recommendations on how to assess cardiac function in this pediatric sub-group, are required. In addition, studies that assess cardiac function in a longitudinal setting [33] could provide better insight into the process of cardiac adaptation in junior athletes, help us to differentiate between physiological and pathological adaptations and to recognize these differences at a very early stage.

## 5. Conclusions

Cardiac adaptation to exercise does occur in children and adolescents—even in very young athletes. These adaptations are more pronounced in structural parameters, whereas functional parameters are preserved or slightly improved. The underlying stimuli for cardiac adaptation have been identified as being factors like the training history, training volume and intensity, the types of sports [70], genetics [58] and pubertal and hormonal status [31,71,72].

The variability, given by the nature of the cohort of junior athletes and the individual sports emphasizes the need to standardize variables, e.g., the test and measures we apply and how results are reported. Recommendations on the assessment of cardiac function in junior athletes are needed as well as studies with a longitudinal design.

## Abbreviations

2D STE, 2-dimensional speckle tracking echocardiography; 2D TTE, 2-dimensional transthoracic echocardiography; A, peak late LV diastolic filling velocity; A', late diastolic myocardial velocity; BMI, body mass index; BSA, body surface area; CG, control group; DBP, diastolic blood pressure; DT, deceleration time of E; E, peak early LV diastolic filling velocity; E', early diastolic myocardial velocity; E'/A', E'/A' ratio; E/A, E/A ratio; E/E', E/E' ratio; EF, ejection fraction; FAC, fractional area change; FS, fractional shortening; GLS, global longitudinal strain; IVS, interventricular septal thickness; LV, left ventricle; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; LVM, left ventricular mass; LVPWT, LV posterior wall thickness; LVWT, LV wall thickness; MAPSE, mitral annulus plane systolic excursion; MWT, mean wall thickness; PACS, peak atrial contraction strain;

PALS, peak atrial longitudinal strain; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; Q, cardiac output; RVOT, right ventricular outflow tract; RWT, relative wall thickness; S', peak systolic myocardial velocity; SBP, systolic blood pressure; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion.

## Author Contributions

HW—designed the research study and drafted the manuscript. HW and TE—performed the literature research and screened publications, performed the data extraction, risk of bias, and quality assessment. LB—performed the risk of bias, and quality assessment, and reviewed the manuscript. FM, NS, ROF—screened and reviewed echocardiographic results, and reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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## 4.3 SUMMARY: TRAINING INTENSITY INFLUENCES LEFT VENTRICULAR DIMENSIONS IN YOUNG COMPETITIVE ATHLETES

In young athletes, exercise causes changes in the heart that include growth in wall thickness and mass of the left ventricle and expansion of the heart's chambers. The heart's function is either preserved or enhanced, but this may change to the opposite over time. Objective: This study aimed to assess structural and functional cardiac adaptations in relation to exercise training time, intensity, and performance in young competitive athletes. A total of 404 children and adolescents (14.23  2.0 years, 97 females) were enrolled in the Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA-Study). Eighty-five participants were examined two times a year. Two-dimensional echocardiography was performed to assess left ventricular structure and function. Training time and intensity was measured with the MoMo physical activity questionnaire, maximum aerobic capacity by cardiopulmonary exercise testing, and strength with the handgrip strength test. Maximum aerobic capacity significantly influenced interventricular septal thickness in diastole. Training intensity significantly influenced left ventricular internal diameter in diastole and systole, and left ventricular mass indexed to body surface area. Within one year, interventricular wall thickness, relative wall thickness and left ventricular mass, indexed to body surface area and height, increased significantly. Training intensity and aerobic capacity contributed to cardiac adaptations in young competitive athletes, as represented by altered structural parameters but preserved cardiac function. Within a year, however, structural changes and a decline in diastolic performance were observed within the longitudinal sub-sample. Our results confirm the hypothesis that cardiac adaptations to exercise occur at a young age. Cardiac adaptation in our cohort was influenced by exercise intensity and maximum aerobic capacity.

Author's contribution: Heidi Weberruß designed the study concept and applied for funding, analyzed the data, and drafted the manuscript.

## 4.4 TRAINING INTENSITY INFLUENCES LEFT VENTRICULAR DIMENSIONS IN YOUNG COMPETITIVE ATHLETES

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# Training intensity influences left ventricular dimensions in young competitive athletes

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**Background:** In young athletes, exercise causes changes in the heart that include growth in wall thickness and mass of the left ventricle and expansion of the heart's chambers. The heart's function is either preserved or enhanced, but this may change to the opposite over time.

**Objective:** This study aimed to assess structural and functional cardiac adaptations in relation to exercise training time, intensity, and performance in young competitive athletes.

**Methods:** A total of 404 children and adolescents (14.23 ± 2.0 years, 97 females) were enrolled in the Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA-Study). Eighty-five participants were examined two times a year. Two-dimensional echocardiography was performed to assess left ventricular structure and function. Training time and intensity was measured with the MoMo physical activity questionnaire, maximum aerobic capacity by cardiopulmonary exercise testing, and strength with the handgrip strength test.

**Results:** Maximum aerobic capacity significantly influenced interventricular septal thickness in diastole. Training intensity significantly influenced left ventricular internal diameter in diastole and systole, and left ventricular mass indexed to body surface area. Within one year, interventricular wall thickness, relative wall thickness and left ventricular mass, indexed to body surface area and height, increased significantly. Training intensity and aerobic capacity contributed to cardiac adaptations in young competitive athletes, as represented by altered structural parameters but preserved cardiac function. Within a year, however, structural changes and a decline in diastolic performance were observed within the longitudinal sub-sample.

**Conclusion:** Our results confirm the hypothesis that cardiac adaptations to exercise occur at a young age. Cardiac adaptation in our cohort was influenced by exercise intensity and maximum aerobic capacity.

KEYWORDS

cardiac remodeling, pre-participation screening, athlete's heart, children, exercise

## Introduction

The heart adapts to exercise beginning at a young age. In young competitive athletes, left ventricular (LV) diameter (1–6), volume (7–10), wall thickness, and mass are increased (1, 3, 4, 6, 10–12). Binnetoglu et al. (13) reported concentric remodeling in 15.7% and concentric hypertrophy in 14.3% of young athletes at a mean age of 12.2 ± 0.8 years. Other authors observed eccentric LV remodeling in endurance athletes and concentric LV remodeling in power athletes (5, 14). The right ventricle (RV) and both atria are also affected by physical training (1, 3, 8, 15, 16). Cardiac function, however, is not affected at a young age (2, 7, 8, 15). In adult athletes, on the contrary, exercise-induced ventricular arrhythmia, atrial dilatation, and tricuspid regurgitation can be observed as a negative consequence of intense exercise (17–21).

As training loads and levels of competitiveness increase over an athlete's career (3, 15), it is essential to follow young athletes regularly to monitor their cardiac adaptations and not to miss the point when positive adaptations may develop in an adverse direction (22, 23).

Therefore, this study investigated the cardiac structure and function by two-dimensional echocardiography in young competitive athletes in relation to training time per week, training intensity, and maximal exercise performance. We hypothesized that young competitive athletes show an altered cardiac structure and function compared to reference values relative to their training volumes and intensity.

## Materials and methods

This work was part of the Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA-Study) (24), which was conducted from September 2018 to September 2020 at the Chair of Preventive Pediatrics, TUM Department of Sport and Health Sciences, Technical University of Munich (TUM). This study was approved by the local ethics committee (301/18S) and is in line with the Declaration of Helsinki (2013). Informed consent was obtained from all participants and their legal guardians.

### Subjects

465 young competitive athletes (7–18 years) visited our department for a pre-participation screening. Only participants who regularly participated in competitions and trained ≥3 h/week were included in further analyses, as this amount of training time has been shown to elicit cardiac adaptations (25, 26). Furthermore, the following inclusion criteria were 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. Participants who did not participate in competitions, did not exercise regularly for ≥3 h/week, or did not meet all inclusion criteria were excluded from participating in the study.

According to the main type of sports, participants were classified into four categories, as defined by Pelliccia et al. (26)—namely mixed category (isotonic and isometric components, moderate cardiac remodeling, e.g., soccer or basketball), endurance (isotonic > isometric, pronounced cardiac remodeling, e.g., cycling or rowing), power (isometric > isotonic, less cardiac remodeling, e.g., weight lifting or boxing) and skill (low isotonic and isometric components, minor cardiac remodeling, e.g., golf or sailing). Participants with one visit were included in the cross-sectional analysis (V1). A longitudinal sub-sample analysis included $n$ = 85 participants (eight girls) with two visits within one year (V1 vs. V2). According to McClean et al. (3), who found significantly increased echocardiographic parameters in subjects ≥14 years compared to subjects <14 years, the sample was sub-divided into these two age groups. The rationale lies in significant pubertal landmarks at this age (27–30). Tanner stages were not assessed due to ethical considerations and child protection.

### Anthropometry

Body height and mass were measured without shoes and standing upright. Body height was registered to the next 0.1 cm and body weight to the next 0.1 kg (seca 799, seca GmbH&Co.KG, Hamburg, Germany). Additionally, body mass index (BMI, in kg/m$^2$), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were calculated. Standardized z-scores for body height, BMI, WHR, and WHtR were compared to German reference values (31). Body surface area (BSA, in m$^2$) was calculated according to Dubois and Dubois (32).

### Heart rate, blood pressure, and pulse wave analysis

Resting heart rate (HR) and peripheral systolic and diastolic blood pressure (SBP/DBP) were measured oscillometrically in a supine position after 10 min of rest (Mobil-O-Graph®, I.E.M., Stolberg, Germany). An appropriate cuff was placed on the participants' left arm. Central systolic blood pressure (cSBP) and pulse wave velocity (PWV) were determined with the ARCSolver pulse wave analysis algorithm (AIT, Austrian Institute of Technology GmbH, Vienna, Austria) (33). The method is validated against invasive catheter measurements of cSBP [$r^2$ = 0.899, $p$ < 0.0001, (34), $r^2$ = 0.97, $p$ < 0.001, (35)] and PWV [$r^2$ = 0.81, $p$ < 0.001, (36)], as well as against

non-invasive measurements with the SphygmoCor [$r^2 = 0.532$, $p < 0.05$ (37)]. Standardized z-scores were compared to German reference values (38, 39).

## Cardiopulmonary exercise testing

After medical clearance, participants performed a cardiopulmonary exercise test (CPET) on an ergobike (Lode Corival, Lode B.V., Groningen, Netherlands) with spirometric measurement (Ergostik, Geratherm Respiratory GmbH, Bad Bissingen, Germany) of maximum aerobic capacity ($VO_{2peak}$), and a 12-lead ECG (CARDIOVIT CS-200 Office, SCHILLER AG, Baar, CH). A modified Godfrey protocol was followed (40). After 2 min of rest, participants started cycling with an initial load of 50% of their body weight. The incline was chosen to reach 4–5 Watt/kg body mass within 6–12 min at a cadence of 60–80 rpm (41, 42). Maximum heart rate (1/min), maximum workload (Watt), relative maximum workload (Watt/kg), and relative $VO_{2peak}$ (ml/min/kg) were assessed.

## Handgrip strength

Participants' handgrip strength (HGS) was assessed in a seated position with the upper body upright, shoulders abducted at 10°, both elbows flexed at 90°, and the forearm in a neutral position, according to the standardized recommendations by the American Society of Hand Therapists (ASHT) (43). As HGS is closely correlated with overall muscular strength, it was applied as a surrogate parameter for muscular strength in this study (44). The handgrip dynamometer (SAEHAN Hydraulic Hand Dynamometer SH5001, SAEHAN Corporation, Masan, South Korea) was pushed at maximum strength, alternately three times with the right hand and three times with the left hand. For further calculations, the maximum attempt was applied in relation to the participants' body mass (45). In a study on children, HGS showed a high correlation with the 1-repetition maximum bench press test ($r = 0.79$, $p < 0.01$; $R^2 = 0.621$, $p < 0.01$) (46).

## Physical activity questionnaire

Participants' training history over the years, exercise training time (h/week), and intensity in metabolic equivalents (METs) were assessed with the self-reported MoMo (Motorik Modul) physical activity questionnaire (47). Participants reported how much they exercised (min/week) and at which intensity rated on a three-item scale (low, moderate, intense). According to this, training time in h/week was calculated and adjusted for a factor depending on how many months a year the sport was performed. An intensity index was derived based on the calculation of METs. One MET refers to the body's oxygen consumption of 3.5 ml $O_2$/min/kg when sitting at rest. In comparison, the body consumes 8.8 METs while playing soccer at moderate intensity. For a soccer game of 90 min, this refers to an intensity of 792 MET-minutes or 13.2 MET-hours, respectively. MET-values for different types of sports were provided by Schmidt et al., Ridley et al., and Ainsworth et al. (47–49). The questionnaire's Kappa coefficient is 0.66, and the intraclass correlation coefficient is 0.68 (50).

## Echocardiography

Transthoracic echocardiographic measurements were performed to assess LV dimensions, such as LV internal diameter in diastole (LVIDd) and systole (LVIDs), interventricular septal thickness in diastole (IVSd), and LV posterior wall thickness in diastole (LVPWd) in M-mode. Relative wall thickness (RWT) was calculated according to Lang et al. (51). Standardized z-scores for LVIDd, LVIDs, IVSd, and LVPWd were derived according to reference values by Pettersen et al. (52). LV mass (LVM) was calculated according to Devereux and Reicheck (53) and presented as indexed values relative to BSA (LVM/BSA) and body height (LVM/height). For the differentiation between LV eccentric hypertrophy (RWT $\leq$ 0.42 and LVM/$m^{2.7}$ > P95) and concentric hypertrophy (RWT > 0.42 and LVM/$m^{2.7}$ > P95), reference intervals for indexed LVM (LVM/$m^{2.7}$) were calculated according to Khoury et al. (54). LV systolic function was assessed by ejection fraction (EF), measured in B-mode (biplane Simpson's method), and fractional shortening (FS), measured in M-mode. LV diastolic function was indirectly assessed by the ratio of mitral E- and A-wave, measured via pulsed-wave Doppler at a standardized position with the sample volume at the tips of the open mitral valve leaflets. All measurements were performed with a GE VIVID 7 Dimension ultrasound system (GE Healthcare, Horten, Norway) and off-line analyses with dedicated software (ECHOPAD Software, GE Healthcare, Horten, Norway). Two experienced pediatric cardiologists performed all measurements and off-line analyses.

## Statistics

The statistical analysis was performed with SPSS statistical software, version 25 (IBM, Chicago, IL, USA). For the cross-sectional sample (V1), descriptive data were calculated for the entire study population, for boys and girls, separately, and for boys and girls within the two age groups (<14 years and ≥14 years). Sex differences within the overall sample and differences between the two age groups were tested by independent $t$-tests. Standardized z-scores were compared to reference values via a one-sample $t$-test.

The influence of training time per week, training intensity, $VO_{2peak}$, and HGS on echocardiographic parameters was examined via linear multiple regression analysis. Quintiles (Q1–Q5) were calculated for boys and girls separately to compare different groups regarding training time, training intensity, $VO_{2peak}$, and HGS. As the data did not meet the assumptions for a one-way non-parametric analysis of covariance (ANCOVA), Quade's non-parametric ANCOVA with Tukey *post hoc* correction was applied (55), controlling for sex, age, BSA (except for the analysis of LVM/BSA), SBP, and training history in years. Differences between athletes performing endurance and power sports were analyzed by an independent *t*-test (parametric data) or Mann–Whitney U-Test (non-parametric data).

The longitudinal sub-sample (V1 vs. V2) was compared via the dependent *t*-test for parametric data and the Wilcoxon Matched-Pairs Test for non-parametric data, respectively. Significant results were reported at a $p$-value $< 0.05$.

## Results

Out of the 465 (7–18 years) children and adolescents, who performed a pre-participation screening at our department, $n$ = 404 (97 girls) matched the criteria to be defined as a young competitive athlete, regularly training ≥3 h/week (25, 56), Figure 1. Participants performed 32 different types of sports in an organized sports club setting with regular competitions. We categorized sports according to Pelliccia et al. (26): 71.8% of the types of sports performed could be assigned to the mixed category (isotonic and isometric components, along with moderate cardiac remodeling); 12.6% were predominantly endurance (isotonic > isometric, pronounced cardiac remodeling), 11.9% were predominantly power (isometric > isotonic, less cardiac remodeling), and 3% were skill types of sports (isotonic and isometric, little cardiac remodeling, Figure 2 and Supplementary Table 1). The average training history, e.g., the time since participants had

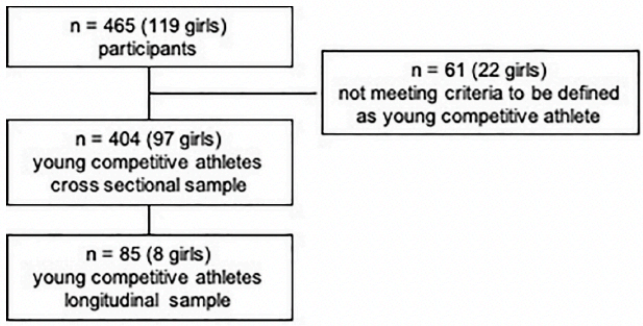


FIGURE 1
Study flow chart.

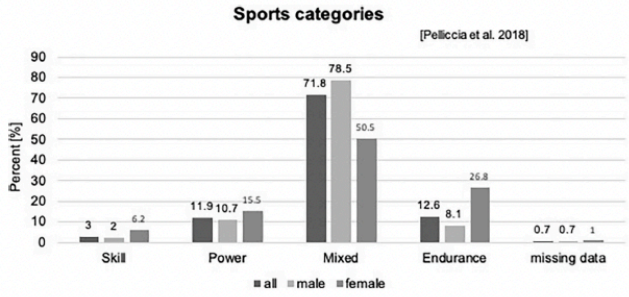


FIGURE 2
Sports categories according to Pelliccia et al. (26).

TABLE 1 Participants' anthropometric characteristics, data on heart rate, blood pressure, and pulse wave analysis, as well as data on physical performance and training time.

| Anthropometry | All | | Males | | Females | *P*-value |
|---|---|---|---|---|---|---|
| | n | mean ± SD | n | mean ± SD | n | mean ± SD | |
| Age [years] | 404 | 14.23 ± 2.00 | 307 | 14.27 ± 1.99 | 97 | 14.11 ± 2.04 | 0.496 |
| Body height [cm] | 403 | 167.14 ± 14.41 | 306 | 168.64 ± 15.02 | 97 | 162.43 ± 11.12 | < **0.001** |
| Body height z-score | 403 | 0.30 ± 1.15 | 306 | 0.29 ± 1.15 | 97 | 0.32 ± 1.15 | 0.836 |
| Body mass [kg] | 403 | 56.62 ± 14.78 | 306 | 57.65 ± 15.52 | 97 | 53.36 ± 11.62 | **0.004** |
| BMI [kg/m$^2$] | 403 | 19.87 ± 2.75 | 306 | 19.84 ± 2.75 | 97 | 19.96 ± 2.73 | 0.716 |
| BMI z-score | 403 | 0.04 ± 0.80 | 306 | 0.04 ± 0.80 | 97 | 0.03 ± 0.80 | 0.938 |
| WHR z-score | 381 | −0.40 ± 1.07 | 293 | −0.47 ± 1.07 | 88 | −0.17 ± 1.04 | **0.018** |
| WHtR z-score | 381 | −0.39 ± 0.71 | 293 | −0.40 ± 0.71 | 88 | −0.38 ± 0.72 | 0.812 |
| BSA [m$^2$] | 403 | 1.61 ± 0.28 | 306 | 1.64 ± 0.29 | 97 | 1.55 ± 0.22 | < **0.001** |
| **Heart rate and blood pressure** | **All** | | **Males** | | **Females** | ***P*-value** |
| | **n** | **mean ± SD** | **n** | **mean ± SD** | **n** | **mean ± SD** | |
| HR [1/min] | 403 | 65.15 ± 10.11 | 307 | 64.70 ± 9.51 | 96 | 66.59 ± 11.76 | 0.110 |
| SBP [mmHg] | 403 | 116.15 ± 8.96 | 307 | 117.23 ± 9.26 | 96 | 112.71 ± 6.88 | < **0.001** |
| SBP z-score | 402 | 0.23 ± 0.89 | 306 | 0.25 ± 0.91 | 96 | 0.15 ± 0.83 | 0.325 |
| DBP [mmHg] | 403 | 63.49 ± 6.21 | 307 | 63.50 ± 6.29 | 96 | 63.46 ± 6.00 | 0.960 |
| DBP z-score | 402 | −0.59 ± 0.92 | 306 | −0.60 ± 0.92 | 96 | −0.57 ± 0.93 | 0.807 |
| **Pulse wave analysis** | **All** | | **Males** | | **Females** | ***P*-value** |
| | **n** | **mean ± SD** | **n** | **mean ± SD** | **n** | **mean ± SD** | |
| PWV [m/s] | 403 | 4.90 ± 0.44 | 307 | 4.94 ± 0.46 | 96 | 4.76 ± 0.34 | < **0.001** |
| PWV z-score | 400 | 0.49 ± 1.35 | 305 | 0.51 ± 1.38 | 95 | 0.45 ± 1.28 | 0.720 |
| cSBP [mmHg] | 403 | 105.13 ± 10.31 | 307 | 105.85 ± 10.65 | 96 | 102.84 ± 8.81 | **0.013** |
| cSBP z-score | 400 | 0.39 ± 1.29 | 305 | 0.41 ± 1.30 | 95 | 0.35 ± 1.24 | 0.719 |
| **Cardiopulmonary exercise test** | **All** | | **Males** | | **Females** | ***P*-value** |
| | **n** | **mean ± SD** | **n** | **mean ± SD** | **n** | **mean ± SD** | |
| Maximum HR [1/min] | 361 | 186.58 ± 11.05 | 282 | 186.42 ± 11.09 | 79 | 187.14 ± 10.99 | 0.609 |
| Maximum power output [Watt] | 363 | 254.07 ± 76.21 | 282 | 264.78 ± 79.43 | 81 | 216.80 ± 48.08 | < **0.001** |
| Relative power output [Watt/kg] | 363 | 4.47 ± 0.63 | 282 | 4.60 ± 0.57 | 81 | 4.03 ± 0.64 | < **0.001** |
| Relative $VO_{2peak}$ [ml/min/kg] | 358 | 44.23 ± 7.49 | 278 | 46.08 ± 6.66 | 80 | 37.78 ± 6.61 | < **0.001** |
| **Handgrip strength** | **All** | | **Males** | | **Females** | ***P*-value** |
| | **n** | **mean ± SD** | **n** | **mean ± SD** | **n** | **mean ± SD** | |
| Maximum HGS/body mass | 366 | 0.53 ± 0.10 | 282 | 0.53 ± 0.10 | 84 | 0.50 ± 0.08 | < **0.001** |
| **Physical activity questionnaire** | **All** | | **Males** | | **Females** | ***P*-value** |
| | **n** | **mean ± SD** | **n** | **mean ± SD** | **n** | **mean ± SD** | |
| Days of physical activity/week | 404 | 5.19 ± 1.20 | 307 | 5.28 ± 1.17 | 97 | 4.92 ± 1.24 | **0.011** |
| Main sport: training/week [h] | 403 | 7.96 ± 3.59 | 306 | 7.94 ± 3.53 | 97 | 7.73 ± 4.14 | 0.464 |
| Sports club activity: training/week [h] | 404 | 8.40 ± 3.59 | 307 | 8.41 ± 3.49 | 97 | 8.36 ± 3.81 | 0.900 |
| Main sport: MET-hours/week | 400 | 72.23 ± 36.39 | 304 | 73.93 ± 33.35 | 96 | 66.83 ± 44.46 | 0.152 |
| Sports club activity: MET-hours/week | 402 | 78.35 ± 33.70 | 306 | 79.23 ± 30.98 | 96 | 75.53 ± 41.26 | 0.419 |

BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; cSBP/cDBP, central SBP/DBP; HR, heart rate; $VO_{2peak}$, maximum oxygen capacity; HGS, hand grip strength; MET, metabolic equivalent. The meaning is that these values are significant results as indicated by a *p*-value of $< 0.05$.

started performing competitive sports, was 3.6 ± 2.5 years. The average training time was 8.40 ± 3.59 h/week at an intensity of 78.35 ± 33.70 MET-h/week (Table 1).

## Anthropometry

The participants' mean age was 14.23 ± 2.00 years. Boys and girls differed significantly in body height and mass, WHR, and BSA. Anthropometric data are displayed in Table 1.

## Heart rate, blood pressure, and pulse wave analysis

There were no significant sex differences in participants' heart rates (boys 64.7 ± 9.51/min vs. girls 66.59 ± 11.76/min, $p = 0.110$). Boys had a significantly higher SBP and PWV ($p < 0.001$) and cSBP ($p = 0.013$) than girls (Table 1). Compared to reference values, boys had significantly higher z-scores for SBP (0.25 ± 0.91), cSBP (0.41 ± 1.3), and PWV (0.51 ± 1.38, $p < 0.001$ for all) and a lower DBP (-0.60 ± 0.92, $p < 0.001$). In girls, cSBP (0.35 ± 1.24, $p = 0.007$) and PWV (0.45 ± 1.28, $p = 0.001$) were significantly higher, and DBP was significantly lower (-0.57 ± 0.93, $p < 0.001$) than observed in the reference population.

## Cardiopulmonary exercise testing, handgrip strength, and physical activity

Boys performed significantly better in CPET testing (+14.1% W/kg and +22% $VO_{2peak}$) and HGS (+6%, for all $p < 0.001$) than girls. Regarding training time and training intensity, no significant sex differences were observed. Boys trained 8.41 ± 3.49 h/week at an intensity of 79.23 ± 30.98 MET-h/week and girls 8.36 ± 3.81 h/week at an intensity of 75.53 ± 41.26 (Table 1).

## Echocardiographic parameters

A total of 391 competitive athletes underwent 2D transthoracic echocardiography. None of the athletes presented with LV hypertrophy (LVPWd > 12 mm). Eccentric hypertrophy was found in 54.1% of males and 45.4% of females, and concentric hypertrophy in 5.5% of males and 8.2% of females. In 34.9% of males and 43.3% of females, normal LV geometry was observed.

In the overall sample, we observed significantly higher values for z-scores of LVIDs (0.16 ± 0.87), IVSd (0.53 ± 0.72), and LVPWd (0.67 ± 0.79, $p < 0.001$ for all). Significant sex differences with higher values in boys were observed for absolute values of LVIDd (+ 5.3%), LVIDs (+ 6.1%), IVSd (+ 7.9%), and LVPWd (+ 9.0%), but not for corresponding z-scores ($p > 0.05$). LVM, indexed for BSA and body height, was significantly higher in males compared to females (LVM/BSA + 15.3%, LVM/body height + 17.6%, $p < 0.001$). Results are displayed in Table 2, and age- and sex-specific z-scores for LVIDd, LVIDs, IVSd, and LVPWd are displayed in Figure 3.

In linear multiregression analysis, controlled for sex, age, BSA, SBP, and training history in years, training intensity (MET-h/week) significantly influenced LVIDd ($\beta = 0.07$, $p = 0.04$), LVIDs ($\beta = 0.10$, $p = 0.01$), and LVM/BSA ($\beta = 0.10$, $p = 0.05$). Sex, BSA, and training intensity predicted LVIDd [$R^2 = 0.610$, $F$ (6, 361) = 94.146, $p < 0.001$] and LVIDs [$R^2 = 0.495$, $F$ (6, 360) = 58.747, $p < 0.001$]. Sex, age, SBP, and training intensity explained 20% of the variance in LVM/BSA [$R^2 = 0.200$, $F$ (5, 362) = 16.991, $p < 0.001$].

Interventricular septal thickness in diastole (IVSd) and LVM/BSA were significantly associated with $VO_{2peak}$ (*IVSd:* $\beta = 0.11$, $p = 0.05$; *LVM/BSA:* $\beta = 0.12$, $p = 0.04$); sex, BSA, training history, and $VO_{2peak}$ explained 26.9% of the variance in IVSd [$R^2 = 0.269$, $F(6, 329) = 20.141$, $p < 0.001$] and 21.9% in LVM/BSA [$R^2 = 0.219$, $F(5, 328) = 18.366$, $p < 0.001$]. Regarding HGS, no significant influence on echocardiographic parameters was observed. Significant results of the linear multi-regression analysis are displayed in Table 3.

Differences in echocardiographic parameters between quintiles (Q1–Q5) for training time, training intensity, $VO_{2peak}$, and HGS were examined using Quade's non-parametric ANCOVA. Ranges for quintiles can be found as Supplementary Table 2. LVIDd differed significantly for quintiles of training time (h/week) between Q1 and Q4 (Q1: 46.26 ± 5.21 mm vs. Q4: 49.26 ± 4.91 mm, $p = 0.024$) and between Q4 and Q5 (Q4: 49.26 ± 4.91 mm vs. Q5: 49.79 ± 4.87 mm, $p = 0.046$; Figure 4). There were no significant differences between quintiles for any of the other parameters.

## Comparison of boys and girls <14 years and ≥14 years

Boys and girls < 14 years did not differ significantly in anthropometric parameters, heart rate, BP and PWV, training time, training intensity, and HGS. Z-scores for LVIDd and LVIDs were significantly higher in boys vs. girls < 14 years (LVIDd: 0.34 ± 0.56 vs. 0.07 ± 0.62, $p = 0.016$; LVIDs: 0.28 ± 0.64 vs. -0.12 ± 0.96, $p = 0.003$). The difference did not persist in the older age group. Absolute values for LVIDd, LVIDs, IVSd, and LVPWd were higher in boys vs. girls ≥14 years. LVM/BSA was higher in boys than in girls in both age groups (see Supplementary Table 3).

TABLE 2 Results of echocardiographic data for all participants and separately for male and female athletes.

| 2D transthoracic echocardiography | All | | Males | | Females | *P*-value |
|---|---|---|---|---|---|---|
| | n | mean ± SD | n | mean ± SD | n | mean ± SD | |
| EF [%] | 389 | 66.61 ± 5.77 | 294 | 66.41 ± 5.75 | 95 | 67.23 ± 5.83 | 0.231 |
| FS [%] | 388 | 37.10 ± 4.62 | 293 | 36.96 ± 4.52 | 95 | 37.54 ± 4.91 | 0.293 |
| LVIDd [mm] | 389 | 48.16 ± 4.89 | 294 | 48.76 ± 5.00 | 95 | 46.29 ± 4.04 | < **0.001** |
| LVIDd z-score | 388 | 0.08 ± 0.90 | 293 | 0.06 ± 0.97 | 95 | 0.12 ± 0.64 | 0.546 |
| LVIDs [mm] | 388 | 30.28 ± 3.97 | 293 | 30.71 ± 4.02 | 95 | 28.95 ± 3.53 | < **0.001** |
| LVIDs z-score | 387 | 0.16 ± 0.87 | 292 | 0.17 ± 0.86 | 95 | 0.13 ± 0.88 | 0.670 |
| IVSd [mm] | 391 | 8.56 ± 1.44 | 296 | 8.72 ± 1.46 | 95 | 8.08 ± 1.26 | < **0.001** |
| IVSd z-score | 390 | 0.53 ± 0.72 | 295 | 0.56 ± 0.71 | 95 | 0.45 ± 0.73 | 0.179 |
| LVPWd [mm] | 389 | 8.07 ± 1.39 | 294 | 8.24 ± 1.34 | 95 | 7.56 ± 1.41 | < **0.001** |
| LVPWd z-score | 388 | 0.67 ± 0.79 | 293 | 0.71 ± 0.75 | 95 | 0.54 ± 0.91 | 0.094 |
| Relative wall thickness | 389 | 0.35 ± 0.05 | 294 | 0.35 ± 0.05 | 95 | 0.34 ± 0.06 | 0.160 |
| LVM/BSA [g/m$^2$] | 388 | 105.04 ± 20.35 | 293 | 108.56 ± 19.98 | 95 | 94.18 ± 17.53 | < **0.001** |
| LVM/body height [g/m] | 388 | 101.30 ± 25.00 | 293 | 105.16 ± 25.41 | 95 | 89.39 ± 19.42 | < **0.001** |
| LVM/body height [g/m$^{2.7}$] | 388 | 42.12 ± 8.14 | 293 | 43.08 ± 8.10 | 95 | 39.16 ± 7.58 | < **0.001** |
| E/A | 278 | 2.46 ± 2.16 | 205 | 2.40 ± 2.10 | 73 | 2.61 ± 2.32 | 0.474 |

EF, ejection fraction; FS, fractional shortening; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; IVSd, interventricular septal thickness in diastole; LVPWd, left ventricular posterior wall thickness in diastole; RWT, relative wall thickness; LVM/BSA, left ventricular mass/body surface area; LVM/body height, left ventricular mass/body height; E/A, ratio of mitral E- and A-wave. The meaning is that these values are significant results as indicated by a *p*-value of < 0.05.

## Comparison of endurance athletes vs. power athletes

Endurance athletes had a significantly lower DBP than power athletes (DBP: 62.06 ± 5.81 vs. 66.08 ± 8.08 mmHg, $p = 0.006$; DBP z-score: -0.81 ± 0.82 vs. -0.23 ± 1.20, $p = 0.007$). Among echocardiographic parameters, E/A was higher in endurance athletes (2.87 ± 3.05 vs. 2.11 ± 0.42, $p = 0.014$). No significant differences were observed for other echocardiographic parameters, as well as HGS, training time, and training intensity. The relative power output in CPET was higher in endurance athletes compared to power athletes (4.65 ± 0.73 vs. 4.31 ± 0.68 W/kg, $p = 0.026$). Results can be found as Supplementary Table 4.

## Longitudinal sub-sample analysis

Eighty-five participants completed two examinations within the MuCAYA-Study and were analyzed as longitudinal sub-samples (V1 vs. V2). The average time between V1 and V2 was 10.6 ± 2.3 months. The majority of athletes performed sports classified as a mixed type of sport (87%). 7% performed power and 6% endurance type of sports. In addition, significant changes in anthropometric parameters, resting heart rate, and z-scores for SBP and DBP were significantly lower at V2 (Table 4). Regarding echocardiographic parameters, absolute values for LVIDd, LVIDs, IVSd, and LVPWd increased significantly from V1 to V2 ($p < 0.01$); however, when data were transformed into z-scores, a significant difference persisted for IVSd, only, (0.34 ± 0.77 vs. 0.73 ± 0.72, $p < 0.001$). For further parameters, a significant increase from V1 to V2 was observed: RWT (+ 9.1%), LVM/BSA (+ 11.1%), and LVM/body height (+ 14.8%, for all $p < 0.001$). E/A decreased by 13.4% (2.98 ± 4.82 vs. 2.58 ± 0.62, p = 0.008), and no significant change was observed in EF and FS (Table 4).

Participants performed significantly better at V2 in CPET (+ 4.3% W/kg and + 5.5% $VO_{2peak}$) and had increased their training time (+ 15.2%) and training intensity (+ 16%, for all $p < 0.001$).

# Discussion

The present study investigated cardiac adaptations to exercise in young competitive athletes, in relation to weekly training time and training intensity, as well as to exercise performance. The main results of this study were a significant influence of training intensity and $VO_{2peak}$ on LV diameter, IVSd, and LVM/BSA. Thus, the intensity at which young competitive athletes exercise as well as their peak performance level determines cardiac adaptations – and therefore can be potential target parameters to further investigate or modify in this context. It can be potential target parameters to further investigate or modify in this context. Diastolic function was significantly higher in endurance athletes compared to power athletes, which underlines the traditional view of improved cardiac function by cyclic and aerobic exercise on the one hand.

TABLE 3 Results of linear multi-regression analysis controlled for sex, age, body surface area, systolic blood pressure, training history, and training intensity or maximum aerobic capacity, respectively.

| **Training intensity [MET-hours/week]** | **LVIDd $R^2$ = 0.610 ($p$ < 0.001)** | | | |
|---|---|---|---|---|
| | **β ± SE** | **$\beta_{standardized}$** | ***P*** | **95% CI** |
| Constant | 25.07 ± 2.27 | | < 0.001 | 20.61–29.54 |
| **Sex [boys vs. girls]** | **−1.10 ± 0.39** | **−0.10** | **0.01** | **−1.85 to 0.34** |
| Age [years] | −0.13 ± 0.14 | −0.05 | 0.35 | −0.39–0.14 |
| **BSA [$m^2$]** | **13.47 ± 0.96** | **0.77** | **< 0.001** | **11.59–15.35** |
| SBP [mmHg] | 0.03 ± 0.02 | 0.05 | 0.22 | −0.02–0.06 |
| Training history [years] | −0.05 ± 0.07 | −0.03 | 0.46 | −0.18–0.08 |
| **Training intensity [MET-hours/week]** | **0.01 ± 0.01** | **0.07** | **0.04** | **0.00–0.02** |
| **Training intensity [MET-hours/week]** | **LVIDs $R^2$ = 0.495 ($p$ < 0.001)** | | | |
| | **β ± SE** | **$\beta_{standardized}$** | ***P*** | **95% CI** |
| Constant | 14.68 ± 2.13 | | < 0.001 | 10.49–18.86 |
| **Sex [boys vs. girls]** | **−0.92 ± 0.36** | **−0.10** | **0.01** | **−1.63 to −0.21** |
| Age [years] | −0.03 ± 0.13 | −0.01 | 0.82 | −0.28–0.22 |
| **BSA [$m^2$]** | **9.74 ± 0.90** | **0.67** | **< 0.001** | **7.97–11.50** |
| SBP [mmHg] | 0.00 ± 0.02 | −0.01 | 0.86 | −0.04–0.03 |
| Training history [years] | 0.01 ± 0.06 | 0.01 | 0.88 | −0.12–0.13 |
| **Training intensity [MET-hours/week]** | **0.01 ± 0.01** | **0.10** | **0.01** | **0.00–0.02** |
| **Training intensity [MET-hours/week]** | **LVM/BSA $R^2$ = 0.200 ($P$ < 0.001)** | | | |
| | **β ± SE** | **$\beta_{standardized}$** | ***P*** | **95% CI** |
| Constant | 32.28 ± 13.36 | | 0.016 | 6.01–58.56 |
| **Sex [boys vs. girls]** | **−12.07 ± 2.28** | **−0.26** | **< 0.001** | **−16.56 to −7.58** |
| **Age [years]** | **1.90 ± 0.54** | **0.18** | **< 0.001** | **0.84–2.96** |
| **SBP [mmHg]** | **0.37 ± 0.12** | **0.16** | **0.002** | **0.14–0.59** |
| Training history [years] | 0.50 ± 0.40 | 0.06 | 0.21 | −0.28–1.28 |
| **Training intensity [MET-hours/week]** | **0.06 ± 0.03** | **0.10** | **0.05** | **0.00–0.12** |
| **$VO_{2peak}$ [ml/min/kg]** | **IVSd $R^2$ = 0.269 ($p$ < 0.001)** | | | |
| | **β ± SE** | **$\beta_{standardized}$** | ***P*** | **95% CI** |
| Constant | 3.54 ± 1.00 | | < 0.001 | 1.58–5.50 |
| **Sex [boys vs. girls]** | **−0.37 ± 0.19** | **−0.11** | **0.05** | **−0.74 to −0.01** |
| Age [years] | −0.05 ± 0.06 | −0.07 | 0.41 | −0.17–0.07 |
| **BSA [$m^2$]** | **2.40 ± 0.42** | **0.46** | **< 0.001** | **1.58–3.21** |
| SBP [mmHg] | 0.01 ± 0.01 | 0.04 | 0.47 | −0.01–0.02 |
| **Training history [years]** | **0.07 ± 0.03** | **0.12** | **0.01** | **0.01–0.13** |
| **$VO_{2peak}$ [ml/min/kg]** | **0.02 ± 0.01** | **0.11** | **0.05** | **0.00–0.04** |
| **$VO_{2peak}$ [ml/min/kg]** | **LVM/BSA $R^2$ = 0.219 ($p$ < 0.001)** | | | |
| | **β ± SE** | **$\beta_{standardized}$** | ***P*** | **95% CI** |
| Constant | 21.89 ± 14.30 | | < 0.001 | 1.58–5.50 |
| **Sex [boys vs. girls]** | **−11.01 ± 2.64** | **−0.24** | **< 0.001** | **−16.25 to −5.86** |
| **Age [years]** | **1.88 ± 0.55** | **0.18** | **0.001** | **0.80–2.97** |
| **SBP [mmHg]** | **0.38 ± 0.12** | **0.17** | **0.001** | **0.15–0.61** |
| Training history [years] | 0.09 ± 0.42 | 0.11 | 0.832 | −0.73–0.91 |
| **$VO_{2peak}$ [ml/min/kg]** | **0.31 ± 0.15** | **0.12** | **0.04** | **0.01–0.60** |

BSA, body surface area; SBP, systolic blood pressure; MET, metabolic equivalent; $VO_{2peak}$, maximum oxygen capacity; LVIDd, left ventricle internal diameter in diastole; LVIDs, left ventricle internal diameter in systole; LVM, left ventricular mass; IVSd, interventricular septal thickness in diastole. The meaning is that these values are significant results as indicated by a $p$-value of < 0.05.

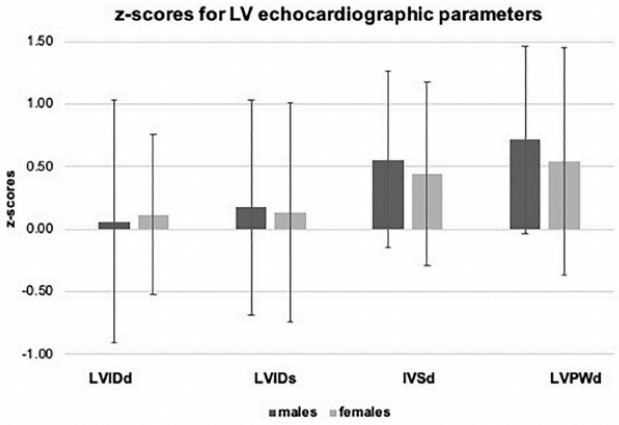


FIGURE 3
z-scores for echocardiographic left ventricular parameters.

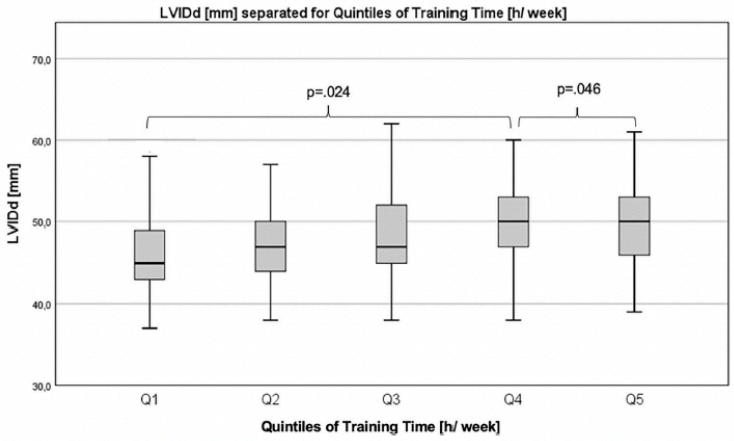


FIGURE 4
Differences in left ventricular internal diameter in diastole between quintiles of training time.

On the other hand, in a longitudinal sub-sample, a reduced diastolic function accompanied by increased RWT and IVSd was observed over the course of a year. This result should be further investigated, especially in a longitudinal setting covering a longer period of time.

The term "athlete's heart" has been under investigation for over 50 years now—for the longest time in adult athletes, only. That cardiac adaptations to exercise are not an exclusive feature of mature athletes but do also happen in children and adolescents has since been recognized (3, 15, 57). In a comprehensive meta-analysis including over 14,000 young competitive athletes, McClean et al. (3) observed larger cardiac diameters and LV wall thickness in young athletes compared to controls. The higher LVIDd, LVIDs, and IVSd compared to reference values in our sample were in the same range as the results by McClean et al. (3). LV systolic and diastolic function,

represented by EF and E/A, were not significantly reduced in our cohort. Whereas Pelliccia et al. (26) refer to studies reporting no differences in athletes and non-active controls with an EF being consistently around 50% (58, 59), we report an EF of 66.61 ± 5.77% that corresponds better with the results of recent studies and points towards an improved systolic function in our cohort (3, 60, 61). The same can be stated for diastolic function with an E/A of 2.46 ± 2.16, which is also similar to findings in the current literature (3, 15, 61, 62). As we observed a significantly increased LVIDs and increased wall thickness accompanied by a preserved EF and E/A, we state a functional cardiac adaptation in young competitive athletes. These results are in line with other studies in young athletes (9, 12, 62).

To be able to sustain high physical demands during endurance exercise, the heart increases its output up to 30–40 l/min, imposing a chronic volume overload on the heart that is the potent stimulus for LV dimensions and LVM to increase to the same extent, defined as eccentric hypertrophy (51, 63–65). During power training, blood pressure, heart rate, and peripheral vascular resistance increases which elicits a concentric adaptation of the cardiac muscle (66). This strict categorization of being either endurance or power type of sports does not apply to most disciplines. Regardless of the type of sports, there is an overlap in training regimes with varying degrees of endurance and power components (25, 26, 67). LV eccentric or concentric remodeling can thus be observed in various kinds of disciplines, regardless of the underlying categorization (68). In our study, eccentric hypertrophy was observed in endurance, power, and mixed sports to the same extent (endurance: 56.9%, power: 56.3%, mixed: 51%). Contrary to other authors, concentric hypertrophy was observed in only a minority of participants, again, in power and mixed athletes to the same extent (power: 6.3% and mixed: 6.6%) and to a lesser percentage in endurance athletes (3.9%). Around 30% of athletes within the three categories had normal LV geometry. These numbers differ from the results of Binnetoglu et al. (13), who observed a higher percentage of concentric remodeling (14.3%) and fewer athletes with eccentric remodeling (28.6%) in athletes of various disciplines. Surprisingly, the highest percentage of athletes with eccentric remodeling in this study was observed in power athletes (39.1% in wrestlers). Results by Sulovic et al. (14) reported results of dynamic and static exercising athletes with eccentric hypertrophy in 79.4% of dynamic exercising athletes. In static exercising athletes, the ratio was nearly balanced (54.05% concentric hypertrophy and 45.95% eccentric hypertrophy). In summary, eccentric hypertrophy was observed in more than 50% of our athletes, regardless of the type of sports they performed. Concentric hypertrophy affected only a minority of athletes. One reason for different results could be a shorter exposure to very intense exercise training over a longer period in our sample. Mean age of our participants was younger compared to other studies (13, 14) as well as training exposure compared to Sulovic et al. (14).

Cardiac adaptations observed in this study could be explained by an independent influence of training intensity on chamber dimensions and LVM/BSA. So far, an influence of training history, the type of sports, sex, age, and genetics has been proven (63, 69), but none of the studies screened assessed athletes' weekly training intensity. We applied a self-reported physical activity questionnaire that allowed the calculation of MET-h/week as an approximate for participants' training loads. In general, it is the combination of training intensity and training time that corresponds to $VO_{2peak}$ and exercise performance (70). The same might be true for cardiac adaptations, where a certain intensity threshold has to be reached to elicit cardiac adaptations. However, exercise training below this threshold might not trigger cardiac adaptations, regardless of the weekly training time this exercise training is performed.

Bjerring et al. (62) and Rundqvist et al. (8, 61) assessed young athletes' $VO_{2max}$. They reported correlations with LV volumes but not with IVSd, as observed in our cohort. The authors did not control parameters for sex, age, SBP, BSA, and training history, which could be potential confounders leading to controversial results. Explaining the association of IVSd and $VO_{2peak}$, we assume that athletes with a certain genetic predisposition better respond to exercise training and thus achieve a higher $VO_{2peak}$, may also be more prone to hypertrophic adaptations, as observed in the higher IVSd (63, 71). Additionally, individuals may choose the type of sports that fits best to their individual genetic profile. In this regard, those who are able sustain higher training intensities may become stronger athletes and show more pronounced cardiac adaptations (69, 72).

Boys had higher values for LVM/BSA (+ 15.3%) and LVM/height (+ 17.6%) than girls, which is in line with the current literature and explained by hormonal influences; thus, higher circulating testosterone levels in boys exceeding female levels up to 15 times (73). The significantly higher LVM/BSA in boys was also observed in two different age categories (<14 and ≥14 years). By implication, this stresses the importance to screen male athletes for cardiac adaptations towards LV hypertrophy, as they might be at higher risk than females.

The comparison between endurance and power athletes resulted in a significantly better diastolic function (E/A) in endurance athletes. Venckunas et al. (6) reported a significantly reduced diastolic function in power athletes compared to basketball players but not compared to endurance runners. Contrary to our findings, no significant differences between endurance and power athletes were reported by Sulovic et al. (14) and Binnetoglu et al. (13). Interindividual differences in training time, training intensity, and overall training history do add to genetic trainability and make a direct comparison of results difficult (69). Further cardiac parameters did not significantly differ between the two groups, which could be due to the young age, a lack of specialization at this age, and the

TABLE 4 Results of the longitudinal sub-sample regarding anthropometry, heart rate, blood pressure, pulse wave analysis, data on physical performance and training time, and echocardiographic data.

| Anthropometry | n | Visit Nr.1 mean ± SD | n | Visit Nr.2 mean ± SD | *P*-value |
|---|---|---|---|---|---|
| Age [years] | 85 | 13.71 ± 1.60 | 85 | 14.63 ± 1.62 | < **0.001** |
| Body height [cm] | 85 | 166.03 ± 14.60 | 85 | 170.51 ± 13.51 | < **0.001** |
| Body height z-score | 85 | 0.32 ± 1.23 | 85 | 0.31 ± 1.24 | 0.332 |
| Body mass [kg] | 85 | 53.23 ± 14.12 | 85 | 58.64 ± 14.30 | < **0.001** |
| BMI [kg/m$^2$] | 85 | 18.93 ± 2.33 | 85 | 19.84 ± 2.46 | < **0.001** |
| BMI z-score | 85 | -0.16 ± 0.70 | 85 | -0.02 ± 0.69 | < **0.001** |
| WHR z-score | 81 | -0.44 ± 0.86 | 81 | -0.61 ± 0.88 | **0.036** |
| WHtR z-score | 81 | -0.54 ± 0.62 | 81 | -0.41 ± 0.65 | **0.004** |
| BSA [m$^2$] | 85 | 1.56 ± 0.27 | 85 | 1.66 ± 0.26 | < **0.001** |
| **Heart rate and blood pressure** | **n** | **Visit Nr.1 mean ± SD** | **n** | **Visit Nr.2 mean ± SD** | ***P*-value** |
| HR [1/min] | 84 | 66.05 ± 9.06 | 84 | 62.62 ± 9.57 | < **0.001** |
| SBP [mmHg] | 84 | 115.19 ± 7.08 | 84 | 115.15 ± 7.90 | 0.964 |
| SBP z-score | 83 | 0.23 ± 0.87 | 83 | -0.04 ± 0.89 | **0.002** |
| DBP [mmHg] | 84 | 63.88 ± 5.70 | 84 | 62.86 ± 5.66 | 0.119 |
| DBP z-score | 83 | -0.46 ± 0.87 | 83 | -0.74 ± 0.81 | **0.003** |
| **Pulse wave analysis** | **n** | **Visit Nr.1 mean ± SD** | **n** | **Visit Nr.2 mean ± SD** | ***P*-value** |
| PWV [m/s] | 84 | 4.84 ± 0.38 | 84 | 4.92 ± 0.42 | 0.145 |
| PWV z-score | 84 | 0.46 ± 1.19 | 84 | 0.34 ± 1.32 | 0.185 |
| cSBP [mmHg] | 84 | 103.69 ± 8.88 | 84 | 105.07 ± 10.01 | 0.263 |
| cSBP z-score | 84 | 0.34 ± 1.15 | 84 | 0.19 ± 1.25 | 0.101 |
| **Cardiopulmonary exercise test** | **n** | **Visit Nr.1 mean ± SD** | **n** | **Visit Nr.2 mean ± SD** | ***P*-value** |
| Maximum HR [1/min] | 70 | 188.79 ± 9.81 | 70 | 187.11 ± 8.78 | 0.148 |
| Maximum power output [Watt] | 71 | 234.41 ± 69.67 | 71 | 269.89 ± 75.81 | < **0.001** |
| Relative power output [Watt/kg] | 71 | 4.47 ± 0.56 | 71 | 4.66 ± 0.69 | **0.004** |
| Relative $VO_{2peak}$ [ml/min/kg] | 67 | 44.23 ± 7.98 | 67 | 46.65 ± 6.12 | **0.012** |
| **Handgrip strength** | **n** | **Visit Nr.1 mean ± SD** | **n** | **Visit Nr.2 mean ± SD** | ***P*-value** |
| Maximum HGS/body mass | 72 | 0.51 ± 0.09 | 72 | 0.52 ± 0.10 | 0.115 |
| **Physical activity questionnaire** | **n** | **Visit Nr.1 mean ± SD** | **n** | **Visit Nr.2 mean ± SD** | ***P*-value** |
| Days of physical activity/week | 85 | 5.16 ± 1.18 | 85 | 5.36 ± 1.07 | 0.090 |
| Main sport: training/week [h] | 84 | 7.88 ± 3.19 | 84 | 8.75 ± 3.56 | **0.003** |
| Sports club activity: training/week [h] | 85 | 8.22 ± 3.07 | 85 | 9.47 ± 3.39 | < **0.001** |
| Main sport: MET-hours/week | 84 | 71.69 ± 24.12 | 84 | 79.87 ± 28.56 | < **0.001** |
| Sports club activity: MET-hours/week | 85 | 74.43 ± 22.24 | 85 | 86.32 ± 24.71 | < **0.001** |

*(Continued)*

TABLE 4 (Continued)

| 2D transthoracic echocardiography | n | Visit Nr.1 mean ± SD | n | Visit Nr.2 mean ± SD | *P*-value |
|---|---|---|---|---|---|
| EF [%] | 79 | 67.06 ± 5.38 | 79 | 66.18 ± 5.41 | 0.383 |
| FS [%] | 79 | 37.37 ± 4.32 | 79 | 36.76 ± 4.20 | 0.505 |
| LVIDd [mm] | 82 | 47.93 ± 5.04 | 82 | 49.12 ± 5.14 | < **0.001** |
| LVIDd z-score | 82 | 0.20 ± 0.89 | 82 | 0.04 ± 1.13 | 0.113 |
| LVIDs [mm] | 81 | 30.10 ± 3.79 | 81 | 31.11 ± 3.94 | **0.011** |
| LVIDs z-score | 81 | 0.25 ± 0.84 | 81 | 0.22 ± 0.99 | 0.397 |
| IVSd [mm] | 82 | 8.05 ± 1.53 | 82 | 9.13 ± 1.35 | < **0.001** |
| IVSd z-score | 82 | 0.34 ± 0.77 | 82 | 0.73 ± 0.72 | < **0.001** |
| LVPWd [mm] | 82 | 7.94 ± 1.33 | 82 | 8.40 ± 1.24 | **0.001** |
| LVPWd z-score | 82 | 0.71 ± 0.73 | 82 | 0.76 ± 0.80 | 0.474 |
| Relative wall thickness | 82 | 0.33 ± 0.05 | 82 | 0.36 ± 0.04 | < **0.001** |
| LVM/BSA [g/m$^2$] | 82 | 101.90 ± 19.65 | 82 | 113. ± 22.87 | < **0.001** |
| LVM/body height [g/m] | 82 | 95.99 ± 24.38 | 82 | 110.21 ± 27.90 | < **0.001** |
| E/A | 37 | 2.98 ± 4.82 | 37 | 2.58 ± 0.62 | **0.008** |

BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; BSA, body surface area; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; cSBP/cDBP, central SBP/DBP. EF, ejection fraction; FS, fractional shortening; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; IVSd, interventricular septal thickness in diastole; LVPWd, left ventricular posterior wall thickness in diastole; RWT, relative wall thickness; LVM/BSA, left ventricular mass/body surface area; LVM/body height, left ventricular mass/body height; E/A, ratio of mitral E- and A-wave. The meaning is that these values are significant results as indicated by a *p*-value of $< 0.05$.

mixed nature of any kind of exercise training, where wrestlers also do aerobic exercises, and runners do power training (17, 68). The more specialized training regimes are and the longer they are followed, the more pronounced cardiac adaptations are. In this regard, baseline data are important to further monitor athletes throughout their careers.

A smaller sub-sample of our cohort was examined twice over one year. We observed a lowering of the diastolic function with a 14.5% decrease in E/A that was accompanied by an increase in LVM/BSA (+11.1%), LVM/height (+14.8%), and IVSd (+13.4%). Only three longitudinal studies that assessed echocardiographic parameters in young athletes could be identified. D'Ascenzi et al. (15, 16) examined swimmers during an exercise period of 5 months and reported significantly increased RV and right atrial dimensions, while RV and biatrial function were preserved. Bjerring et al. (74) followed $n = 36$ cross-country skiers over six years. From baseline to the first follow up, participants underwent eccentric cardiac remodeling with significantly increased LV volumes and a reduction in RWT from age 12 to 15, whereas from age 15 to 18 concentric remodeling was observed with a significant higher increase in IVSd, LVPWd, LVM, and RV area. Weekly training time significantly influenced the increase in LVM and IVSd. Furthermore, a non-significant trend toward a reduction in systolic and diastolic LV function was observed. As an adverse consequence of cardiac remodeling, ventricular arrhythmia was observed in senior athletes associated with a longer duration of exercise training (17–19) and a higher risk of tricuspid regurgitation in athletes vs. controls (21). Pelliccia et al. (20) observed the association between adaptations of the LV and left atrium with an LV increase by one mm that was accompanied by a 0.4 mm increase in LA diameter. As an adverse consequence, atrial flutter or fibrillation could occur over time.

Our results confirm the hypothesis that cardiac adaptations to exercise do happen already at a young age in young competitive athletes. In our sample, cardiac adaptation was influenced by exercise intensity and maximum aerobic capacity. These results emphasize how important it is to screen young competitive athletes regularly and to monitor cardiac structure and function in response to exercise training. Parameters in children and adolescents should be compared to sex- and age-adjusted z-scores to better define if values are still within the normal range or exceed the upper limit of normal, thus pointing towards a pathological adaptation. To prevent these adverse adaptations in children and adolescents, a closer observation is needed – especially in a longitudinal setting.

The limitations of this study are the focus on the echocardiographic assessment of LV structure and function, whereas the athlete's heart does not consist of an altered left ventricle, only. Cardiac adaptations to exercise also affect the right ventricle as well as both atria (15, 19). Pelliccia et al. (26) define a consistent increase in all chambers of the heart as a harmonic adaptation, whereas an inconsistent, e.g., non-harmonic increase, would rather be associated with a non-physiological process. Recent methods like 2D speckle tracking echocardiography or 3D echocardiography would add to better assess the athlete's heart (60, 62). To better determine training intensity, self-reported activity questionnaires like the one we applied would be the minimum requirement for future studies. Due to technical advances, digital monitoring of training loads

via heart rate monitors or smart watches could be easily realized. Most importantly, longitudinal studies are needed with a focus on boys and girls to the same extent and on different training stimuli imposed by different types of sports. We calculated LVM according to the formula of Devereux and Reicheck, published in 1977 (53), which overestimated LVM. The same authors published another formula in 1986 (75), which is recommended by Lang et al. (51) and should be applied in future studies to determine LVM to the latest standards.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

This work was part of the Munich Cardiovascular Adaptations in Young Athletes Study (MuCAYA-Study) (24), which was conducted from September 2018 to September 2020 at the Chair of Preventive Pediatrics, TUM Department of Sport and Health Sciences, Technical University of Munich (TUM). This study was approved by the local ethics committee (301/18S) and is in line with the Declaration of Helsinki (2013). Written informed consent was obtained by all participants and legal guardians.

## Author contributions

HW contributed to the study concept and funding, analyzed the data, and drafted the manuscript. LB contributed to the study concept, funding, and reviewed the manuscript. FM and NS performed echocardiographic measurements and reviewed the manuscript. RO-F contributed to the study concept and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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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.2022.961979/full#supplementary-material

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# 5 DISCUSSION

This work presents results of the MuCAYA-Study, a cross-sectional echocardiographic study of 404 young competitive athletes, 7 - 18 years old, and the results of a longitudinal sub-sample of 85 participants, examined twice during the study period of two years. As basis for this work, a systematic review of echocardiographic studies in young athletes including eight publications has been performed beforehand. The main results of the systematic review regarding 2DE were:

(1) there are structural LV adaptations in young athletes vs. controls such as a significantly increased LVIDd and LVIDs, IVSd, LVPWd, and LVM, which could not be attributed to the type of exercise, being either dynamic or static;

(2) there are inconsistent results regarding LV function such as an increased EF and E in dynamic athletes and, compared to dynamic athletes, a reduced EF and E in static athletes vs. no differences in EF and FS in athletes vs. controls;

(3) there are conflicting results regarding RV structure being significantly increased in one study and not different in athletes vs. controls in the second study, and also regarding RV function with only TAPSE/ BSA being significantly higher in athletes in one study;

(4) bi-atrial remodelling was observed reflected by increased left and right atrial diameters and volumes.

These results, however, are limited to eight studies only, which differed in the number of participants, athletes' age, different types of sports performed as well as various training regimes with different volumes and intensities. Hence, the comparability of studies is difficult.

The MuCAYA-Study tried to overcome some of these difficulties by a larger sample size than addressed in most studies in young competitive athletes and via the assessment of training volume and training intensity with the MoMo-AFB. The more, participants' exercise performance was assessed via CPET. Main results of this study were:

(1) LV eccentric hypertrophy in the majority of young competitive athletes that was observed in dynamic, static, and mixed exercising athletes to the same extent;

(2) significantly increased z-scores for LVIDs, IVSd, and LVPWd in our cohort;

(3) training intensity had a significant influence on LVIDd, LVIDs, and LVM/ BSA pointing towards increased cardiac dimensions with higher training intensities;

(4) $VO_{2peak}$ significantly influenced IVSd and LVM/ BSA, also pointing towards increased parameters the higher participants' $VO_{2peak}$;

(5) the comparison of endurance vs. strength athletes revealed an improved diastolic function (E/A) in endurance athletes.

Analysis of the longitudinal sub-sample showed:

(1) a significantly increased LV structure over time, such as an increased IVSd, RWT, LVM/ BSA, and LVM/ height;

(2) a significant reduction in diastolic function (E/A) between the two visits.

The following section will discuss the above mentioned results, including publications and results entailed in the systematic review. Publications referred to within this discussion focus on studies in young competitive athletes. Results of studies on adult athletes will be referred to for further comparison. Furthermore, general problems within studies investigating cardiovascular adaptations in young competitive athletes will be discussed, starting with the definition of an paediatric athlete.

## 5.1 THE PAEDIATRIC ATHLETE

In 2016, Araujo and Scharhag [20] published the definition of an athlete. So far, the term 'athlete' is used extensively in scientific work, covering the range of recreational sportsmen to elite athletes competing at an international level. Thus, the term 'athlete' includes a variety of subjects that cannot be compared to each other, especially within a research setting. Therefore, Araujo and Scharhag [20] made the effort to define an athlete by four unique features as (1) participating in sports training to improve one's performance; (2) actively participating in sports competitions; (3) being formally registered as competitor on a local to international level and (4) training and competitions as one's major activity. To further specify an athlete, they introduced three age categories, namely 'young' (12 - 17 years), 'adult' (18 - 35 years), and 'master' (35 - 60 years). Now, per

definition, children and adolescents can only be defined as an athlete, being 12 years and older. Their training volume and training intensity at that age, is reported to reach that of adult athletes, already [35, 146]. However in some disciplines, like gymnastics or figure skating for example, regular training and a strict course of specialization, begins at the age of six years [35, 147]. To define a young athlete starting at the age of 12 years is a theoretical approach. It helps to standardize comparisons, especially in research. However, training loads in children < 12 years are already high and reaching up to levels of older athletes.

Therefore, we included children and adolescents, aged 7 - 18 years in our study and defined them as being 'young competitive athletes'. Except for the younger age, participants fulfilled all four criteria developed by Araujo and Scharhag [20] to be defined as an athlete.

Given the nature of motor development and development of aerobic and anaerobic capacity, athletic training in younger children differs from that in older ones, adolescents and adult athletes [147]. If training times and intensities of boys and girls were compared, divided into two age groups, < 12 years and $\geq$ 12 years, there are significant differences in training volume and training intensity per week in boys, but not in girls. Boys < 12 years trained 6.0±2.7 h/ week regarding their main type of sports and 7.2±2.9 h/ week in total which corresponds to a training intensity of 58.9±28.0 MET-h/ week regarding their main type of sports and 68.3±27.2 MET-h/ week in total. In comparison, boys $\geq$ 12 years trained 8.0±3.5 h/ week regarding their main type of sports and 8.6±3.6 h/ week in total which corresponds to a training intensity of 76.8±33.6 MET-h/ week regarding their main type of sports and 81.3±31.3 MET-h/ week in total ($p < .01$ for all). Girls < 12 years trained 5.5±3.0 h/ week regarding their main type of sports and 7.4±2.9 h/ week in total which corresponds to a training intensity of 47.2±31.0 MET-h/ week regarding their main type of sports and 61.2±26.6 MET-h/ week in total. In comparison, girls $\geq$ 12 years trained 7.6±4.2 h/ week regarding their main type of sports and 8.5±3.9 h/ week in total which corresponds to a training intensity of 70.2±45.7 MET-h/ week regarding their main type of sports and 78.0±42.9 MET-h/ week in total ($p > .05$ for all). These differences in training volume and training intensity might account for differences regarding cardiac

adaptations by providing a lower stimulus in the younger athletes and a higher or more potent stimulus within athletes ≥ 12 years – in boys more than in girls.

## 5.2 THE MORGANROTH HYPOTHESIS REVISED

In 1975, Morganroth et al. [13], published results of echocardiographic examinations in 42 male athletes (swimmers, long-distance runners, wrestlers) and 14 athletes, competing at an international level (long-distance runners and shot putters). The authors observed increased LVM in all athletes compared to controls that were accompanied by sports-specific adaptations, such as enlarged LV cavity dimensions in swimmers and runners and an increased LVPWd and IVSd in wrestlers. This led to the concept of eccentric hypertrophy in dynamic type of sports, where the hemodynamic stimulus on the heart is a volume load, leading to an increase in LV cavity dimensions and a proportional increase in LVPWd in order to keep myocardial strain at a constantly average level [13, 17]. Resistance or static type of sports led to concentric hypertrophy, where a pressure load triggers an increase in LVPWd with no subsequent increase in LV cavity size. The higher LVPWd helps to normalize the increased wall tension caused by the pressure load [13, 17]. As a result, RWT is increased in resistance athletes but unchanged in endurance athletes [17]. This concept sounds logical on the one hand, but also very black and white on the other hand. The rational aspect can be explained with the Law of La Place: cardiac muscle mass increases to keep the balance between intracardial pressure and RWT [17]. However, this dichotomous classification of either eccentric hypertrophy in endurance athletes and concentric hypertrophy in resistance athletes is being refused as there is no discipline and training regime that is a 100% dynamic or a 100% static, thus the load on the heart is also not exclusively a volume load or a pressure load [17, 36].

We observed eccentric hypertrophy in endurance and resistance athletes to the same extent (endurance: 56.9% and resistance: 56.3%) and concentric hypertrophy in only a minority of athletes (endurance: 3.9% and resistance: 6.3%). These results do not support the ‘Morganroth Hypothesis’, but are in line with results in adults, published by Naylor et al. [17] who state limited evidence for concentric hypertrophy in resistance athletes. Binnetoglu et al. [84] reported a lower percentage of eccentric hypertrophy (28.6%) and more athletes with concentric

hypertrophy (14.3%) in 140 young athletes (14.4±1.5 years) compared to our results. In this study, eccentric hypertrophy was observed in strength and endurance athletes to a similar extent. 9 wrestlers out of 23 (39.1%) showed eccentric hypertrophy vs. 16 swimmers out of 45 (35.6%). On the contrary, a study by Sulovic et al. [83], observed eccentric hypertrophy to a higher percentage in endurance athletes compared to static athletes (79.4% vs. 45.9%) and vice versa for concentric hypertrophy (endurance: 27.6% vs. static: 54.05%).

A systematic review compared the results of 92 studies, investigating cardiac adaptations in male endurance and resistance athletes (18-38 years old) compared to sedentary controls [46]. The main results were increased LV dimensions in both athlete groups compared to controls, and the more in endurance athletes, pointing towards an eccentric hypertrophy. LVPWd was similar in both groups, hence, no concentric hypertrophy could be demonstrated in resistance athletes [46]. In another study, analyzing 20 cross-sectional studies on adult resistance athletes, 37.5% presented with concentric hypertrophy, but also 37.5% with normal LV geometry and 25% with eccentric hypertrophy [1]. In addition, Haykowski et al. [148], examined central arterial pressure (descending aorta) and intrathoracic pressures (esophageal pressure as a surrogate) in five men (27.6±2.9 years) during submaximal (80% and 95%) and maximal leg press exercise with a brief Valsalva manoeuvre. The exercise resulted in a significant increase in SBP and DBP as well as intrathoracic pressure. There were no changes in LV systolic function or end-systolic wall stress. The authors concluded that the heart is protected during such exercise via an increased intrathoracic pressure, elicited by the Valsalva manoeuvre. The pressure, to which the heart was exposed to, was similar to baseline levels. As consequence, the pressure stimulus imposed on the cardiac muscle is reduced and does not trigger an increase in LVPWd [17].

Most studies, and especially those published in the first era of studies investigating the ‘athlete’s heart’, focused on the LV, only. However, exercise has an influence on the entire heart. La Gerche et al. [45] investigated the effects of cycle exercise on the left and right heart by measuring LV and RV end-systolic wall stress, pulmonary artery pressure and SBP in 39 endurance athletes (36±8 years). Results of their work were a higher increase in RV end-systolic wall stress and pulmonary artery pressure compared to LV end-systolic wall stress and SBP.

However, both ventricles, the left and the right one, were exposed to increased pressures, thus, endurance exercise causes a volume and pressure load on the heart [9, 15].

Summarized, the results of our study reject the 'Morganroth Hypothesis' in young competitive athletes, as eccentric hypertrophy was not an exclusive feature in endurance athletes but to the same extent also present in resistance athletes. Concentric hypertrophy was observed in a minority of endurance and resistance athletes, only. These results are consistent with findings in studies in adults. We did not assess RV characteristics – in future studies focus should be put on the entire heart, including both ventricles as well as both atria, to examine the influence of exercise on the heart and to define a comprehensive definition of an athlete's heart.

## 5.3 Structural and Functional adaptations of the left ventricle in a cross-sectional sample of young competitive athletes

We assessed left ventricular function via 2D TTE in a cross-sectional sample of 404 (97 girls) young competitive athletes. Additionally, a longitudinal sub-sample of 85 (8 girls) young competitive athletes was examined twice within the study period of two years. Standardized z-scores for LVIDs, IVSd, and LVPWd were significantly increased in our cohort, confirming the hypothesis that LV structural adaptations do occur in young competitive athletes. RWT, however, as parameter of LV geometry was within a normal range and not increased above the threshold value of 0.42. Thus, LV cardiac adaptations in our cohort can be considered as a harmonic adaptation, bearing no reduction of cardiac diameter relative to ventricular wall dimensions.

The percentage of young competitive athletes with normal LV geometry (34.9 % males and 43.3 % females) is in line with results by Binnetoglu et al. [84] who reported normal LV geometry in 38.7 % out of a sample of 95 male athletes (14.4±1.2 years) participating in various sports similar to our sample. Regarding eccentric and concentric hypertrophy, our results differ from Binnetoglu et al. [84]. We observed eccentric hypertrophy in 54.1 % of males and 45.4 % of females compared to 28.6%, and concentric hypertrophy in 5.5 % of males and 8.2 % of females compared to 14.3 %. It is of particular interest that power athletes (23

wrestlers, 15.5±1.5 years) in the study by Binnetoglu et al. [84] showed the highest percentage of eccentric hypertrophy with 39.1 %. In our results, eccentric hypertrophy was observed in 56.3 % of power athletes, and to a similar extent in endurance and mixed type of sports (56.9 % and 51 %).

These results reject the traditional view of static exercise leading to concentric hypertrophy in athletes. Reasons for the lower percentage of eccentric hypertrophy and a higher percentage of concentric hypertrophy in the study by Binnetoglu et al. [84] compared to our results may be found in athletes' training time per week and training intensity, which is not measured and indicated by the authors, and additionally by further influencing factors like hormonal influences, ethnicity or the genetic predisposition to perform sports [89, 149, 150]. The latter is important to perform sports at a very high level [89]. An athlete has its own genetic profile that predisposes him to sustain high training intensities and extensive training volumes. According to Epstein [71] this profile is not to overcome, hence, an athlete with the genetic profile to run a marathon won't be able to become an Olympic weight lifter.

Our results of a structural cardiac adaptation to exercise are in line with results by McClean et al. [22] and other authors [82, 85, 86, 151, 152]. Among these studies, McClean et al. [22] provided data of the largest sample of young competitive athletes. The authors compared 14 278 paediatric athletes (13.8±1.3 years; 2 374 females) vs. 1668 controls (12.6±0.6 years; 358 females). They reported significantly increased LVIDd (+13.5 %), LVIDs (+15.9 %), IVSd (+15.2 %), and LVPWd (+21.3 %) in athletes vs. controls. Simsek et al. [82] observed significantly increased cardiac dimensions, such as LVIDd, LVIDs, LVEDV and LVESV in 22 male runners (17.5±2.2 years) vs. 24 male wrestlers (16.8±1.9 years) and 20 male controls (16.4±1.8 years) and significantly increased wall thickness (IVSd and LVPWd) in wrestlers vs. runners and controls. Kayali et al. [87] studied 126 active children (13.5±2.7 years; sex distribution not indicated) and observed a significantly increased IVSd and LVPWd. These two studies are in line with the traditional view of increased dimensions in endurance athletes and increased LV muscle mass in resistance athletes [13]. However, the authors did not report z-scores of LV parameters nor indexed values to better account for an influence of sex, age, and body dimensions.

Binnetoglu et al. [84], for example, presented increased absolute values for LVIDd in 23 wrestlers (15.5±1.5 years) in comparison with 16 Tennis players (12.2±0.8 years; 7 females) and 43 swimmers (12.9±1.6 years; 26 females), but not compared to controls (14.7±1.5 years, all males). However, when LVIDd was indexed to BSA, values for wrestlers, swimmers, soccer players, and controls did not differ significantly which emphasizes the influence of body dimensions on cardiac parameters [50, 153, 154].The latter was considered by Zdravkovic et al. [85] who reported parameters indexed to $BSA^{0.5}$ and by Rundqvist et al. [86] who reported parameters indexed to BSA, respectively. Zdravkovic et al. [85] observed significantly increased LVIDd/ $BSA^{0.5}$, LVIDs/ $BSA^{0.5}$, IVSd/ $BSA^{0.5}$, LVPWd/ $BSA^{0.5}$, and LVM/ $BSA^{0.5}$ in 94 soccer players (12.85±0.84 years, all males) vs. 47 controls (12.85±0.86 years, all males). The same parameters were significantly increased in the study by Rundqvist et al. [86] in 27 endurance athletes (15.5 (13 - 19) years; 11 females) vs. 27 controls (15.4 (13 - 19) years; 11 females) pointing towards increased dimensions, but also increased wall thickness of the heart in mixed sports and endurance athletes. Another study in 36 younger soccer players (10.1±1.4 years; all males), conducted by Barczuk-Falecka et al. [151], presented a significantly increased IVSd/$\sqrt{m^2}$, and further on, a significantly increased LVM/ BSA, compared to a control group of 24 males (10.4±1.7 years). The results point towards a concentric remodelling of the LV in very young athletes. However, none of the young soccer players had a LVM/ BSA above the upper level of normal.

Another way to normalize data is to report standardized z-scores relative to the participant's body size [21, 136]. Gerling et al. [152] investigated 359 male soccer players (12.8±0.65 years), playing at federal level, compared to 53 controls (12.6±0.8 years; all males). The authors reported significantly increased z-scores for IVSd and LVPWd in soccer players which is in line with our results. Rodriguez-Lopez et al. [88] observed significantly increased z-scores for IVSd in 58 tennis players (12.1±2.9 years; 12 females) and 99 swimmers (12.3±3.1 years; 48 females) compared to soccer players, basketball players and participants performing athletics. Standardized z-scores for LVPWd did not differ significantly between the groups.

In summary, there is the need to report cardiac parameters relative to body dimensions or transformed into z-scores, for absolute values do not consider body compositions and physical growth. Results that are not presented relative to body dimensions could potentially be distorted.

Contrary to the majority of studies reporting significant differences in young athletes compared to controls, Beaumont et al. [89] did not observe significantly different structural parameters in 22 athletes (12.0±0.3 years, all males) vs. 22 controls (11.7±0.3 years, all males). In this study, soccer players presented a training history of 4.5±1.5 years of soccer training and a training time of 9.4±2.4 h/ week. Both, training history and training time per week were lower in our sample (training history: 3.6±2.5 years; training time: 8.4±3.59 h/ week). As we compared cardiac parameters to age- and sex-specific z-scores, Beaumont et al. [89] compared study results to a control group that performed 1.53±1.77 h of physical activity per week. Potentially, the fitness level, that was not indicated, of this control group was already too high, accounting for non-significant results in this study.

Other factors influencing studies' results are participants' age which varies a lot within the studies presented (min: 10.1±1.4 years; max: 19.0±1.0 years), sports disciplines, training volumes and training intensity as well as training history. Especially regarding training volumes and intensity, there's a lack of data assessed in young athletes [19]. The time of data assessment during an athlete's sporting season has also an impact on a study's results, due to variations in training volume and intensity at the beginning of a season, at the end or at peak season [155]. Furthermore, most studies are performed in male athletes. For example, the relation of males to females in the meta-analysis by McClean et al. [22] was 5 : 1. The studies mentioned in this paragraph comprised in total 13 023 young male athletes but only 2 591 females which is also a ratio of 5 : 1. Studies conducted in females only, are rare. Kooreman et al. [16] performed one study on 103 female college athletes, participating in dynamic sports, divided into two categories: high-intensity (19±1 years; 37 females), low-intensity (19±1 years; 35 females), and a control group (19±1 years; 31 females). LVPWd/ m was significantly increased in the high intensity group compared to controls, LVIDd/ m and LVM/ BSA was significantly increased in the high intensity group compared to

controls and compared to the low intensity group. Pelà et al. [156] investigated sex differences in 158 male athletes (13.8±1.6 years) and 48 females (13.7±1.4 years). All structural parameters, LVIDd, LVIDs, LVEDV, LVESV, IVSd, LVPWd, and LVM/ BSA, were significantly increased in males compared to females. Contrary to these findings, only LVM/ BSA was significantly increased in male athletes compared to females in our study. Absolute values for LVIDd, LVIDs, IVSd, and LVPWd were significantly increased in males, however not, when transferred into z-scores. In females, z-scores for LVIDd, LVIDs, IVSd, and LVPWd were not significantly increased in our cohort. Data of studies listed in the paragraph above are displayed as supplementary information (9.5, Supplementary table S18).

Even though, we observed a significantly increased LVIDs z-score, LVIDd was not increased compared to reference values. One could expect a harmonic adaptation of the LV in a healthy study population like ours, as stated by Pelliccia et al. [42] referring to a well-balanced increase in cardiac dimensions, thus an increase in LVIDs and LVIDd. LVIDs refers to the LV diameter at the end of systole, when the heart has ejected the volume of blood stored during diastole. There is a positive correlation between LVIDs and LVESV as LVESV is derived from LVIDs [157]. Thus, the higher LVIDs, the higher LVESV. In specific pathologies, LVIDs and LVESV are increased, for example in heart failure, dilated cardiomyopathy or hypertrophic cardiomyopathy [158-160]. However, other reasons might account for the increased LVIDs in our cohort of healthy children and adolescents. De Simone et al. [161] reported a linear relationship between SBP and LVIDs with a constant reduction in LVIDs with decreasing SBP. The authors considered the ratio of SBP/ LVIDs as contractility index. In our cohort, we reported a significantly increased SBP z-score which corresponds well with the increased LVIDs and supports the finding of De Simone et al. [161]. Vice versa, looking at LVIDd and DBP, we noted a significantly reduced DBP z-score which we can relate to the non-significantly increased LVIDd.

Compared to results by McClean et al. [22], LVIDs was similar in this study (29.6 (28.4 - 30.8) mm) and our work (30.28±3.97 mm). The authors reported significantly increased values for LVIDs and LVIDd in athletes vs. controls. Also, EF and FS were similar in the study by McClean et al. [22] and ours, both within normal levels (EF: 65.6 (61.1 - 70.1) % vs. 66.1±5.77 % and FS: 37.2 (35.5 -

38.9) % vs. 37.10±4.62 %). Thus, LV function is not impaired in our cohort and the increased LVIDs cannot be regarded as a negative or pathological adaptation.

Results for LVIDd in the study by McClean et al. [22] are in the same range than our results (47.3 (46.2 - 48.3) mm vs. 48.16 ± 4.89 mm) and those observed by Rundqvist et al. (48.14 mm) [86]. Simsek et al. [82] reported higher values in 22 runners (52.1±4.4 mm) and similar values in 24 wrestlers (47.2±6.2 mm). Participants of that study were older than our cohort (runners: 17.5±2.2 years and 24 wrestlers: 16.8±1.9 years) which could be a reason for the higher values observed in runners, thereby reflecting the interaction of age and endurance type of sports that leads to an increase in cavity dimensions. The studies mentioned above [22, 82, 86] reported significantly increased results for LVIDd, contrary to our study. In line with our results of no significant differences in LVIDd, are studies by Gerling et al. [152], Barczuk-Falecka et al. [151], and Beaumont et al. [89].

In the context of an increased LVIDs accompanied by a non-significantly increased LVIDd, we hypothesize that cardiac work is sufficient to supply the body with an adequate amount of blood. As consequence of regular exercise all systems of the body work most efficiently and are able to extract required substrates to supply organs and working muscles with energy sufficiently [50, 162, 163]. Therefore, we state a physiological and non-pathological cardiac adaptation in our cohort. In line with our work, the majority of studies conducted on young competitive athletes observed cardiac adaptations in response to chronic exercise training. These adaptations are benign and not associated with impaired cardiac function or pathologies.

To investigate if different training stimuli had a distinct influence on the heart, we compared 51 endurance athletes (14.42±1.83 years, 26 females) with 48 strength athletes (14.67±1.70 years, 15 females). Our data did not support the traditional view of increased cardiac dimensions in endurance athletes and increased wall thickness in strength athletes as we observed no significant differences in LV structure between the two groups. However, endurance athletes presented a significantly increased E/A pointing towards a better diastolic function. Data in children and adolescents that compared endurance or dynamic type of sports with strength or static type of sports are rare. Only three studies could be identified

that looked at different training stimuli in response to cardiac remodelling in young adolescents [82-84]. Sulovic et al. [83] compared 100 dynamic athletes (15.0±1.5 years) with 100 static athletes (15.4±1.6 years) and 100 controls (15.2±1.6 years). Contrary to our results, the authors found a significantly increased LVIDd in dynamic athletes vs. static athletes and controls, and a significantly higher IVSd in dynamic and static athletes vs. controls. However, static athletes showed no significantly increased wall thickness compared to dynamic athletes. The opposite was reported by Simsek et al. [82] who found increased IVSd and LVPWd in 24 wrestlers (16.8±1.9 years) compared to 20 runners (17.5±2.2 years) and controls (16.4±1.8 years) and, furthermore, increased cardiac dimensions in runners compared to wrestlers and controls. Whereas these two studies, are more in favour of the traditional 'Morganroth Hypothesis', Binnetoglu et al. [84] reported an increased wall thickness in 45 (26 females) swimmers (12.9±1.6 years) vs. 25 basketball players (16.2±1.1 years), 31 soccer players (15.1±1.1 years), 16 (7 females) tennis players (12.2±0.8 years), 23 wrestlers (15.5±1.5 years), and 25 (7 females) controls (14.7±1.5 years). Significantly increased cavity dimensions (LVIDd and LVIDs) were observed in basketball players compared with swimmers, tennis players, wrestlers, and controls but not compared with soccer players, who also belong to the mixed-sports category according to Pelliccia et al. [42]. Contrary to our results, none of the three studies reported a significantly different E/A between their athletes' groups and controls.

Comparing these three studies, it is to notice that groups differ according to the number of participants per group (100 vs. 16), regarding the sex distribution, with females being represented only in the study by Binnetoglu et al. [84], and regarding participants' age distribution (17.5±2.2 years vs. 12.2±0.8 years). Comparing young athletes of the same age group, for example 12 - 14 years, the pubertal status determines bodily development and also cardiac remodelling [164, 165]. Malina et al. [165] reported the pubertal status of 498 male soccer players, aged 11 - 18 years, by stage of pubic hair growth. Within the chronological age group of 12 years (71 boys), all five stages of pubic hair growth, that define the time between pre-puberty and being mature, were represented. Those males within the higher pubic hair stage were taller and heavier than those within lower stages. Another method to define the maturity status of children and adolescents is the age at peak height velocity (PHV). It refers to the estimated chronological age

during the adolescent spurt, that is the maximum rate of growth in height [165]. It provides an approximate to classify an adolescent's growth status referring to body height but also to growth of tissue, organs, and systems that happen during puberty [165, 166]. Perkins et al. [164] observed cardiac remodelling in 42 endurance-trained boys (9 - 17.1 years) and 45 girls (8.0 - 17.2 years) that did occur pre-PHV but was more pronounced post-PHV. McClean et al. [22] subdivided their sample into young athletes < 14 years and ≥ 14 years and noticed significantly increased LVIDd, LVIDs, IVSd, LVPWd, and LVM in athletes ≥ 14 years. Testosterone levels rise during puberty. In males, they are 15 times higher post-puberty compared to pre-puberty and compared to females of any age [150]. The higher testosterone levels in males are the major stimulus for an increase in muscle mass and higher circulating haemoglobin levels [150, 167], both are a strong trigger for more pronounced cardiac adaptations to exercise observed in older age groups [164]. To ideally examine cardiac dimensions in young competitive athletes, puberty status, should also be assessed and taken into account in future studies.

There is a trend towards an earlier specialization in sports in young age groups, with young competitive athletes performing one main type of sports with specialized training, only [38, 168]. Specialization in sports is defined as performing one main type of sports for more than eight months per year and quitting all other sports to pursue a single type of sports [38]. In most types of sports, specialization begins with 12 years or older [168]. One study in Tennis players reported a degree of specialization of 70 % in participants by the age of 10 years already [169] whereas another study reported 28 % out of 1191 athletes being highly specialized by the age of 14 [38]. In our study, a quarter of participants performed more than one main type of sports. In detail, 26 % (104 participants) regularly trained in two sports disciplines, 8 % (32 participants) in three, and a low percentage of 2 % (7 participants) performed four different types of sports. Thus, their training regimes consist of different stimuli within the continuum of endurance and strength training, leading to a harmonic cardiac adaptation and not being a stimulus, strong enough to account for significant differences between endurance and strength athletes.

In summary, results of this study did not reveal a distinct effect of endurance or strength training on cardiac dimensions. Other studies reported increased wall thickness in strength athletes [82, 83] and increased cardiac diameters in endurance athletes [83] or increased wall thickness and cardiac dimensions in mixed types of sports [84]. Therefore, it is to conclude that the type of sports, being strength, endurance or mixed type of sports, cannot be attributed to a certain form of cardiac adaptation. Furthermore, regardless of the type of sports being performed, exercise training cannot be exclusively defined as being 100 % dynamic or 100 % static but does contain elements of both components to a certain degree [15]. Thus, the training stimulus does not lead to either eccentric or concentric hypertrophy, but rather results in a physiologic adaptation of the heart in all sports categories within young competitive athletes.

Among the studies on young competitive athletes mentioned so far, none of the authors recorded the exact amount of training hours per week nor the intensity of each training session. Furthermore, no other study on young competitive athletes could be identified that monitored training intensity in relation to echocardiographic parameters comparable to our work. Binnetoglu et al. [84] indicated a minimum amount of 3 h of training/ week whereas participants in the study by Simsek et al. [82] trained > 15 h/ week. In our study, participants' average training time was 8.4±3.6 h/ week. The weekly amount of training time, however, had no significant influence on cardiac parameters, other than training intensity and $VO_{2peak}$. In detail, training intensity significantly influenced LVIDd, LVIDs, and LVM/ BSA. $VO_{2peak}$ significantly influenced IVSd and LVM/ BSA. Parameters were controlled for sex, age, BSA (except for LVM/ BSA), SBP, and training history. $VO_{2peak}$ in our study was measured directly via CPET, training intensity, however, was only assessed indirectly via MET-hours per week with the MoMo-AFB [122]. This is only an approximation of athletes' training intensity and no direct measurement. The latter could be assessed directly via wearables such as heart rate monitors, smart watches or activity trackers. In future studies, these more accurate methods should be taken into account to analyse the influence of training intensity on cardiac parameters more precisely.

The acute effects of a competitive 60 minutes high-intensity cycling race intervention were investigated by Balmain et al. [170] in 11 male cyclists (24±4

years) with a training load of > 10 hours/ week and a $VO_{2peak}$ of > 50 ml/ min/ kg. The authors observed no significant differences on LVEDV and LVESV pre- vs. post-intervention. They did not compare further structural parameters within their study's sample. Kayali et al. [87] and Rodriguez-Lopez et al. [88] compared athletes regarding their training duration. Kayali et al. [87] reported a significantly increased LVPWd in athletes who trained > 8 hours/ week compared to athletes who trained $\leq$ 8 hours/ week (10.5±2.8 mm vs. 9.3±1.9 mm, $p < .01$). Rodriguez-Lopez et al. [88] found an association between training time per week and IVS z-scores. Athletes who trained $\leq$ 5 hours/ week had an IVS z-score < 1 vs. athletes who trained > 15 hours/ week had an IVS z-score close to 2. Arbab-Zadeh et al. [171] investigated the effect of a 12-month training intervention in 12 adults (29±6 years, five females). Training intensity was calculated as training impulse score (TRIMP) which is derived from the duration of a training session, the average heart rate during the session, and participants' heart rate reserve. The authors observed a positive association of participants' TRIMP score and LVM with a linear relationship within the first nine month. However, both authors did not report if the association they observed was significant. Furthermore, authors only indicated training time/ week and no intensity level and training history in years of their participants. On the contrary, our results were controlled for training history in years and revealed no significant influence of athletes' training time per week on cardiac parameters. We, therefore, state that it is the training intensity not training duration per week that elicits cardiac adaptations in young competitive athletes. If a certain intensity threshold is reached, cardiac adaptations might occur. If training intensity remains below that threshold the stimulus will be insufficient to cause cardiac adaptations, independent of the training time per week.

Rundqvist et al. [86] and Bjerring et al. [31] were the only authors who also observed $VO_{2peak}$ in young competitive athletes. Both reported a significant influence of $VO_{2peak}$ on LVEDV ($R^2 = 0.593$, $p < .0001$ and $r = 0.76$, $p < .0001$) but not on LVM or wall thickness. In the synopsis of our findings, $VO_{2peak}$ does have an influence on young competitive athletes' heart. The higher $VO_{2peak}$, the more pronounced are cardiac adaptations. Furthermore, higher $VO_{2peak}$ is elicited by higher training intensities [171]. Thus, cardiac adaptations might be caused by the interplay of these parameters.

In summary, this work found structural cardiac adaptations to exercise in young competitive athletes, that cannot be attributed to the underlying sports discipline being performed, but that depend on participants' training intensity and $VO_{2peak}$. As structural cardiac changes have not been accompanied by a reduction in cardiac function or physical performance, this study reported functional cardiac adaptations to exercise in young competitive athletes. Considering the large variety of variables influencing a study's results – the number of participants, participants' age, maturity status, the distribution of male to female athletes, training time per week, training intensity and training history, and additionally the combination of these variables – it is difficult to compare studies performed in young competitive athletes and to find a consensus within these complex results in heterogenous studies.

## 5.4 Structural and Functional adaptations of the left ventricle in a longitudinal sample of young competitive athletes

One important factor regarding cardiac adaptations to exercise is age [172-175]. Therefore, we analysed data of 85 participants with two visits within the study period of two years. The average time between the two visits was 10.6±2.3 months, participants mean age was 13.7±1.6 years at the first and 14.6±1.6 at the second visit ($p < .001$). All anthropometric measures, except for body height z-score, increased significantly between the two visits. Participants improved their maximum power output by 15.1 % ($p < .001$), power output/ kg by 4.3 % ($p = .004$), and $VO_{2peak}$ by 5.5 % ($p = .012$). Their training load in training hours/ week increased by 11 % ($p = .003$) and their training intensity in MET-hours/ week increased by 16 % ($p < .001$). Regarding cardiac parameters, absolute values for LVIDd (2.5 %, $p < .001$), LVIDs (3.4 %, $p = .001$), and LVPWd (5.8 %, $p < .001$) increased significantly, but not corresponding z-scores, indicating that the changes observed were due to physical growth and cannot be regarded as an adaptative process to exercise. Contrary, absolute values for IVSd and corresponding z-scores increased significantly from 8.05±1.53 mm vs. 9.13±1.35 mm ($p < .001$) and 0.34±0.77 vs. 0.73±0.72 ($p < .001$), respectively. Furthermore, a significant increase in RWT (9.1 %, $p < .001$), LVM/ BSA (11.1 %, $p < .001$), LVM/ body height (14.8 %, $p < .001$) was observed.

In adults, with increasing age, the activation of the sympathetic nervous system increases, thereby causing a reduced β-adrenergic sensitivity, downregulation of receptors and decreased cardiac responsiveness to β-adrenergic stimulation [173, 175]. As consequence, a decline in LV compliance could be observed [172] and an increasing pulmonary vascular resistance [176]. A decline in LVEDV, LVESV, and an increase in LV stiffness was observed in individuals $\geq$ 50 years compared to younger persons [172]. Balmain et al. [170] compared acute effects on cardiac parameters pre and post a competitive 60 minutes high-intensity cycling race intervention in 11 younger male cyclists (24±4 years) with 11 older male cyclists (47±6 years). At baseline, older participants had a significantly lower LVEDd (153±20 mm vs. 174±23 mm, $p < .05$) and LVEDd/ BSA (76±3 mm/ $m^2$ vs. 88±3 mm/ $m^2$, $p < .05$). Post the cycling intervention, LVEDV was also significantly lower within the older group (143±9 ml vs. 167±7 ml, $p < .05$). In young competitive athletes, contrary to adult athletes, cardiac dimensions are higher compared to inactive controls [22, 30]. Especially during maturity, caused by a rise in testosterone levels, cardiac adaptations are more pronounced than prepuberty [22, 30, 167]. And due to circulating testosterone levels in males, being 15 - 20 times higher than in females, cardiac adaptations are more pronounced in male athletes [150]. Thus, in young competitive athletes, age positively influences cardiac dimensions whereas in the older age group, cardiac parameters show opposite adaptations in response to a lifelong training as well.

In summary, above mentioned significant results of our study observed over two years can be interpreted as cardiac adaptation to exercise independent of physical growth. Our results correspond well with those by Galanti et al. [149] and Bjerring et al. [32] in young athletes and Spence et al. [18] in adults. Galanti et al. [149] followed 57 young athletes, in detail 30 Afro-Caribbean athletes, 12.47±0.6 years at baseline, and 27 Caucasian athletes, 13.60±0.38 years at baseline, over a period of four years. All parameters, except for LVPWd in Caucasian athletes (- 1.2 %) vs. Afro-Caribbean athletes (+12.2 %), increased over time. Changes were more pronounced in Afro-Caribbean athletes compared to Caucasian athletes, which emphasizes the influence of ethnicity and genetics, respectively, on cardiac adaptations. In detail, IVSd increased by 12.9 % in Afro-Caribbean athletes and 5.9 % in Caucasian athletes, respectively, RWT by 3.1 % and 2.9 %,

LVM/ BSA by 13.9 % and 11.4%, LVIDd by 7.5 % and 3.3 %, and LVIDs by 7.4 % and 2.0 %. Bjerring et al. [32] reported results of a period of six years with two follow-ups in 31 active athletes and 15 former athletes, aged 15 years, after three years, and 20 active athletes (18.3±0.3 years) and 16 former athletes (18.3±0.3 years) after another three years. All structural parameters increased between the first and second follow-up in both athlete groups (active vs. former athletes): IVSd by 1.8±1.4 mm and 0.6±1.0 mm, LVIDd by 3.9±5.4 mm and 2.2±2.1 mm, LVPWd by 1.6±1.2 mm and 0.8±0.8 mm, and LVM by 63±30 g and 27±21 g. Regarding LV function, the authors observed a decline in LV EF by 1±3 % in active athletes and 2±4 % in former athletes as well as a reduction in E/A by 0.3±0.4 in active athletes and 0.2±0.8 in former athletes. The latter corresponds with our results, showing a significant decrease in E/A from 2.98±0.55 at V1 to 2.58±0.62 at V2 ($p = .006$). However, in our cohort, the interval between the two visits is much shorter pointing towards a more pronounced reduction of athletes' diastolic function within one year in our cohort compared to a three year period in the study by Bjerring et al. [32]. On the other hand, our participants' physical performance improved significantly over time which shows that we did not observe an adverse adaptation and an impaired cardiac function. According to Genger [177], an E/A > 2 can be observed in young persons without being associated to a diastolic dysfunction.

In 23 untrained male adults, Spence et al. [18] investigated cardiac parameters pre and post six month of an endurance training intervention (n = 10, 28.4±1.9 years) and resistance training intervention (n = 13, 26.6±1.3 years). The time period of six months corresponds better to our follow-up period of 10.6±2.3 months. Within the endurance training group, LVM increased significantly from 112.5±7.3 g to 121.8±6.6 g, LVM/ BSA from 57.1±2.6 g/ $m^2$ to 61.9±2.8 g/ $m^2$, and IVSd from 10.2±0.6 mm to 11.2±0.5 mm ($p < .05$ for all). No significant differences in structural parameters have been observed within the resistance training group. Regarding systolic function, EF increased non-significantly from 57.9±1.4 % to 59.1±1.4 % within the endurance group and from 59.6±1.2 % to 59.8±1.6 % within the resistance group. In our cohort, EF decreased slightly from 67.06±5.38 % to 66.18±5.41 % ($p = .383$) as well as FS from 37.37±4.32 % to 36.76±4.2 % ($p = .505$).

The significant increase in RWT, IVSd, LVM/ BSA, and LVM/ body height, hence an overall increase in cardiac muscle mass, might account for the observed reduction in functional parameters. Potentially, we examined the initial step of an adaptive cardiac process, where structural parameters changed already and will be followed by functional parameters over time. On an extended follow-up time, the heart's chambers will adapt, too, in order to maintain the ratio of wall thickness to cardiac diameter and to preserve the heart's function. Thus, increased cardiac diameters and an increase in functional parameters could potentially be observed. To better examine this process and to better understand cardiac adaptations, young competitive athletes should be followed over a longer period of time. The more, these follow-up examinations should take part in regular intervals adapted to an athlete's season, for example at pre-season, peak-season and post the competitive period.

However, as young competitive athletes' performance and training loads increased within the follow-up period in our cohort, the reduction in E/A and changes in EF and FS cannot be considered as adverse cardiac adaptations. We therefor state a functional adaptation of cardiac parameters to exercise independent of physical growth.

# 6 LIMITATIONS OF THE STUDY

The ideal setting to conduct a study investigating cardiac adaptations in young competitive athletes would enrol balanced groups of male and female athletes, with the same number of participants within the skill, power, mixed, and endurance group. Our cohort consisted of 76 % male and 24 % female athletes, which is a ratio of 3.2 males : 1 female. The majority of males (78.5 %) and females (50.5 %) belonged to the mixed category. Skill (2 % males, 6.2 % females), power (10.7 % males, 15.5 % females), and endurance (8.1 % males, 26.8 % females) are represented by smaller proportions. Almost half of all males played soccer (47.6 %) followed by volleyball (9.4 %) and wrestling (7.2 %), being the second and third most popular sport. In females, the distribution of different types of sports was a bit more balanced. Field hockey (17.5 %), cross-country skiing (14.4 %), and volleyball (9.4 %) were the most popular disciplines.

Ideally, participants would be matched for anthropometric data. This would require a much larger population of young competitive athletes to form appropriate sub-samples. Our cohort consisted of male and female athletes who visited our department for a pre-participation screening, either as obligatory screening imposed by their sports association or voluntarily by themselves. Due to a cooperation with one soccer club, soccer players formed the biggest sub-group within our study population. Better recruiting measures and cooperations with other sports clubs or societies would be necessary to achieve a larger sample size and to be able to match participants equally into groups according to their anthropometric data and according to sports categories.

A young athlete's maturity status is a central component influencing growth of all tissues of the body [165], as well as athletic performance [150] and cardiac adaptations [178, 179]. We did not assess pubertal status with Tanner Stages due to child protection concerns [22]. However, assessing PHV would have been possible and thus, the differentiation of participants into pre-PHV and post-PHV, to account for participants' maturity status and the influence on cardiac parameters. And even though, cardiac adaptations to exercise have been observed in pre-pubertal athletes, too, a sufficient maturity status is necessary to elicit cardiac adaptations to exercise [89].

How to index cardiac parameters is an important question. Cardiac parameters strongly depend on body dimensions [50, 154] and can be indexed to BSA, to the square root of BSA or fat-free mass, body length, body length$^{0.5}$ or body length$^{2.7}$. BSA, furthermore, can be calculated according to the formula by Haycock [180], Du Bois and Du Bois [129] or Mosteller [181]. In any case, calculated BSA is an estimate and not an accurate measure of BSA [154]. In our study, BSA was calculated according to Du Bois and Du Bois [129]. The Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council however recommends to calculate BSA according to Haycock [182]. Other authors do not recommend which formula to apply [102, 108, 118]. Thus, either a consensus should be made, or absolute values for cardiac parameters should be published and values for BSA, separately, to calculate the respective ratio that corresponds with other studies' results.

A quarter of the young competitive athletes in our study performed more than one type of sports. Furthermore, a minority of participants regularly practised three or four different types of sports. Hence, their training regimes potentially contained elements of different sports, being defined within the endurance, resistance, mixed, and skill category. To better account for this independent influence, the degree of specialization, applying defined criteria [38], should have been asked within the questionnaire in this work. In a cohort, that is not specialized in any sports but does practise different types of sports, it is not possible to analyse an independent influence of different training stimuli, like the influence of endurance training or strength training, on echocardiographic data.

The MoMo-AFB [122] that was applied within this work is a method to indirectly assess an athlete's training volume and training intensity. It is therefore only an approximate measure, that relies on the participants' memory and ability to honestly and correctly fill in the questionnaire. Direct and therefore more reliable assessment tools would be accelerometers, pedometers, heart-rate monitors, or smart watches [183, 184]. However, in most studies in young competitive athletes, training volumes and training intensity was not assessed at all. Therefore, the application of the MoMo-AFB was a feasible way to assess an athlete's training volume and training intensity.

Compared to 2D TTE, more recent assessment modalities include 3D echocardiography, 2D or 3D speckle tracking echocardiography, or cMRI. Subtle changes in cardiac structure and function can be better detected with these methods. However, a rational decision should be made upon the costs and benefits in the use of these methods. Furthermore, reference data, either z-scores or data assessed in a large control group, would be needed for each method.

In this work, echocardiographic z-scores were applied, if available, to compare the study's cohort to a reference population. However, for some parameters, no z-scores were available. In this respect, comparing these data with an inactive control group, matched for sex and age, would be ideal to account for cardiac adaptations to exercise and should be taken into account in future studies. Additionally, cardiac adaptations to exercise do not exclusively affect the left ventricle [11, 23, 34, 90, 185]. The right ventricle as well as both atria do also adapt to exercise training and should therefore be addressed in future studies.

# 7 CONCLUSIONS

Cardiac adaptations to exercise can be observed in young competitive athletes, which was observed in a systematic review presented in this work and confirmed by results of the MuCAYA-Study. These adaptations can be considered as physiologic response to exercise training. In detail, structural adaptations like an increased LVIDs, IVSd and LVPWd were observed in our cross-sectional cohort. Training intensity and peak oxygen uptake significantly influenced cardiac parameters, expressed by a positive association between training intensity and LVIDd, LVIDs, and LVM/ BSA, and between peak oxygen uptake and IVSd and LVM/ BSA. The majority of young competitive athletes presented characteristics of an athlete's heart that were defined as eccentric hypertrophy, where an increase in wall thickness is accompanied by an enlargement of cardiac diameters in order to preserve the cardiac function and myocardial strain at a constant level. In a sub-sample, examined twice over the study period of two years, left ventricular wall thickness and muscle mass increased significantly while cardiac diastolic function was lower compared to the first assessment. As this reduction was still within a normal range and accompanied by an improvement in young competitive athletes' performance over the same time we consider the adaptations observed as functional and positive adaptations that are necessary to sustain high training loads and high training intensities.

However, in adult athletes, intensive exercise training can cause adverse adaptations of the heart, leading to atrial dilatation and atrial fibrillation or ventricular tachycardia. In this regard, it is important to include young competitive athletes in a regular medical screening program, with regular echocardiographic examinations, to better understand the course of cardiac adaptations, factors leading to structural and functional cardiac adaptations, and to detected potential adverse adaptations at an early point in time.

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# 9 ATTACHMENTS

## 9.1 REPRINT PERMISSION REVIEWS IN CARDIOVASCULAR MEDICINE: CARDIAC STRUCTURE AND FUNCTION IN JUNIOR ATHLETES: A SYSTEMATIC REVIEW OF ECHOCARDIOGRAPHIC STUDIES



## 9.2 REPRINT PERMISSION FRONTIERS IN CARDIOVASCULAR MEDICINE: TRAINING INTENSITY INFLUENCES LEFT VENTRICULAR DIMENSIONS IN YOUNG COMPETITIVE ATHLETES

## 9.3 Supplementary Information Reviews in Cardiovascular Medicine: cardiac structure and function in junior athletes: a systematic review of echocardiographic studies

**Supplementary Table S1** Risk of bias assessment for methods.

| Risk of bias assessment: methods | | Beaumont et al. (2019) | Binnetolgu et al. (2017) | D'Ascenzi et al. (2017) | D'Ascenzi et al. (2016) | Rundqvist et al. (2016) | Simsek et al. (2013) | Sulovic et al. (2017) | Zdravkovic et al. (2010) | Summary |
|---|---|---|---|---|---|---|---|---|---|---|
| **Criterion** | | | | | | | | | | |
| **Selection bias** | Were cases and controls selected appropriately (e.g., appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status) | x | x | x | x | x | x | | x | 87.5% |
| | Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches? | | | x | x | | | | x | 37.5% |
| **Performance bias** | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? | | | | | | | | | 0% |
| | Did the study maintain fidelity to the intervention protocol? | x | x | x | x | x | x | x | x | 100% |
| **Attrition bias** | If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)? | | | | | | | | | 0% |

**Supplementary Table S1 (continued)** Risk of bias assessment for methods.

| **Risk of bias assessment: methods** | | Beaumont et al. (2019) | Binnetolgu et al. (2017) | D'Ascenzi et al. (2017) | D'Ascenzi et al. (2016) | Rundqvist et al. (2016) | Simsek et al. (2013) | Sulovic et al. (2017) | Zdravkovic et al. (2010) | Summary |
|---|---|---|---|---|---|---|---|---|---|---|
| **Criterion** | | | | | | | | | | |
| **Detection bias** | In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls? | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **100%** |
| | Were the outcome assessors blinded to the intervention or exposure status of participants? | | | | | | | | **x** | **12.5%** |
| | Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants? | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **100%** |
| | Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants? | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **100%** |
| | Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? | **x** | **x** | **x** | **x** | | | **x** | **x** | **75%** |
| **Reporting bias** | Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **x** | **100%** |

**Supplementary Table S2** Risk of bias assessment for methods.

**Risk of bias assessment: results**

| | Criterion 1 | Criterion 2 | Criterion 3 | Criterion 4 | Criterion 5 | Criterion 6 | Criterion 7 | Criterion 8 | Criterion 9 | Criterion 10 | Criterion 11 | Criterion 12 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Athletes details specified | Assessment of athletes fitness level ($VO_{2max}$) | Non-active controls[a] | Age-matched controls | Puberty status | Non-significant anthropometric differences in athletes vs. controls | Non-significant physiologic differences[b] in athletes vs. controls | Measurements performed according to standardized guidelines | One observer performing all measurements / Interobserver reliability | Statistical methods explained in detail | No missing data, all p-values given | No inconsistent/ incorrect data[c] | Total (%) |
| Beaumont et al. 2019 | x | | x | | x | x | x | x | | x | x | x | 9 (75%) |
| Binnetoglu et al. 2017 | x | | x | | | | | x | | x | x | x | 6 (50%) |
| D'Ascenzi et al. 2017 | x | | x | x | x | x | | x | x | x | x | x | 10 (84%) |
| D'Ascenzi et al. 2016 | x | | x | x | x | x | | x | x | x | x | x | 10 (84%) |
| Rundqvist et al. 2016 | x | x | x | x | | x | x | x | x | x | x | x | 11 (92%) |
| Simsek et al. 2013 | x | | x | x | | x | x | x | x | x | x | x | 10 (84%) |
| Sulovic et al. 2017 | x | | x | x | | | | x | | x | x | x | 7 (59%) |
| Zdravkovic et al. 2010 | x | | x | x | | | | x | x | x | x | x | 8 (67%) |

[a] Non-active controls are defined by not participating in organized physical activity/ exercise training of > 3 h/week.

[b] Physiologic differences reffering to blood pressure.

[c] For any data in question, the authors were contacted and asked for clarification. If there was no answer or the data in quesiton could not be clarified, 0 P were assigned. If data could be clarified, x = 1 P was assigned.

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**Supplementary Table S3** Study quality assessment.

| | Beaumont 2019 | | | Binnetoglu 2017 | | | D'Ascenzi 2017 | | | D'Ascenzi 2016 | | | Rundqvist 2016 | | | Simsek 2013 | | | Sulovic 2017 | | | Zdravkovic 2010 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X |
| Was the research question or objective in this paper clearly stated and appropriate? | x | | | x | | | x | | | x | | | x | | | x | | | x | | | x | | |
| Was the study population clearly specified and defined? | x | | | x | | | x | | | x | | | x | | | x | | | x | | | x | | |
| Did the authors include a sample size justification? | | x | | | x | | | x | | | x | | | x | | | x | | | x | | x | | |
| Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? | x | | | | | NR | x | | | x | | | x | | NR | | | NR | | | NR | | | NR |
| Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? | x | | | x | | | x | | | x | | | x | | | | x | | | x | | x | | |
| Were the cases clearly defined and differentiated from controls? | x | | | x | | | x | | | x | | | x | | | x | | | x | | | x | | |
| If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? | x | | | | | NA | x | | | x | | | | | NA | | | NA | | | NA | | | NA |
| Was there use of concurrent controls? | x | | | | | NR | | | NR | | | NR | | | NR | | | NR | | | NR | | | NR |

**Supplementary Table S3 (continued)** Study quality assessment.

| | Beaumont 2019 | | | Binnetoglu 2017 | | | D'Ascenzi 2017 | | | D'Ascenzi 2016 | | | Rundqvist 2016 | | | Simsek 2013 | | | Sulovic 2017 | | | Zdravkovic 2010 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X | Y | N | X |
| Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? | x | | | x | | | x | | | x | | | x | | | x | | | x | | | x | | |
| Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? | x | | | x | | | x | | | x | | | x | | | x | | | x | | | x | | |
| Were the assessors of exposure/risk blinded to the case or control status of participants? | | | NR | | | NR | | x | | | x | | | | NR | | x | | | | | NR | x | | |
| Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? | | x | | | x | | x | | | x | | | x | | | | x | | | | x | | | x | |
| Quality Rating (Good, Fair, or Poor) | GOOD | | | FAIR | | | GOOD | | | GOOD | | | GOOD | | | POOR[a] | | | POOR[b] | | | GOOD | | |

* CD - cannot determine. NA - not applicable. NR - not reported.
[a] No evaluation of physical activity behaviour in controls; no sample size calculation; weak statistics, no covariance analysis.
[b] Insufficient description of recruitment of controls; no evaluation of physical activity behaviour in athletes and controls; no application of inclusion criteria for controls; no sample size calculation weak statistics, no covariance analysis.

**Supplementary Table S4** Study characteristics.

| Author | Athletes | Mitchell Classification | 4-Step-Classification | Sex [m/f] | Age [years] | Athletes' training profile | Controls | Sex [m/f] | Age [years] | Controls' profile | Pubertal status | 2D Echo | 2D STE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Beaumont et al. 2019 | n = 22 soccer | IC | Mixed | 22 / 0 | 12.0±0.3 | 4.5±1.5 years<br>11±1 months/year<br>4±1 sessions/week<br>9.4±2.4 h/week<br>1 match/week | n = 22 | 22 / 0 | 11.7±0.3 | 1.53±1.77 h/week Recreational physical activity | Maturity offset | ASE/ EAVCI Recommendations, Lang 2015 | 40-90 frames/s measurement at endocardial border EchoPac, GE Healthcare |
| Binnetoglu et al. 2013 | n = 25 basketball<br>n = 31 soccer<br>n = 45 swimming<br>n = 16 tennis<br>n = 23 wresting | IIC<br>IC<br>IIC<br>IC<br>IIIB | Mixed<br>Mixed<br>Endurance<br>Mixed<br>Power | 25 / 0<br>31 / 0<br>19 / 26<br>9 / 7<br>23 / 0 | 16.2±1.1<br>15.1±1.1<br>12.9±1.6<br>12.2±0.8<br>15.5±1.5 | Minimum: 2 years<br>Minimum: 3 h/week | n = 25 | 18 / 7 | 14.7±1.5 | Sedentary | Not mentioned | ASE/ EAVCI Recommendations, Lang 2015 | 60-90 frames/s measurement at endocardial border EchoPac, GE Healthcare<br>ASE/ EAE Recommendations, Lang 2005 |
| D'Ascenzi et al. 2017* | n = 57 swimming | IIC | Endurance | 57 / 0 | 10.8±0.2 | 5-6 sessions/week<br>105-135 min/session | n = 37 | 37 / 0 | 10.2±0.2 | <2h/day Recreational physical activity | Tanner's stages | ASE/ EACVI/ EAE Recommendations, Lang 2015/ Lai 2010 | 60-90 frames/s measurement at endocardial border EchoPac, GE Healthcare Recommendations, Mor-Avi 2011 |
| D'Ascenzi et al. 2016* | n = 57 swimming | IIC | Endurance | 57 / 0 | 10.8±0.2 | 5-6 sessions/week<br>105-135 min/session | n = 37 | 37 / 0 | 10.2±0.2 | <2h/day Recreational physical activity | Tanner's stages | ASE/ EACVI/ EAE Recommendations, Lang 2015/ Lai 2010 | 60-80 frames/s measurement at endocardial border EchoPac, GE Healthcare Recommendations, Mor-Avi 2011 |
| Rundqvist et al. 2016 | n = 27 endurance | IIC/ IIIC | Endurance | 16 / 11 | 15.5 (13 - 19) | Minimum: 2 years<br>Minimum: 5x30 min/week | n = 27 | 16 / 11 | 15.4 (13 -19) | No regular exercise | Not mentioned | ASE/ EAVCI Recommendations, Lang 2015 | >40 frames/s measurement at endocardial border EchoPac, GE Healthcare |

**Supplementary Table S4 (continued)** Study characteristics.

| Author | Athletes | Mitchell Classification | 4-Step-Classification | Sex [m/f] | Age [years] | Athletes' training profile | Controls | Sex [m/f] | Age [years] | Controls' profile | Pubertal status | 2D Echo | 2D STE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Simsek et al. 2013 | n = 24 wrestling<br>n = 22 marathon | IIIB<br>IIC | Power<br>Endurance | 24 / 0<br>22 / 0 | 16.8±1.9<br>17.5±2.2 | Minimum: 2 years<br>>15 h/week | n = 20 | 20 / 0 | 16.4±1.8 | Sedentary/ no sports activities | Not mentioned | ASE/ EAE Recommendations, Lang 2005 | 60-100 frames/s measurement at endocardial border EchoPac, GE Healthcare |
| Sulovic et al. 2017 | n = 100 dynamic<br>n = 100 static | IC/ IIC<br>IIIA | Endurance<br>Power | 100 / 0<br>100 / 0 | 15.0±1.0<br>15.4±1.6 | Minimum: 2 years<br>5-7 sessions/week<br>Dynamic: 4.1±1.2 years<br>Static: 3.9±1.0 years | n = 100 | 100 / 0 | 15.2±1.6 | No competitive sports | Not mentioned | Devereux 1986 | 2D STE was not assessed |
| Zdravkovic et al. 2010 | n = 94 soccer | IC | Endurance | 94 / 0 | 12.85±0.84 | 4.6±1.2 years | n = 47 | 47 / 0 | 12.85±0.86 | <2h/week physical activity | Not mentioned | ASE/ EAE Recommendations, Lang 2005 | 2D STE was not assessed |

* D'Ascenzi 2017 and D'Ascenzi 2016 report data on the same study collective, but different parameters.

Overview of studies, involved in this review. Information is given on the study collective, if 2D echocardiography and/ or 2D speckle tracking analysis was applied and according to which recommendations.

**Supplementary Table S5** Anthropometric data of study participants.

| Author | Beaumont et al. 2019 | | Binnetoglu et al. 2013 | | | | | | D'Ascenzi et al. 2017 | | D'Ascenzi et al. 2016 | | Rundqvist et al. 2016 | | Simsek et al. 2013 | | | Sulovic et al. 2017 | | | Zdravkovic et al. 2010 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Athletes | CG | Athletes | | | | | CG | Athletes | CG | Athletes | CG | Athletes | CG | Athletes | | CG | Athletes | | CG | Athletes | CG |
| Sports | Soccer | | Basketball | Soccer | Swimmer | Wrestling | Tennis | | Swimmer | | Swimmer | | Endurance | | Running | Wrestling | | Dynamic | Static | | Soccer | |
| Sex [m / f] | 22 / 0 | 22 / 0 | 25 / 0 | 31 / 0 | 19 / 26 | 23 / 0 | 9 / 7 | 18 / 7 | 57 / 0 | 37 / 0 | 57 / 0 | 37 / 0 | 16 / 11 | 16 / 11 | 22 / 0 | 24 / 0 | 20 / 0 | 100 / 0 | 100 / 0 | 100 / 0 | 94 / 0 | 47 / 0 |
| Age [years] | 12.0 ±0.3 | 11.7 ±0.3 | 16.2 ±1.1 | 15.1 ±1.1 | 12.9 ±1.6 | 15.5 ±1.5 | 12.2 ±0.8 | 14.7 ±1.5 | 10.8 ±0.2 | 10.2 ±0.2 | 10.8 ±0.2 | 10.2 ±0.2 | 15.5 (13-19) | 15.4 (13-19) | 17.5 ±2.2 | 16.8 ±1.9 | 16.4 ±1.8 | 15.0 ±1.5 | 15.4 ±1.6 | 15.2 ±1.6 | 12.85 ±0.84 | 12.85 ±0.86 |
| Height [cm] | 151 ±6 | 149 ±7 | 179.2 ±8.7 | 168.8 ±6.2 | 154.6 ±10.6 | 163.2 ±9.3 | 157.5 ±9.9 | 161.8 ±15.4 | 146.3 ±10.9 | 142.2 ±8.3 | 146.3 ±10.9 | 142.2 ±8.3 | n.m. | n.m. | 170 ±5.1 | 164.9 ±6.5 | 166.8 ±7.1 | 169.5 ±7.8 | 167.1 ±10.0 | 166.8 ±13.0 | 159 ±11 | 163 ±13 |
| Body Mass [kg] | 40.2 ±5.8 | 44.0 ±11.7 | 72 ±11.4 | 59.8 ±7.11 | 47 ±10.7 | 59.1 ±13.5 | 47.4 ±9.3 | 56.6 ±12.2 | 41.4 ±9.9 | 41.5 ±12.0 | 41.4 ±9.9 | 41.5 ±12.0 | n.m. | n.m. | 63.8 ±5.3 | 68.8 ±5.6 | 66.4 ±5.7 | 59.7 ±7.6 | 60.9 ±10.5 | 59.2 ±10.2 | 48.3 ±10.6 | 58.3 ±13 |
| SBP [mmHg] | 100 ±8 | 105 ±13 | 119.4 ±10.4 | 112.6 ±8.6 | 109.6 ±10.1 | 115.7 ±8.2 | 109 ±8 | 113 ±9.2 | 109 ±10 | 104 ±12 | 109 ±10 | 104 ±12 | 120 (95-155) | 115 (105-130) | 105.9 ±12 | 113.5 ±14 | 115.6 ±10 | 115.8 ±7.4 | 119.1 ±7.6 | 117.1 ±7.0 | 110 ±8 | 108 ±7 |
| DBP [mmHg] | 61 ±9 | 61 ±10 | 63.4 ±7.3 | 63.3 ±9.1 | 60.4 ±5.4 | 61.3 ±7.7 | 64.9 ±12 | 64.1 ±9.5 | 70 ±7 | 66 ±8 | 70 ±7 | 66 ±8 | 65 (55-80) | 65 (50-85) | 67.5 ±7.5 | 71 ±4.5 | 70.5 ±6.0 | 69.9 ±5.9 | 72.4 ±9.0 | 68.4 ±0 | 66 ±8 | 61 ±6 |
| HR [bpm] | 65 ±8 | 74 ±10 | 72.7 ±13.5 | 74.5 ±15.4 | 77.6 ±15.1 | 72.7 ±13.3 | 85.3 ±11.6 | 74.6 ±10.5 | 72 ±9 | 77 ±12 | 72 ±9 | 77 ±12 | 63 (42-85) | 71 (49-88) | 51.5 ±8.3 | 55.8 ±10.5 | 65.5 ±15.4 | 55.58 ±5.88 | 54.54 ±6.69 | 73.37 ±6.83 | n.m. | n.m. |
| BSA [$m^2$] | n.m. | n.m. | 1.8 ±0.2 | 1.6 ±0.1 | 1.41 ±0.2 | 1.6 ±0.2 | 1.43 ±0.2 | 1.5 ±0.2 | 1.29 ±0.20 | 1.27 ±0.20 | 1.29 ±0.20 | 1.27 ±0.20 | 1.66 (1.37-1.98) | 1.72 (1.26-2.23) | n.m. | n.m. | n.m. | 1.7 ±0.1 | 1.7 ±0.2 | 1.7 ±0.2 | 1.45 ±0.2 | 1.61 ±0.24 |
| BMI [$kg/m^2$] | n.m. | n.m. | 22.5 ±2.6 | 20.9 ±1.42 | 19.4 ±2.53 | 21.9 ±3.28 | 18.9 ±2.3 | 21.8 ±6.1 | n.m. | n.m. | n.m. | n.m. | n.m. | n.m. | 22.7 ±2.1 | 25.41 ±2.2 | 24.5 ±1.9 | 20.4 ±1.8 | 21.6 ±2.0 | 21.2 ±1.4 | 18.75 ±1.92 | 21.59 ±1.86 |

**Supplementary Table S6** Left ventricular structural parameters assessed with 2D transthoracic echocardiography.

| | Beaumont et al. 2019 | | | Binnetoglu et al. 2013 | | | | | | | Rundqvist et al. 2016 | | | Simsek et al. 2013 | | | | Sulovic et al. 2017 | | | | Zdravkovic et al. 2010 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | athletes | CG | | athletes | | | | | CG | | athletes | CG | | athletes | | CG | | athletes | | CG | | athletes | CG | |
| **Left ventricular structure** | n = 22 [22 / 0] Soccer | n = 22 [22 / 0] | p | n = 25 [25 / 0] Basketball | n = 31 [31 / 0] Soccer | n = 45 [19 / 26] Swimming | n = 23 [23 / 0] Wrestling | n = 16 [9 / 7] Tennis | n = 25 [25 / 0] | p | n = 27 [16 / 11] Endurance | n = 27 [16 / 11] | p | n = 22 [22 / 0] Running | n = 24 [24 / 0] Wrestling | n = 20 [22 / 0] | p | n = 100 [100 / 0] Dynamic | n = 100 [100 / 0] Static | n = 100 [100 / 0] | p | n = 94 [94 / 0] Soccer | n = 47 [47 / 0] | p |
| LVEDD [mm] | 42±4 | 44±4 | 0.142 | **48.6±4.5** | **48.7±3.8** | **44.2±7.5** | **49.1±3.5**[f] | **43.9±3.5** | **47.1±4.6** | **<.001** | | | | **52.1±4.4**[a] | **47.2±6.2** | **46.7±4.7** | **0.01** | **49.8±3.3**[a] | **46.3±5.4**[b] | **45.0±2.8** | **<0.05** | **46.58±3.91** | **45.12±2.95** | **<0.05** |
| LVEDD index [mm/m$^2$] | | | | **25.8±2.7**[a] | **29.2±2.8** | **31.61±6.7** | **30.5±4.02** | **30.9±3.8** | **29.9±2.6** | **<.001** | **29 (26-37)** | **26 (22-37)** | **<0.001** | | | | | | | | | | | |
| LVEDD index [mm/(m$^2$)$^{0.5}$] | 37±3 | 38±3 | 0.343 | | | | | | | | | | | | | | | | | | | **38.72±2.53** | **35.68±2.54** | **<0.001** |
| LVESD [mm] | 28±3 | 29±3 | 0.403 | | | | | | | | | | | **32.4±3.7**[a] | **29.2±5.7** | **29.3±4.3** | **0.047** | **31.6±3.0**[a] | **26.6±3.4**[c] | **28.0±2.9** | **<0.05** | **31.09±3.61** | **26.28±3.05** | **<0.001** |
| LVESD index [mm/m$^2$] | | | | **16.7±2**[b] | **18.87±2.1** | **19.6±3.5** | **19.3±2.9** | **19.6±2.4** | **18.7±2.9** | **0.002** | | | | | | | | | | | | | | |
| LVESD index [mm/(m$^2$)$^{0.5}$] | 25±3 | 25±2 | 0.725 | | | | | | | | | | | | | | | | | | | **25.83±2.58** | **20.75±2.30** | **<0.001** |
| IVS [mm] | | | | **9.4±1.4** | **9.6±1.5**[c] | **9.2±1.4** | **9±1.3** | **7.6±1.2** | **7.5±0.9** | **<.001** | | | | **9.5±1.1** | **11.3±1.2**[b] | **9.4±1.3** | **<0.001** | **9.0±1.2** | **9.1±1.7**[c] | **7.3±1.1** | **<0.05** | **8.51±0.99** | **8.27±1.06** | **<0.001** |
| IVS index [mm/m$^2$] | | | | **5±7.7** | **5.8±0.97** | **6.6±1.2**[d] | **5.6±0.7** | **5.3±0.9** | **4.8±0.8** | **<.001** | **3.7 (2.9-4.8)** | **3.1 (2.5-4.9)** | **<0.001** | | | | | | | | | | | |
| IVS index [mm/(m$^2$)$^{0.5}$] | | | | | | | | | | | | | | | | | | | | | | **7.08±0.70** | **6.53±0.81** | **<0.001** |
| LVWT [mm] | | | | | | | | | | | | | | | | | | | | | | 16.71±1.50 | 16.47±2.05 | n.s. |
| LVWT index [mm/(m$^2$)$^{0.5}$] | | | | | | | | | | | | | | | | | | | | | | **13.09±1.19** | **13.00±1.51** | **<0.001** |
| LVPWT [mm] | | | | | | | | | | | | | | **10.2±0.9**[a] | **11.1±1.1**[b] | **9.4±0.9** | **<0.001** | **8.6±1.0** | **8.9±1.6**[c] | **7.0±1.1** | **<0.05** | 8.19±0.77 | 8.19±1.11 | n.s. |
| LVPWT index [mm/m$^2$] | | | | **5.2±0.6** | **5.7±1.12** | **6.6±1.2**[e] | **5.5±0.8** | **5.3±1.2** | **4.9±0.7** | **<.001** | **4.5 (3.8-6.7)** | **4.0 (3.2-4.9)** | **<0.001** | | | | | | | | | | | |
| LVPWT index [mm/(m$^2$)$^{0.5}$] | | | | | | | | | | | | | | | | | | | | | | **6.82±0.73** | **6.46±0.80** | **<0.001** |
| MWT [mm] | 6.0±0.4 | 6.1±0.5 | 0.754 | | | | | | | | | | | | | | | | | | | | | |
| MWT index [mm/(m$^2$)$^{0.5}$] | 5.3±0.4 | 5.3±0.5 | 0.769 | | | | | | | | | | | | | | | | | | | | | |
| RWT | 0.29±0.04 | 0.28±0.04 | 0.387 | | | | | | | | | | | | | | | **0.35±0.01**[a] | **0.43±0.01**[c] | **0.30±0.01** | **<0.05** | 0.36±0.04 | 0.36±0.04 | n.s. |
| LVM [g] | 75±14 | 82±18 | 0.204 | | | | | | | | | | | **202±24** | **208±30** | **155±28**[c] | **0.001** | **154.6±35.2** | **148.1±57.0**[c] | **99.7±28.4** | **<0.05** | 160.14±33.14 | 149.49±34.01 | n.s. |
| LVM index [g/m$^2$] | | | | **86.9±15.1** | **94.9±15.1**[c] | **91.6±16.6** | **94.4±14** | **74±16.7** | **76.8±15.7** | **<.001** | **67 (48-100)** | **45 (37-73)** | **<0.001** | **115±15**[a] | **119±18** | **88±14**[c] | **0.001** | | | | | **109.79±15.04** | **92.84±18.29** | **<0.001** |
| LVM index [g/(m$^2$)$^{1.5}$] | | | | | | | | | | | | | | | | | | | | | | **91.55±13.86** | **73.73±16.54** | **<0.001** |
| LVM index [g/m$^{2.7}$] | 25±5 | 28±7 | 0.051 | **34.1±7.2** | **38.6±6.8** | **39.8±7.1** | **40.9±7.4**[g] | **31.4±8.2** | **34.2±11.9** | **<.001** | | | | | | | | **36.9±7.3**[a] | **41.6±11.7**[c] | **24.8±5.0** | **<0.05** | | | |
| LV length [mm] | 76±6 | 74±5 | 0.316 | | | | | | | | | | | | | | | | | | | | | |
| LV length index [mm/(m$^2$)$^{0.5}$] | 67±5 | 64±5 | 0.14 | | | | | | | | | | | | | | | | | | | | | |
| LVEDV [ml] | 75±10 | 69±15 | 0.106 | | | | | | | | | | | **138±39**[a] | **121±32** | **116±34** | **0.016** | | | | | | | |
| LVEDV index [ml/m$^2$] | | | | | | | | | | | **60 (50-80)** | **50 (38-72)** | **<0.001** | | | | | | | | | | | |
| LVEDV index [ml/(m$^2$)$^{1.5}$] | **51±8** | **45±6** | **0.007** | | | | | | | | | | | | | | | | | | | | | |
| LVESV [ml] | 26±4 | 26±8 | 0.696 | | | | | | | | | | | **45±21**[a] | **40±22** | **41±20** | **0.045** | | | | | | | |
| LVESV index [ml/m$^2$] | | | | | | | | | | | **24 (18-31)** | **20 (15-29)** | **0.002** | | | | | | | | | | | |
| LVESV index [ml/(m$^2$)$^{1.5}$] | 18±2 | 17±3 | 0.625 | | | | | | | | | | | | | | | | | | | | | |

[a] p < 0.001 vs. swimming; p = 0.004 vs. wrestling; p = 0.006 vs. tennis; p = 0.02 vs. control
[b] p = 0.001 vs. swimming; p = 0.024 vs. wrestling; p = 0.022 vs. tennis
[c] p < 0.001 vs. tennis and control
[d] p < 0.001 vs. basketball, tennis, and control; p = 0.003 vs. soccer; p = 0.001 vs. wrestling
[e] p < 0.001 vs. basketball, tennis, and control; p = 0.001 vs. wrestling; p = 0.006 vs. soccer
[f] p = 0.007 vs. swimming; p = 0.026 vs. tennis
[g] p = 0.006 vs. tennis

[a] p < 0.05 vs. wrestling; p < 0.05 vs. controls
[b] p < 0.05 vs. running; p < 0.05 vs. controls
[c] p < 0.05 vs. running; p < 0.05 vs. wrestling

[a] p = 0.001 vs. static and controls
[b] p = 0.044 vs. controls
[c] p = 0.001 vs. controls

Parameter of left ventricular structure assessed in 6 studies. Parameters are displayed in mean values ± standard deviation and median with range in parentheses (Rundqvist et al.), respectively. LVDD = left ventricular end-diastolic diameter. LVDD index = LVDD/ BSA. LVDS = left ventricular end-systolic diameter. LVDS index = LVDS/ BSA. IVSD = interventricular septal thickness in diastole. IVSD index = IVSD/ BSA. LVWT = left ventricular wall thickness. LVWT index = LVWT/ BSA. LVPWT = left ventricular posterior wall thickness. LVPWT index = LVPWT/ BSA. MWT = mean wall thickness. MWT index = MWT/ BSA. RWT = relative wall thickness. LVM = left ventricular mass. LVM index = LVM/ BSA. LV length = left ventricular length. LV length index = LV length/ BSA. LVEDV = left ventricular enddiastolic volume. LVEDV index = LVEDV/ BSA. LVESV = left ventricular endsystolic volume. LVESV index = LVESV/ BSA.

**Supplementary Table S7** Left ventricular functional parameters assessed with 2D transthoracic echocardiography.

| | Beaumont et al. 2019 | | | Binnetoglu et al. 2013 | | | | | | | Rundqvist et al. 2016 | | | Simsek et al. 2013 | | | | Sulovic et al. 2017 | | | | Zdravkovic et al. 2010 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Left ventricular function** | **athletes** n = 22 [22 / 0] Soccer | **controls** n = 22 [22 / 0] | **p** | n = 25 [25 / 0] Basketball | n = 31 [31 / 0] Soccer | **athletes** n = 45 [19 / 26] Swimming | n = 23 [23 / 0] Wrestling | n = 16 [9 / 7] Tennis | **CG** n = 25 [25 / 0] | **p** | **athletes** n = 27 [16 / 11] Endurance | **CG** n = 27 [16 / 11] | **p** | **athletes** n = 22 [22 / 0] Running | n = 24 [24 / 0] Wrestling | **CG** n = 20 [22 / 0] | **p** | **athletes** n = 100 [100 / 0] Dynamic | n = 100 [100 / 0] Static | **CG** n = 100 [100 / 0] | **p** | **athletes** n = 94 [94 / 0] Soccer | **CG** n = 47 [47 / 0] | **p** |
| Tei Index | | | | **0.37±0.08** | **0.44±0.07** | **0.41±0.06** | **0.43±0.07** | **0.50±0.06**[a] | **0.45±0.10** | **<.001** | | | | | | | | | | | | | | |
| Concentricity [g/ml]$^{1.667}$ | **4.3±0.7** | **4.9±1.0** | **0.017** | | | | | | | | | | | | | | | | | | | | | |
| Sphericity index | **1.8±0.2** | **1.7±0.1** | **0.034** | | | | | | | | | | | | | | | | | | | | | |
| SV [ml] | **49±8** | **43±10** | **0.031** | | | | | | | | | | | **115±32**[a] | **95±29** | **91±26** | **0.038** | | | | | | | |
| SV index [ml/(m$^2$)$^{1.0}$] | **38±6** | **32±5** | **0.002** | | | | | | | | | | | | | | | | | | | | | |
| Q [l/min] | 3.19±0.63 | 3.12±0.67 | 0.741 | | | | | | | | | | | | | | | | | | | | | |
| Cardiac index [l/min/ m$^2$]$^{1.0}$ | 2.48±0.46 | 2.36±0.42 | 0.391 | | | | | | | | | | | | | | | | | | | | | |
| LV EF [%] | | | | 64.6±5.1 | 64.1±4.3 | 67.4±6.1 | 65.2±5.6 | 66±3.8 | 65.9±5.1 | 0.098 | **61 (57-67)** | **59 (54-67)** | **0.036** | 68±5.5 | 68.4±7.2 | 70.1±3.4 | 0.45 | **80.1±7.2**[a] | **74.2±3.9**[d] | **75.6±5.2** | **<0.05** | 68.23±4.36 | 68.49±4.72 | n.s. |
| FS [%] | | | | 35.1±4.2 | 35±3.5 | 37±5.1 | 35.9±4.8 | 36.2±2.9 | 36.3±4 | 0.412 | | | | | | | | | | | | 38.01±3.84 | 38.36±3.95 | n.s. |
| S' [cm/s] | | | | | | | | | | | 7.5 (5.3-9.3) | 7.8 (6.4-11.3) | 0.13 | | | | | | | | | | | |
| MAPSE [cm] | | | | | | | | | | | | | | | | | | | | | | | | |
| MAPSE index [mm/m$^2$] | | | | | | | | | | | 8.3 (6.2-10.7) | 8.4 (5.6-10.8) | 0.574 | | | | | | | | | | | |
| E [cm/s] | | | | **89 ± 11** | **92 ± 16** | **100 ± 13** | **89 ± 15** | **97 ± 13** | **95 ± 16** | **0.026** | 102 (76-125) | 96 (72-117) | 0.08 | 101±18 | 99±16 | 106±25 | 0.497 | **125±10**[b] | **117±13**[d] | **123±10** | **<0.05** | | | |
| A [cm/s] | | | | **53 ± 10** | **52 ± 10** | **52 ± 10** | **47 ± 10**[b] | **56 ± 13** | **60 ± 10** | **0.043** | 42 (31-56) | 43 (30-68) | 0.277 | 56±16 | 57±14 | 65±17 | 0.115 | **93±0.9**[c] | **90±0.9**[d] | **95±0.7** | **<0.05** | | | |
| E/A | | | | 1.7 ± 0.4 | 1.8 ± 0.4 | 1.9 ± 0.4 | 1.9 ± 0.4 | 1.75 ± 0.28 | 1.7 ± 0.4 | 0.06 | **2.5 (1.8-3.6)** | **2.1 (1.3-3.5)** | **0.046** | 1.81±0.15 | 1.74±0.18 | 1.65±0.21 | 0.085 | 1.35±0.11 | 1.33±0.13 | 1.34±0.10 | n.s. | | | |
| DT [ms] | | | | **100.2 ± 11.1** | **102.9 ± 24.7** | **111.7 ± 14.5** | **102.2 ± 14.6** | **136.56 ± 26.39**[c] | **101.8 ± 18.6** | **<0.001** | | | | | | | | | | | | | | |
| E' [cm/s] | | | | 19 ± 3 | 19 ± 3 | 18 ± 2 | 20 ± 3 | 19 ± 3 | 19 ± 3 | 0.255 | 14 (12-18) | 13 (10-15) | 0.452 | | | | | | | | | | | |
| A' [cm/s] | | | | 7 ± 1 | 6 ± 1 | 6 ± 1 | 6 ± 1 | 9 ± 13 | 6 ± 10 | 0.547 | 4.7 (2.5-7.2) | 4.9 (3.2-8.2) | 0.489 | | | | | | | | | | | |
| E/E' | | | | | | | | | | | 7.6 (5.8-9.6) | 7.5 (5.7-9.5) | 0.477 | | | | | | | | | | | |
| E'/A' | | | | 2.67 ± 0.56 | 3.22 ± 0.99 | 2.77 ± 0.61 | 3.14 ± 0.92 | 3.08 ± 0.63 | 2.95 ± 0.93 | 0.06 | | | | | | | | | | | | | | |
| S' septal annulus [cm/s] | | | | | | | | | | | | | | 9.2±1.4 | 9.8±1.2 | 9.4±1.5 | 0.377 | | | | | | | |
| E' septal annulus [cm/s] | | | | | | | | | | | | | | 15.3±2.8 | 14.7±2.5 | 14.3±2.7 | 0.43 | | | | | | | |
| A' septal annulus [cm/s] | | | | | | | | | | | | | | 8.2±2.1 | 9.3±2.7 | 9.4±2.1 | 0.177 | | | | | | | |

**Supplementary Table S7 (continued)** Left ventricular functional parameters assessed with 2D transthoracic echocardiography.

| 4 | Beaumont et al. 2019 | | | Binnetoglu et al. 2013 | | | | | | | Rundqvist et al. 2016 | | | Simsek et al. 2013 | | | | Sulovic et al. 2017 | | | | Zdravkovic et al. 2010 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Left ventricular function** | **athletes** | **controls** | **p** | **athletes** | | | | | **CG** | **p** | **athletes** | **CG** | **p** | **athletes** | | **CG** | **p** | **athletes** | | **CG** | **p** | **athletes** | **CG** | **p** |
| | n = 22 [22 / 0] Soccer | n = 22 [22 / 0] | | n = 25 [25 / 0] Basketball | n = 31 [31 / 0] Soccer | n = 45 [19 / 26] Swimming | n = 23 [23 / 0] Wrestling | n = 16 [9 / 7] Tennis | n = 25 [25 / 0] | | n = 27 [16 / 11] Endurance | n = 27 [16 / 11] | | n = 22 [22 / 0] Running | n = 24 [24 / 0] Wrestling | n = 20 [22 / 0] | | n = 100 [100 / 0] Dynamic | n = 100 [100 / 0] Static | n = 100 [100 / 0] | | n = 94 [94 / 0] Soccer | n = 47 [47 / 0] | |
| S' lateral annulus [cm/s] | | | | | | | | | | | | | | **8.8±2.3[a]** | **10.4±1.8** | **9.9±2.1** | **0.045** | | | | | | | |
| E' lateral annulus [cm/s] | | | | | | | | | | | | | | 17.7±5.1 | 17.1±3.8 | 18.2±3.1 | 0.685 | | | | | | | |
| A' lateral annulus [cm/s] | | | | | | | | | | | | | | 7.8±2.3 | 8.5±3.4 | 8.6±2.4 | 0.56 | | | | | | | |
| | | | | [a] p < 0.001 vs. basketball and swimming<br>[b] p = 0.037 vs. control<br>[c] p < 0.001 vs. basketball, soccer, swimming, wrestling, and controls | | | | | | | | | | [a] p < 0.05 vs. wrestling and controls | | | | [a] p = 0.001 vs. static; p = 0.036 vs. controls<br>[b] p = 0.001 vs. static<br>[c] p = 0.004 vs. static<br>[d] p = 0.001 vs. controls | | | | | | |

Parameters of left ventricular function assessed in 6 studies. Parameters are displayed in mean values ± standard deviation and median with range in parentheses (Rundqvist et al.), respectively. Tei Index = left ventricular index of myocardial performance. SV = stroke volume. SV index = SV/ BSA. Q = cardiac output. Cardiac index = Q/ BSA. LV EF = left ventricular ejection fraction. FS = fractional shortening. S' = systolic peak velocity at m
annulus plane systolic excursion. MAPSE index = MAPSE/ BSA. E = early diastolic peak velocity. A = late diastolic peak velocity. E/A = E/A ratio. DT = deceleration time. E' = early diastolic peak velocity at mitral valve. A' = late diastolic peak velocity at mitral valve. E/E' = E/E' ratio. E'/A' = E'/A' ratio.

**Supplementary Table S8** Right ventricular structure parameters assessed with 2D transthoracic echocardiography.

| | D'Asecenzi et al. 2017 | | | Rundqvist et al. 2016 | | |
|---|---|---|---|---|---|---|
| **Right ventricular structure** | **athletes** n = 57 [57 / 0] Swimmer | **controls** n = 37 [37 / 0] | **p** | **athletes** n = 27 [16 / 11] Endurance | **controls** n = 27 [16 / 11] | **p** |
| RVOT PLAX [mm] | **23.4±2.3** | **22.3±2.4** | **0.035** | | | |
| RVOT PLAX index [mm/m$^2$] | 18.5±2.7 | 16.8±5.0 | 0.18 | | | |
| RVOT PSAX [mm] | 25.5±4.2 | 24.5±3.2 | 0.23 | | | |
| RVOT PSAX index [mm/m$^2$] | 20.1±3.6 | 19.0±4.2 | 0.95 | **16 (14-23)** | **15 (11-19)** | **0.006** |
| RVOT distal diameter [mm] | **22.2±3.1** | **20.2±2.8** | **0.005** | | | |
| RVOT distal diameter index [mm/m$^2$] | 17.3±3.1 | 16.4±2.0 | 0.15 | | | |
| RV basal diameter [mm] | **31.4±3.2** | **29.5±2.7** | **0.007** | | | |
| RV basal diameter index [mm/m$^2$] | 24.9±4.1 | 23.6±3.0 | 0.15 | **23 (19-28)** | **20 (17-28)** | **<.001** |
| RV mid-cavity diameter [mm] | **29.1±3.3** | **24.5±2.8** | **<0.0001** | | | |
| RV mid-cavity diameter index [mm/m$^2$] | 23.1±4.2 | 19.4±2.7 | 0.07 | | | |
| RV end-diastolic area [cm$^2$] | **14.7±2.8** | **13.8±2.8** | **0.05** | | | |
| RV end-diastolic area index [cm$^2$/m$^2$] | 11.5±1.8 | 10.6±2.3 | 0.12 | **15 (11-21)** | **13 (9-17)** | **<0.001** |
| RV end-systolic area [cm$^2$] | **8.3±1.7** | **7.2±1.9** | **0.002** | | | |
| RV end-systolic area index [cm$^2$/m$^2$] | **6.6±1.5** | **5.5±1.6** | **0.003** | | | |

Parameters of right ventricular structure assessed in 2 studies. Parameters are displayed as mean values ± standard deviation (D'Ascenzi et al.) or as median and range in parentheses (Rundqvist et al.). RVOT = right ventricular outflow tract. PLAX = parasternal long axis. PSAX = parasternal short axis. RV = right ventricle. All indexed values are indexed to BSA.

**Supplementary Table S9** Right ventricular function parameters assessed with 2D transthoracic echocardiography.

| | D'Asecenzi et al. 2017 | | | Rundqvist et al. 2016 | | |
|---|---|---|---|---|---|---|
| **Right ventricular function** | **athletes** n = 57 [57 / 0] Swimmer | **controls** n = 37 [37 / 0] | **p** | **athletes** n = 27 [16 / 11] Endurance | **controls** n = 27 [16 / 11] | **p** |
| TAPSE [cm] | 2.2±0.31 | 2.18±0.26 | 0.63 | | | |
| TAPSE index [mm/m$^2$] | | | | **12 (7–16)** | **10 (8–16)** | **0.008** |
| E/A | 1.6±0.4 | 1.6±0.4 | 0.37 | | | |
| E' [cm/s] | 15.9±3.1 | 18.8±3.2 | 0.32 | 11 (7–16) | 11 (8–15) | 0.697 |
| A' [cm/s] | 9.5±2.3 | 10.4±2.8 | 0.18 | 6.2 (3.4–10.6) | 5.3 (2.3–10.2) | 0.169 |
| E/E' | 4.6±1.4 | 4.2±0.9 | 0.33 | | | |
| E'/A' | 1.8±0.6 | 1.7±0.5 | 0.64 | | | |
| S' [cm/s] | 14.1±2.1 | 14.2±2.4 | 0.75 | **11 (7–15)** | **10 (8–14)** | **0.031** |
| RV FAC [%] | **42.9±7.5** | **48.6±8.2** | **0.007** | 42 (36–49) | 41 (35–48) | 0.119 |

Parameters of right ventricular function assessed in 2 studies. Parameters are displayed as mean values ± standard deviation (D'Ascenzi et al.) or as median and range in parentheses (Rundqvist et al.). TAPSE = tricuspid annulus plane systolic excursion. TAPSE index = TAPSE/ BSA. E/A = early diastolic peak velocity/ late diastolic peak velocity ratio. E' = early diastolic peak velocity at tricuspid valve. A' = late diastolic peak velocity at tricuspid valve. E/E' = E/E' ratio. E'/A' = E'/A' ratio. S' = systolic peak velocity at mitral valve. RV FAC = right ventricular fractional area change.

**Supplementary Table S10** Left atrial structure parameters assessed with 2D transthoracic echocardiography.

| | D'Asecenzi et al. 2016 | | | Rundqvist et al. 2016 | | | Simsek et al. 2013 | | | | Sulovic et al. 2017 | | | | Zdravkovic et al. 2010 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **athletes** | **controls** | | **athletes** | **controls** | | **athletes** | | **controls** | | **athletes** | | **controls** | | **athletes** | **controls** | |
| **Left atrial structure** | n = 57 [57 / 0] Swimmer | n = 37 [37 / 0] | **p** | n = 27 [16 / 11] Endurance | n = 27 [16 / 11] | **p** | n = 22 [22 / 0] Running | n = 24 [24 / 0] Wrestling | n = 20 [22 / 0] | **p** | n = 100 [100 / 0] Dynamic | n = 100 [100 / 0] Static | n = 100 [100 / 0] | **p** | n = 94 [94 / 0] Soccer | n = 47 [47 / 0] | **p** |
| LA diameter [mm] | | | | | | | **31.8±3.6**[a] | **29.6±4.8** | **28.5±4.4** | **0.046** | 30.5±2.4 | 29.4±4.1 | 29.8±3.0 | n.s. | **27.95±3.43** | **25.49±3.57** | **<0.001** |
| LA diameter index [mm/m$^2$] | | | | **21 (17-27)** | **19 (12-25)** | **0.001** | | | | | | | | | **23.18±2.07** | **20.15±2.87** | **<0.001** |
| LA volume index [ml/m$^2$] | 17.2±3.3 | 16.2±2.4 | 0.14 | **27 (21-36)** | **19 (14-31)** | **<0.001** | | | | | | | | | | | |

[a] $p < 0.05$ vs. wrestling and controls

Parameters of left atrial structure assessed in 5 studies. Parameters are displayed as mean values ± standard deviation or as median and range in parentheses (Rundqvist et al.). LA = left atrium. Indexed parameters are indexed to BSA.

**Supplementary Table S11** Right atrial structure parameters assessed with 2D transthoracic echocardiography.

| | D'Asecenzi et al. 2016 | | | Rundqvist et al. 2016 | | |
|---|---|---|---|---|---|---|
| **Right atrial structure** | **athletes** n = 57 [57 / 0] Swimmer | **controls** n = 37 [37 / 0] | **p** | **athletes** n = 27 [16 / 11] Endurance | **controls** n = 27 [16 / 11] | **p** |
| RA area [$cm^2$] | **10.0±2.2** | **9.0±1.4** | **0.022** | | | |
| RA area index [$cm^2/m^2$] | | | | **9.1 (6.6-11.4)** | **7.2 (5.1-8.7)** | **<0.001** |
| RA diameter index [$mm/m^2$] | | | | **23 (17-28)** | **20 (15-27)** | **0.008** |
| RA volume index [$ml/m^2$] | **17.6±3.9** | **15.4±2.9** | **0.007** | | | |

Parameters of right atrial structure assessed in 2 studies. Parameters are displayed as mean values ± standard deviation (D'Ascenzi et al.) or as median and range in parentheses (Rundqvist et al.). RA = right atrium. Indexed parametrs are indexed to BSA.

**Supplementary Table S12** Left ventricular function assessed with 2D speckle tracking echocardiography.

| | **Beaumont et al. 2019** | | | **Binnetoglu et al. 2013** | | | | | | | **Rundqvist et al. 2016** | | | **Simsek et al. 2013** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **athletes** | **CG** | | **athletes** | | | | | **CG** | | **athletes** | **CG** | | **athletes** | | **CG** | |
| **2D STE of the left ventricle** | n = 22 [22 / 0] Soccer | n = 22 [22 / 0] | **p** | n = 25 [25 / 0] Basketball | n = 31 [31 / 0] Soccer | n = 45 [19 / 26] Swimming | n = 23 [23 / 0] Wrestling | n = 16 [9 / 7] Tennis | n = 25 [25 / 0] | **p** | n = 27 [16 / 11] Endurance | n = 27 [16 / 11] | **p** | n = 22 [22 / 0] Running | n = 24 [24 / 0] Wrestling | n = 20 [22 / 0] | **p** |
| Longitudinal strain at 4 chamber view [%] | 20.3±1.6 | 19.6±2.5 | 0.283 | **14.3±3.7[a]** | **17.5±3** | **18.3±2.1** | **17.9±3.3** | **16.5±3.6** | **18.4±2.4** | **<.001** | | | | **21.4±2.6[a]** | **21.7±2[b]** | **17.2±2.3** | **<.001** |
| Longitudinal strain at 2 chamber view [%] | | | | **17.1±2.3[b]** | **20±2.3** | **20±2.5** | **19.1±2.5** | **19.3±2.5** | **18.8±2.8** | **<.001** | | | | **23.3±2.8[a]** | **22.7±2.6[b]** | **19.4±2.7** | **<.001** |
| Longitudinal strain at 3 chamber view [%] | | | | **13.4±3.3[c]** | **16.1±2.6** | **16.4±2.5** | **17.5±3** | **16.5±3.5** | **17.9±2.7** | **<.001** | | | | **22.2±2.9[a]** | **21.1±2.2[b]** | **19.1±2.1** | **<.001** |
| Global longitudinal strain [%] | | | | **14.9±2.6[c]** | **17.8±1.9** | **18.2±1.8** | **18.6±2.4** | **17.4±2.4** | **18.4±2.2** | **<.001** | 22 (19-25) | 21 (19-27) | 0.802 | **22.3±2.2[a]** | **21.8±1.7[b]** | **18.5±2.4** | **<.001** |
| Circumferential strain at MV base [%] | **22.2±2.5** | **20.2±2.5** | **0.029** | | | | | | | | | | | | | | |
| Radial strain at MV base [%] | 38.3±13.7 | 33.7±15.4 | 0.304 | | | | | | | | | | | | | | |
| Circumferential strain at papillary muscle [%] | **20.1±1.5** | **18.3±2.5** | **0.007** | **11.8±3.3** | **14.2±3.2** | **13.8±3** | **13.4±3.2** | **12±3.7** | **12.9±3.1** | **0.041** | | | | | | | |
| Radial strain at papillary muscle [%] | 61.6±15.8 | 62.2±20.9 | 0.918 | 31.8±14.9 | 42.4±16.2 | 37.9±14 | 40.7±18.17 | 34.6±21 | 41.9±14.1 | 0.110 | | | | | | | |

**Supplementary Table S12 (continued)** Left ventricular function assessed with 2D speckle tracking echocardiography.

| | **Beaumont et al. 2019** | | | **Binnetoglu et al. 2013** | | | | | | | **Rundqvist et al. 2016** | | | **Simsek et al. 2013** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **athletes** | **CG** | | **athletes** | | | | | **CG** | | **athletes** | **CG** | | **athletes** | | **CG** | |
| **2D STE of the left ventricle** | n = 22<br>[22 / 0]<br>Soccer | n = 22<br>[22 / 0] | **p** | n = 25<br>[25 / 0]<br>Basketball | n = 31<br>[31 / 0]<br>Soccer | n = 45<br>[19 / 26]<br>Swimming | n = 23<br>[23 / 0]<br>Wrestling | n = 16<br>[9 / 7]<br>Tennis | n = 25<br>[25 / 0] | **p** | n = 27<br>[16 / 11]<br>Endurance | n = 27<br>[16 / 11] | **p** | n = 22<br>[22 / 0]<br>Running | n = 24<br>[24 / 0]<br>Wrestling | n = 20<br>[22 / 0] | **p** |
| Apical rotation [°] | **11.95±5.31** | **7.58±3.55** | **0.005** | | | | | | | | | | | | | | |
| Basal rotation [°] | 5.69±3.14 | 5.64±2.65 | 0.959 | | | | | | | | | | | | | | |
| Twist [°] | **16.92±7.55** | **12.34±4.99** | **0.035** | | | | | | | | | | | | | | |
| | | | | [a] p < 0.001 vs. soccer, swimming, wrestling and controls<br>[b] p < 0.001vs. soccer and swimming<br>[c] p < 0.001vs. soccer, swimming, wrestling, tennis and controls | | | | | | | | | | [a] p < 0.05 vs. controls<br>[b] p < 0.05 vs. controls | | | |

Overview of 2D STE parameters of the left ventricle in 4 studies. Parameters are displayed as mean values ± standard deviation or as median and range in parentheses (Rundqvist et al.), respectively.

**Supplementary Table S13** Right ventricular function, left and right atrial function assessed with 2D speckle tracking echocardiography.

| | D'Asecenzi et al. 2017 | | | D'Asecenzi et al. 2016 | | | Rundqvist et al. 2016 | | |
|---|---|---|---|---|---|---|---|---|---|
| **2D STE of the right ventricle, right and left atrium** | **athletes** n = 57 [57 / 0] Swimmer | **controls** n = 37 [37 / 0] | **p** | **athletes** n = 57 [57 / 0] Swimmer | **controls** n = 37 [37 / 0] | **p** | **athletes** n = 27 [16 / 11] Endurance | **controls** n = 27 [16 / 11] | **p** |
| Longitudinal strain RV at 4 chamber view [%] | 29.2±5.8 | 31.6±7.0 | 0.063 | | | | 27 (19-34) | 28 (19-33) | 0.25 |
| L-PALS [%] | | | | 61.1±10.2 | 64.2±6.8 | 0.15 | | | |
| L-PACS [%] | | | | 16.4±4.8 | 15.5±4.1 | 0.41 | | | |
| LA total strain [%] | | | | | | | 39 (31-53) | 38 (28-52) | 0.873 |
| R-PALS [%] | | | | 53.1±11.7 | 58.2±12.6 | 0.071 | | | |
| R-PACS [%] | | | | 16.9±4.6 | 11.8±6.2 | 0.58 | | | |

Overview of 4 studies reporting 2D speckle tracking echocardiography parameters of the right ventricle. Parameters are displayed in mean values ± standard deviation (D'Ascenzi et al.) and median with range in parentheses (Rundqvist et al.), respectively. L-PALS = left peak atrial longitudinal strain. L-PACS = left peak atrial contraction strain. R-PALS = right peak atrial longitudinal strain. R-PACS = right peak atrial contraction strain.

## 9.4 SUPPLEMENTARY INFORMATION FRONTIERS IN CARDIOVASCULAR MEDICINE: TRAINING INTENSITY INFLUENCES LEFT VENTRICULAR DIMENSIONS IN YOUNG COMPETITIVE ATHLETES

**Supplementary Table S34** Types of different sports that are represented in the MuCAYA-Study.

| **Main type of sports** | **all** | | **males** | | **females** | |
|---|---|---|---|---|---|---|
| | **n = 404** | **%** | **n = 307** | **%** | **n = 97** | **%** |
| American Football | | | | | | |
| Athletic training | 1 | 0.2 | | | 1 | 1.0 |
| Badminton | 1 | 0.2 | | | 1 | 1.0 |
| Basketball | 17 | 4.2 | 15 | 4.9 | 1 | 1.0 |
| Biathlon | 3 | 0.7 | 2 | 0.7 | 1 | 1.0 |
| Billard | 5 | 1.2 | 2 | 0.7 | 3 | 3.1 |
| Climbing | 2 | 0.5 | 1 | 0.3 | 1 | 1.0 |
| Cross Country skiing | 23 | 5.7 | 9 | 2.9 | 14 | 14.4 |
| Cycle ball | 1 | 0.2 | 1 | 0.3 | | |
| Cycling | 2 | 0.5 | 1 | 0.3 | 1 | 1.0 |
| Downhill skiing | 6 | 1.5 | 4 | 1.3 | 2 | 2.1 |
| Field hockey | 36 | 8.9 | 19 | 6.2 | 17 | 17.5 |
| Floorball | 1 | 0.2 | 1 | 0.3 | | |
| Gymnastics | 3 | 0.7 | 1 | 0.3 | 2 | 2.1 |
| Handball | 15 | 3.7 | 12 | 3.9 | 3 | 3.1 |
| Hockey | 6 | 1.5 | 6 | 2.0 | | |
| Jiu Jitsu | 4 | 1.0 | 1 | 0.3 | 3 | 3.1 |
| Judo | 4 | 1.0 | 4 | 1.3 | | |
| Kickboxing | 1 | 0.2 | 1 | 0.3 | | |
| Rowing | 20 | 5.0 | 11 | 3.6 | 9 | 9.3 |
| Rugby | 1 | 0.2 | | | 1 | 1.0 |
| Running | 3 | 0.7 | 2 | 0.7 | 1 | 1.0 |
| Sailing | 1 | 0.2 | 1 | 0.3 | | |
| Ski jumping | 2 | 0.5 | 2 | 0.7 | | |
| Snowboarding | 1 | 0.2 | | | 1 | 1.0 |
| Soccer | 147 | 36.4 | 146 | 47.6 | 1 | 1.0 |
| Swimming | 18 | 4.5 | 10 | 3.3 | 8 | 8.2 |
| Synchronized swimming | 2 | 0.5 | | | 2 | 2.1 |
| Taekwondo | 1 | 0.2 | | | 1 | 1.0 |
| Track and field | 4 | 1.0 | 2 | 0.7 | 2 | 2.1 |
| Volleyball | 40 | 9.9 | 29 | 9.4 | 11 | 11.3 |
| Wrestling | 30 | 7.4 | 22 | 7.2 | 8 | 8.2 |
| Missing data | 3 | 0.7 | 2 | 0.7 | 1 | 1.0 |

**Supplementary Table S15** Echocardiographic parameters for quintiles of training time, training intensity, $VO_{2peak}$, and maximum handgrip strength/ body mass.

| | Q1 | | | Q2 | | | Q3 | | | Q4 | | | Q5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dependent variable: **Training time [h/ week]** | males < 5.8 females < 5.4 | | | males 5.8-7 females 5.4-6.8 | | | males 7-8.3 females 6.7-8.9 | | | males 8.3-10.6 females 8.9-11.0 | | | males>10.6 females>11.0 | | | p-value |
| **EF [%]** | 66.92 | ± | 5.21 | 66.58 | ± | 5.25 | 67.26 | ± | 6.23 | 65.85 | ± | 5.73 | 66.16 | ± | 5.70 | .953 |
| **FS [%]** | 37.16 | ± | 4.02 | 36.94 | ± | 4.16 | 37.79 | ± | 5.25 | 36.57 | ± | 4.29 | 36.77 | ± | 4.52 | .937 |
| **LVIDd [mm]**[1) 2)] | 46.48 | ± | 5.06 | 47.42 | ± | 3.98 | 48.33 | ± | 4.70 | 49.69 | ± | 4.99 | 49.66 | ± | 4.51 | **.021** |
| **LVIDs [mm]** | 29.21 | ± | 3.73 | 29.88 | ± | 3.20 | 30.09 | ± | 3.95 | 31.54 | ± | 4.10 | 31.36 | ± | 3.88 | .226 |
| **IVSd [mm]** | 8.10 | ± | 1.36 | 8.66 | ± | 1.57 | 8.51 | ± | 1.37 | 8.55 | ± | 1.24 | 8.71 | ± | 1.46 | .657 |
| **LVPWd [mm]** | 7.59 | ± | 1.45 | 7.95 | ± | 1.18 | 8.14 | ± | 1.33 | 7.96 | ± | 1.34 | 8.48 | ± | 1.26 | .103 |
| **Relative wall thickness** | 0.34 | ± | 0.06 | 0.35 | ± | 0.05 | 0.35 | ± | 0.05 | 0.33 | ± | 0.04 | 0.35 | ± | 0.04 | .056 |
| **LVM/ BSA [g/m$^2$]** | 170.92 | ± | 31.10 | 177.76 | ± | 25.38 | 179.65 | ± | 31.15 | 184.26 | ± | 30.85 | 179.65 | ± | 32.08 | .470 |
| **E/A** | 2.68 | ± | 3.09 | 2.22 | ± | 0.50 | 2.10 | ± | 0.40 | 2.35 | ± | 0.57 | 3.04 | ± | 4.73 | .281 |

[1)] Q1 vs. Q4, p=.024
[2)] Q4 vs. Q5, p=.046

| | Q1 | | | Q2 | | | Q3 | | | Q4 | | | Q5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dependent variable: **Training intensity [MET-hours/ week]** | males<55.0 females<40.7 | | | males 55.0-66.7 females 40.7-58.1 | | | males 66.7-80.8 females 58.1-76.7 | | | males 80.8-100.0 females 76.7-101.5 | | | males > 100.0 females > 101.5 | | | p-value |
| **EF [%]** | 67.61 | ± | 6.68 | 67.57 | ± | 5.06 | 67.20 | ± | 5.79 | 65.42 | ± | 4.42 | 65.06 | ± | 5.83 | .170 |
| **FS [%]** | 37.96 | ± | 5.62 | 37.73 | ± | 4.11 | 37.47 | ± | 4.53 | 36.20 | ± | 3.42 | 35.97 | ± | 4.39 | .274 |
| **LVIDd [mm]** | 47.61 | ± | 5.51 | 47.81 | ± | 4.55 | 47.80 | ± | 4.61 | 48.60 | ± | 4.80 | 49.97 | ± | 4.18 | .125 |
| **LVIDs [mm]** | 29.57 | ± | 4.42 | 29.70 | ± | 3.35 | 29.94 | ± | 4.01 | 31.03 | ± | 3.31 | 31.94 | ± | 3.78 | .053 |
| **IVSd [mm]** | 8.16 | ± | 1.31 | 8.37 | ± | 1.32 | 8.53 | ± | 1.65 | 8.59 | ± | 1.36 | 8.89 | ± | 1.33 | .489 |
| **LVPWd [mm]** | 7.89 | ± | 1.57 | 7.99 | ± | 1.28 | 8.02 | ± | 1.25 | 8.02 | ± | 1.27 | 8.26 | ± | 1.32 | .922 |
| **Relative wall thickness** | 0.34 | ± | 0.06 | 0.34 | ± | 0.04 | 0.35 | ± | 0.06 | 0.34 | ± | 0.04 | 0.34 | ± | 0.04 | .744 |
| **LVM/ BSA [g/m$^2$]** | 173.68 | ± | 32.37 | 179.27 | ± | 27.62 | 173.79 | ± | 31.47 | 181.52 | ± | 30.86 | 184.92 | ± | 28.21 | .245 |
| **E/A** | 2.21 | ± | 0.60 | 2.60 | ± | 2.82 | 2.83 | ± | 4.47 | 2.25 | ± | 0.53 | 2.34 | ± | 0.47 | .582 |

**Supplementary Table S15 (continued)** Echocardiographic parameters for quintiles of training time, training intensity, $VO_{2peak}$, and maximum handgrip strength/ body mass.

| | Q1 | | | Q2 | | | Q3 | | | Q4 | | | Q5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dependent variable: **$VO_{2peak}$ [ml/min/kg]** | males < 41.2 females < 32.6 | | | males 41.2-44.9 females 32.6-35.6 | | | males 44.9-48 females 35.6-39.3 | | | males 48.0-52.0 females 39.3-43.0 | | | males > 52.0 females > 43.0 | | | p-value |
| **EF [%]** | 67.23 | ± | 5.97 | 66.87 | ± | 5.65 | 65.82 | ± | 4.36 | 66.30 | ± | 6.32 | 66.61 | ± | 5.81 | .548 |
| **FS [%]** | 37.62 | ± | 5.06 | 37.24 | ± | 4.38 | 36.38 | ± | 3.47 | 36.95 | ± | 4.84 | 37.12 | ± | 4.57 | .508 |
| **LVIDd [mm]** | 48.28 | ± | 5.31 | 47.05 | ± | 4.76 | 48.96 | ± | 4.46 | 48.19 | ± | 4.54 | 49.24 | ± | 4.77 | .075 |
| **LVIDs [mm]** | 30.13 | ± | 4.75 | 29.60 | ± | 3.79 | 31.11 | ± | 3.14 | 30.37 | ± | 3.54 | 30.93 | ± | 3.95 | .057 |
| **IVSd [mm]** | 8.15 | ± | 1.57 | 8.31 | ± | 1.27 | 8.56 | ± | 1.23 | 8.79 | ± | 1.56 | 8.71 | ± | 1.36 | .448 |
| **LVPWd [mm]** | 7.73 | ± | 1.35 | 7.94 | ± | 1.34 | 7.83 | ± | 1.24 | 8.31 | ± | 1.47 | 8.30 | ± | 1.23 | .162 |
| **Relative wall thickness** | 0.33 | ± | 0.06 | 0.35 | ± | 0.04 | 0.34 | ± | 0.05 | 0.36 | ± | 0.05 | 0.35 | ± | 0.04 | .215 |
| **LVM/ BSA [g/m$^2$]** | 174.77 | ± | 29.20 | 170.27 | ± | 31.66 | 180.33 | ± | 26.56 | 181.47 | ± | 33.22 | 185.92 | ± | 28.97 | .140 |
| **E/A** | 2.16 | ± | 0.51 | 2.90 | ± | 4.26 | 2.26 | ± | 0.61 | 2.62 | ± | 2.86 | 2.24 | ± | 0.42 | .659 |

| | Q1 | | | Q2 | | | Q3 | | | Q4 | | | Q5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dependent variable: **Maximum HGS/ body mass** | males < 0.45 females < 0.44 | | | males 0.45-0.51 females 0.44-0.47 | | | males 0.51-0.56 females 0.47-0.52 | | | males 0.56-0.62 females 0.52-0.56 | | | males > 0.62 females > 0.56 | | | p-value |
| **EF [%]** | 67.57 | ± | 6.29 | 67.26 | ± | 5.44 | 66.31 | ± | 5.41 | 66.38 | ± | 5.57 | 65.21 | ± | 5.25 | .680 |
| **FS [%]** | 37.74 | ± | 5.25 | 37.66 | ± | 4.30 | 36.91 | ± | 4.04 | 36.94 | ± | 4.35 | 36.00 | ± | 4.20 | .586 |
| **LVIDd [mm]** | 45.65 | ± | 4.41 | 47.89 | ± | 4.36 | 49.28 | ± | 4.99 | 49.25 | ± | 4.90 | 49.78 | ± | 4.17 | .503 |
| **LVIDs [mm]** | 28.47 | ± | 4.05 | 29.77 | ± | 3.13 | 31.07 | ± | 3.85 | 31.16 | ± | 4.02 | 31.76 | ± | 3.32 | .689 |
| **IVSd [mm]** | 8.25 | ± | 1.65 | 8.16 | ± | 1.18 | 8.56 | ± | 1.40 | 8.65 | ± | 1.35 | 8.95 | ± | 1.31 | .484 |
| **LVPWd [mm]** | 7.50 | ± | 1.40 | 7.77 | ± | 1.12 | 8.15 | ± | 1.43 | 8.38 | ± | 1.33 | 8.37 | ± | 1.18 | .676 |
| **Relative wall thickness** | 0.35 | ± | 0.06 | 0.33 | ± | 0.04 | 0.34 | ± | 0.05 | 0.35 | ± | 0.05 | 0.35 | ± | 0.04 | .407 |
| **LVM/ BSA [g/m$^2$]** | 169.91 | ± | 28.44 | 176.96 | ± | 28.72 | 179.98 | ± | 30.04 | 182.12 | ± | 31.85 | 184.58 | ± | 31.31 | 990 |
| **E/A** | 2.95 | ± | 4.26 | 2.32 | ± | 0.57 | 2.18 | ± | 0.43 | 2.60 | ± | 3.03 | 2.17 | ± | 0.43 | .472 |

**Supplementary Table S16.** Anthropometric data, heart rate and blood pressure, pulse wave analysis, cardiopulmonary exercise testing, maximum handgrip strength/ body mass, physical activity questionnaire, and echocardiographic data for boys and girls < 14 years and ≥ 14 years.

| | AGE < 14 years | | | | | | | AGE ≥ 14 years | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Anthropometry** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** |
| Age [years] | 124 | 12.27 | ± 1.30 | 38 | 12.13 | ± 1.62 | .583 | 183 | 15.62 | ± 1.00 | 59 | 15.38 | ± 1.00 | .113 |
| Body height [cm] | 124 | 155.75 | ± 11.08 | 38 | 155.10 | ± 12.14 | .759 | 182 | 177.42 | ± 10.26 | 59 | 167.15 | ± 7.27 | **<.001** |
| Body height z-score | 124 | 0.12 | ± 0.91 | 38 | 0.20 | ± 1.21 | .644 | 182 | 0.41 | ± 1.28 | 59 | 0.39 | ± 1.12 | .934 |
| Body mass [kg] | 124 | 44.27 | ± 9.77 | 38 | 46.28 | ± 12.90 | .308 | 182 | 66.77 | ± 11.61 | 59 | 57.91 | ± 7.97 | **<.001** |
| BMI [kg/m$^2$] | 124 | 18.03 | ± 2.16 | 38 | 18.86 | ± 3.39 | .162 | 182 | 21.08 | ± 2.42 | 59 | 20.67 | ± 1.93 | .237 |
| BMI z-score | 124 | -0.19 | ± 0.84 | 38 | -0.01 | ± 1.00 | .264 | 182 | 0.19 | ± 0.73 | 59 | 0.05 | ± 0.65 | .197 |
| WHR z-score | 111 | -0.52 | ± 1.09 | 29 | -0.26 | ± 0.96 | .242 | 182 | -0.45 | ± 1.05 | 59 | -0.12 | ± 1.09 | **.042** |
| WHtR z-score | 111 | -0.56 | ± 0.71 | 29 | -0.31 | ± 0.92 | .111 | 182 | -0.30 | ± 0.70 | 59 | -0.41 | ± 0.60 | .268 |
| BSA [m$^2$] | 124 | 1.38 | ± 0.20 | 38 | 1.40 | ± 0.25 | .594 | 182 | 1.81 | ± 0.20 | 59 | 1.64 | ± 0.14 | **<.001** |
| **Heart rate and blood pressure** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** |
| HR [1/min] | 124 | 66.22 | ± 8.37 | 37 | 71.24 | ± 11.59 | .018 | 183 | 63.68 | ± 10.10 | 59 | 63.68 | ± 10.99 | .999 |
| SBP [mmHg] | 124 | 113.49 | ± 7.99 | 37 | 112.70 | ± 7.00 | .563 | 183 | 119.76 | ± 9.23 | 59 | 112.71 | ± 6.86 | **<.001** |
| SBP z-score | 124 | 0.54 | ± 0.86 | 37 | 0.47 | ± 0.73 | .685 | 182 | 0.06 | ± 0.90 | 59 | -0.05 | ± 0.83 | .395 |
| DBP [mmHg] | 124 | 63.57 | ± 6.42 | 37 | 63.70 | ± 6.05 | .913 | 183 | 63.44 | ± 6.21 | 59 | 63.31 | ± 6.02 | .882 |
| DBP z-score | 124 | -0.29 | ± 0.93 | 37 | -0.26 | ± 0.93 | .893 | 182 | -0.81 | ± 0.85 | 59 | -0.76 | ± 0.89 | .727 |
| **Pulse wave analysis** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** |
| PWV [m/s] | 124 | 4.69 | ± 0.36 | 37 | 4.64 | ± 0.29 | .435 | 183 | 5.11 | ± 0.44 | 59 | 4.83 | ± 0.35 | **<.001** |
| PWV z-score | 122 | 0.57 | ± 1.37 | 36 | 0.50 | ± 0.96 | .758 | 183 | 0.46 | ± 1.38 | 59 | 0.42 | ± 1.45 | .842 |
| cSBP [mmHg] | 124 | 100.31 | ± 8.83 | 37 | 100.35 | ± 8.76 | .978 | 183 | 109.60 | ± 10.15 | 59 | 104.41 | ± 8.54 | **<.001** |
| cSBP z-score | 122 | 0.46 | ± 1.26 | 36 | 0.50 | ± 1.19 | .873 | 183 | 0.37 | ± 1.34 | 59 | 0.26 | ± 1.27 | .588 |
| **Cardiopulmonary exercise test** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** |
| Maximum HR [1/min] | 118 | 188.84 | ± 10.39 | 32 | 185.09 | ± 13.32 | .092 | 164 | 184.68 | ± 11.28 | 47 | 188.53 | ± 8.95 | **.032** |
| Maximum power output [Watt] | 118 | 195.39 | ± 49.84 | 32 | 186.75 | ± 48.01 | .382 | 164 | 314.70 | ± 55.67 | 49 | 236.43 | ± 37.01 | **<.001** |
| Relative power output [Watt/kg] | 118 | 4.37 | ± 0.56 | 32 | 4.00 | ± 0.75 | **.002** | 164 | 4.76 | ± 0.52 | 49 | 4.06 | ± 0.55 | **<.001** |
| Relative VO2peak [ml/min/kg] | 118 | 44.52 | ± 5.96 | 31 | 36.31 | ± 7.38 | **<.001** | 160 | 47.23 | ± 6.93 | 49 | 38.71 | ± 5.97 | **<.001** |
| **Handgrip strength** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** |
| Maximum HGS/ body mass | 112 | 0.47 | ± 0.09 | 34 | 0.46 | ± 0.08 | .523 | 170 | 0.58 | ± 0.08 | 50 | 0.52 | ± 0.07 | **<.001** |
| **Physical activity questionnaire** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** | **n** | **males mean ± SD** | | **n** | **females mean ± SD** | | **p-value** |
| Days of physical activity/ week | 124 | 5.24 | ± 1.19 | 38 | 4.95 | ± 1.39 | .203 | 183 | 5.30 | ± 1.16 | 59 | 4.91 | ± 1.14 | **.023** |
| Main sport: training/ week [h] | 124 | 6.67 | ± 2.95 | 38 | 6.70 | ± 3.31 | .951 | 183 | 8.96 | ± 3.54 | 59 | 8.39 | ± 4.50 | .312 |
| Sports club activity: training/ week [h] | 124 | 7.27 | ± 2.93 | 38 | 7.59 | ± 3.15 | .560 | 183 | 9.19 | ± 3.69 | 59 | 8.85 | ± 4.12 | .559 |
| Main sport: MET-hours/ week | 123 | 64.09 | ± 26.88 | 37 | 54.43 | ± 31.19 | .067 | 181 | 80.61 | ± 35.65 | 59 | 74.61 | ± 49.74 | .393 |
| Sports club activity: MET-hours/ week | 124 | 70.61 | ± 23.63 | 37 | 65.01 | ± 31.18 | .318 | 182 | 85.10 | ± 33.94 | 59 | 82.12 | ± 45.50 | .644 |

**Supplementary Table S16 (continued).** Anthropometric data, heart rate and blood pressure, pulse wave analysis, cardiopulmonary exercise testing, maximum handgrip strength/ body mass, physical activity questionnaire, and echocardiographic data for boys and girls < 14 years and ≥ 14 years.

| | AGE < 14 years | | | | | | | | AGE ≥ 14 years | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2D transthoracic echocardiography** | **n** | **males mean ± SD** | | | **n** | **females mean ± SD** | | | **p-value** | **n** | **males mean ± SD** | | | **n** | **females mean ± SD** | | | **p-value** |
| EF [%] | 119 | 67.77 | ± | 5.12 | 37 | 69.19 | ± | 6.26 | .166 | 175 | 65.49 | ± | 5.99 | 58 | 65.98 | ± | 5.22 | .577 |
| FS [%] | 119 | 37.75 | ± | 4.07 | 37 | 39.16 | ± | 5.54 | .094 | 174 | 36.43 | ± | 4.74 | 58 | 36.50 | ± | 4.19 | .915 |
| LVIDd [mm] | 119 | 45.27 | ± | 3.60 | 37 | 44.41 | ± | 3.99 | .221 | 175 | 51.13 | ± | 4.39 | 58 | 47.48 | ± | 3.62 | **<.001** |
| LVIDd z-score | 119 | 0.34 | ± | 0.56 | 37 | 0.07 | ± | 0.62 | **.016** | 174 | -0.12 | ± | 1.13 | 58 | 0.14 | ± | 0.65 | .091 |
| LVIDs [mm] | 119 | 28.20 | ± | 2.90 | 37 | 27.02 | ± | 3.26 | .038 | 174 | 32.42 | ± | 3.78 | 58 | 30.17 | ± | 3.14 | **<.001** |
| LVIDs z-score | 119 | 0.28 | ± | 0.64 | 37 | -0.12 | ± | 0.96 | **.003** | 173 | 0.10 | ± | 0.99 | 58 | 0.29 | ± | 0.79 | .136 |
| IVSd [mm] | 119 | 8.04 | ± | 1.45 | 37 | 7.80 | ± | 1.31 | .371 | 177 | 9.17 | ± | 1.29 | 58 | 8.26 | ± | 1.20 | **<.001** |
| IVSd z-score | 119 | 0.72 | ± | 0.72 | 37 | 0.54 | ± | 0.67 | .194 | 176 | 0.45 | ± | 0.68 | 58 | 0.38 | ± | 0.76 | .523 |
| LVPWd [mm] | 119 | 7.40 | ± | 1.14 | 37 | 7.41 | ± | 1.42 | .993 | 175 | 8.81 | ± | 1.15 | 58 | 7.66 | ± | 1.41 | **<.001** |
| LVPWd z-score | 119 | 0.81 | ± | 0.68 | 37 | 0.74 | ± | 0.81 | .560 | 174 | 0.64 | ± | 0.78 | 58 | 0.41 | ± | 0.95 | .069 |
| Relative wall thickness | 119 | 0.34 | ± | 0.05 | 37 | 0.34 | ± | 0.05 | .905 | 175 | 0.35 | ± | 0.05 | 58 | 0.34 | ± | 0.06 | .066 |
| LVM/ BSA [g/m$^2$] | 119 | 170.67 | ± | 25.99 | 37 | 159.58 | ± | 22.14 | **.020** | 174 | 193.29 | ± | 30.89 | 58 | 163.51 | ± | 25.97 | **<.001** |
| LVM/ body height [g/m] | 119 | 88.47 | ± | 20.17 | 37 | 84.48 | ± | 20.01 | .294 | 174 | 116.58 | ± | 22.12 | 58 | 92.52 | ± | 18.53 | **<.001** |
| E/A | 79 | 2.69 | ± | 3.31 | 29 | 2.95 | ± | 3.64 | .726 | 126 | 2.22 | ± | 0.50 | 44 | 2.39 | ± | 0.54 | .061 |

BMI = body mass index, WHR = waist-to-hip ratio, WHtR = waist-to-height ratio, BSA = body surface area, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PWV = pulse wave velocity, cSBP/ cDBP = central SBP/ DBP. EF = ejection fraction, FS = fractional shortening, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, IVSd = interventricular septal thickness in diastole, LVPWd = left ventricular posterior wall thickness in diastole, RWT = relative wall thickness, LVM/ BSA = left ventricular mass/ body surface area, LVM/ body height = left ventricular mass/ body height, E/A = ratio of mitral E- and A-wave.

**Supplementary Table S17.** Anthropometric data, heart rate and blood pressure, pulse wave analysis, cardiopulmonary exercise testing, maximum handgrip strength/ body mass, physical activity questionnaire, and echocardiographic data for athletes performing endurance and power type of sports.

| **Anthropometry** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| Age [years] | 51 | 14.42 ± 1.83 | 48 | 14.67 ± 1.70 | .481 |
| Body height [cm] | 51 | 165.98 ± 12.77 | 47 | 165.51 ± 11.98 | .852 |
| Body height z-score | 51 | 0.24 ± 1.03 | 47 | -0.29 ± 1.07 | **.015** |
| Body mass [kg] | 51 | 56.21 ± 13.88 | 47 | 57.66 ± 14.77 | .617 |
| BMI [kg/m$^2$] | 51 | 20.10 ± 2.85 | 47 | 20.71 ± 3.16 | .504 |
| BMI z-score | 51 | 0.03 ± 0.91 | 47 | 0.20 ± 0.87 | .351 |
| WHR z-score | 49 | -0.24 ± 0.95 | 45 | -0.33 ± 1.28 | .686 |
| WHtR z-score | 49 | -0.33 ± 0.82 | 45 | -0.20 ± 0.67 | .390 |
| BSA [m$^2$] | 51 | 1.60 ± 0.26 | 47 | 1.62 ± 0.26 | .744 |

| **Heart rate and blood pressure** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| HR [1/min] | 51 | 66.04 ± 12.20 | 48 | 68.54 ± 12.21 | .310 |
| SBP [mmHg] | 51 | 115.08 ± 10.92 | 48 | 118.58 ± 9.46 | .092 |
| SBP z-score | 51 | 0.16 ± 1.04 | 47 | 0.49 ± 0.88 | .091 |
| DBP [mmHg] | 51 | 62.06 ± 5.81 | 48 | 66.08 ± 8.08 | **.006** |
| DBP z-score | 51 | -0.81 ± 0.82 | 47 | -0.23 ± 1.20 | **.007** |

| **Pulse wave analysis** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| PWV [m/s] | 51 | 4.85 ± 0.50 | 48 | 4.97 ± 0.46 | .168 |
| PWV z-score | 51 | 0.39 ± 1.58 | 48 | 0.59 ± 1.39 | .512 |
| cSBP [mmHg] | 51 | 103.55 ± 12.04 | 48 | 107.67 ± 11.61 | .086 |
| cSBP z-score | 51 | 0.21 ± 1.50 | 48 | 0.62 ± 1.55 | .182 |

| **2D transthoracic echocardiography** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| EF [%] | 48 | 66.52 ± 5.74 | 48 | 65.25 ± 5.16 | .256 |
| FS [%] | 48 | 37.06 ± 4.46 | 48 | 35.88 ± 3.99 | .215 |
| LVIDd [mm] | 48 | 48.48 ± 4.76 | 48 | 48.05 ± 5.33 | .670 |
| LVIDd z-score | 48 | 0.22 ± 0.86 | 47 | 0.08 ± 0.86 | .319 |
| LVIDs [mm] | 48 | 30.59 ± 4.09 | 48 | 30.73 ± 4.16 | .873 |
| LVIDs z-score | 48 | 0.30 ± 0.90 | 47 | 0.30 ± 0.81 | .963 |
| IVSd [mm] | 48 | 8.47 ± 1.45 | 48 | 8.55 ± 1.26 | .769 |
| IVSd z-score | 48 | 0.51 ± 0.79 | 47 | 0.56 ± 0.66 | .721 |
| LVPWd [mm] | 48 | 7.83 ± 1.29 | 48 | 8.25 ± 1.25 | .238 |
| LVPWd z-score | 48 | 0.56 ± 0.85 | 47 | 0.81 ± 0.86 | .159 |
| Relative wall thickness | 48 | 0.34 ± 0.05 | 48 | 0.35 ± 0.05 | .128 |
| LVM/ BSA [g/m$^2$] | 48 | 179.16 ± 31.60 | 47 | 180.34 ± 35.25 | .864 |
| LVM/ body height [g/m] | 48 | 100.59 ± 24.80 | 47 | 104.51 ± 25.70 | .451 |
| E/A | 41 | 2.87 ± 3.05 | 33 | 2.11 ± 0.42 | **.014** |

**Supplementary Table S17 (continued).** Anthropometric data, heart rate and blood pressure, pulse wave analysis, cardiopulmonary exercise testing, maximum handgrip strength/ body mass, physical activity questionnaire, and echocardiographic data for athletes performing endurance and power type of sports.

| **Cardiopulmonary exercise test** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| Maximum HR [1/min] | 46 | 189.46 ± 8.35 | 43 | 186.07 ± 14.60 | .375 |
| Maximum power output [Watt] | 47 | 264.91 ± 80.74 | 43 | 245.33 ± 68.09 | .232 |
| Relative power output [Watt/kg] | 47 | 4.65 ± 0.73 | 43 | 4.31 ± 0.68 | **.026** |
| Relative $VO_{2peak}$ [ml/min/kg] | 46 | 44.68 ± 9.16 | 42 | 42.82 ± 5.74 | .254 |

| **Handgrip strength** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| Maximum HGS/ body mass | 46 | 0.53 ± 0.11 | 47 | 0.56 ± 0.08 | .098 |

| **Physical activity questionnaire** | **n** | **endurance mean ± SD** | **n** | **power mean ± SD** | **p-value** |
|---|---|---|---|---|---|
| Days of physical activity/ week | 51 | 5.17 ± 1.13 | 48 | 4.89 ± 1.14 | .220 |
| Main sport: training/ week [h] | 50 | 382.40 ± 181.06 | 48 | 409.08 ± 208.97 | .839 |
| Sports club activity: training/ week [h] | 51 | 457.39 ± 163.30 | 48 | 505.68 ± 233.73 | .522 |
| Main sport: MET-hours/ week | 50 | 66.44 ± 37.23 | 48 | 74.48 ± 45.09 | .493 |
| Sports club activity: MET-hours/ week | 51 | 76.45 ± 33.14 | 48 | 86.42 ± 40.95 | .261 |

BMI = body mass index, WHR = waist-to-hip ratio, WHtR = waist-to-height ratio, BSA = body surface area, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PWV = pulse wave velocity, cSBP/ cDBP = central SBP/ DBP. EF = ejection fraction, FS = fractional shortening, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, IVSd = interventricular septal thickness in diastole, LVPWd = left ventricular posterior wall thickness in diastole, RWT = relative wall thickness, LVM/ BSA = left ventricular mass/ body surface area, LVM/ body height = left ventricular mass/ body height, E/A = ratio of mitral E- and A-wave.

## 9.5 SUPPLEMENTARY INFORMATION: STUDIES INVESTIGATING LEFT VENTRICULAR CARDIAC STRUCTURE IN YOUNG ATHLETES COMPARED TO CONTROLS.

**Supplementary Table S18** Studies investigating left ventricular cardiac structure in young athletes compared to controls.

| Author | Athletes (females) | Age (years) | LVIDd | LVIDs | IVSd | LVPWd | LVM/ BSA |
|---|---|---|---|---|---|---|---|
| Barczuk-Falecka et al. [151] | Soccer: 36 (0) | 10.1 ± 1.4 | 38.3±3.3 mm/$\sqrt{m^2}$ | - | 6.9±0.8 mm/$\sqrt{m^2}$ | 7.1±1.3 mm/$\sqrt{m^2}$ | 57.1±7.4 g/$m^{2*}$ |
| Beaumont et al. [89] | Soccer: 22 (0) | 12.0±0.3 | 37±3 mm/$(m^2)^{0.5}$ | 25±3 mm/$(m^2)^{0.5}$ | - | - | 25±5 g/$m^{2.7}$ |
| Binnetoglu et al. [84] | Tennis: 16 (0) | 12.2±0.8 | 30.9±3.8 mm/$m^2$ | 19.6±2.4 mm/$m^2$ | 5.3±0.9 mm/$m^2$ | 5.3±1.2 mm/$m^2$ | 74±16.7 g/$m^2$ |
| | Swimming: 45 (0) | 12.9±1.6 | 31.61±6.7 mm/$m^2$ | 19.6±3.5 mm/$m^2$ | 6.6±1.2 mm/$m^2$ | 6.6±1.2 mm/$m^2$ | 91.6±16.6 g/$m^2$ |
| Gerling et al.[152] | Soccer: 315 (0) | 12.8±0.65 | 0.58 (z-score) | 0.32 (z-score) | 2.47 (z-score)* | 1.15 (z-score)* | 94±12 g/$m^{2*}$ |
| Kayali et al. [87] | Various sports: 126 (NR) | 13.5±2.6 | 43.5±5.7 mm | 25.3±4.4 mm | 10.5±2.2 mm* | 9.6±2.2 mm | - |
| Kooreman et al. [16] | High intensity: 37 (37) | 19±1 | 3.0±0.2 cm/m* | - | - | - | 74±11g/$m^{2*}$ |
| | Low intensity: 35 (35) | 19±1 | 2.9±0.2 cm/m | | | | 63±8 g/$m^2$ |
| McClean et al.[22] | Various Sports: 14 278 (2 374) | 13.8 ± 1.3 | 47.3 (46.2-48.3 ) mm* | 29.6(28.4-30.8) mm* | 8.5(8.2-8.8) mm* | 8.2(7.8-8.6) mm* | 135.7(122.2-149.1) g* |
| Pelà et al. [156] | Endurance males: 158 | 13.8±1.6 | 47±4 mm* | 29±4mm* | 8.4±1.2 mm* | 8.1±1.2 mm* | 100±18 g/$m^{2*}$ |
| | Endurance females: 48 | 13.7±1.4 | 44±3 mm | 27±4 mm | 7.6±0.9 mm | 7.2±0.9 mm | 79±12 g/$m^2$ |
| Rodriguez-Lopez et al. [88] | Various Sports: 331 (86) | 11.9±3.2 | z-score 0.26 (-2.5 - 3.27) | - | z-score 1.18 (-2.42-4.09) | z-score 0.06(-2.64-2.93) | - |
| Rundqvist et al. [86] | Endurance: 27 (11) | 15.5 (13-19) | 29 (26-37) mm/$m^{2*}$ | - | 3.7 (2.9-4.8) mm/$m^{2*}$ | 4.5 (3.8-6.7) mm/$m^{2*}$ | 67 (48-100) g/$m^{2*}$ |
| Simsek et al. [82] | Running: 22 (0) | 17.5±2.2 | 52.1±4.4 mm* | 32.4±3.7 mm* | 9.5±1.1 mm | 10.2±0.9 mm | 115±15 g/$m^2$ |
| | Wrestling: 24 (0) | 16.8±1.9 | 47.2±6.2 mm | 29.2±5.7 mm | 11.3±1.2 mm* | 11.1±1.2 mm* | 119±18 g/$m^{2*}$ |
| Zdravkovic et al. [85] | Soccer: 94 (0) | 12.85±0.84 | 38.72±2.53 mm/$(m^2)^{0.5*}$ | 25.83±2.58 mm/$(m^2)^{0.5*}$ | 7.08±0.70 mm/$(m^2)^{0.5*}$ | 6.82±0.73 mm/$(m^2)^{0.5*}$ | 109.79±15.04 g/$m^{2*}$ |

* $p < .05$
NR – not recorded

**Supplementary Table S18 (continued)** Studies investigating left ventricular cardiac structure in young athletes compared to controls.

| Author | Controls | Age (years) | LVIDd | LVIDs | IVSd | LVPWd | LVM/ BSA |
|---|---|---|---|---|---|---|---|
| Barczuk-Falecka et al. [151] | 24 (0) | 10.4±1.7 | 37.2±3.2 mm/$\sqrt{m^2}$ | - | 6.2±0.9 mm/$\sqrt{m^2}$ | 6.5±1.3 mm/$\sqrt{m^2}$ | 50.0±7.1 g/$m^2$ |
| Beaumont et al. [89] | 22 (0) | 11.7±0.3 | 38±3 mm/$(m^2)^{0.5}$ | 25±2 mm/$(m^2)^{0.5}$ | - | - | 28±7 g/$m^{2.7}$ |
| Binnetoglu et al. [84] | 25 (7) | 14.7±1.5 | 29.2±2.6 mm/$m^2$ | 18.7±2.9 mm/$m^2$ | 4.8±0.8 mm/$m^2$ | 4.9±0.7 mm/$m^2$ | 76.8±15.7 g/$m^2$ |
| Gerling et al.[152] | 53 (0) | 12.6±0.8 | 0.19 (z-score) | 0.05 (z-score) | 1.72 (z-score) | 0.47 (z-score) | 81±13 g/$m^2$ |
| Kayali et al. [87] | 62 (NR) | 13.5±2.6 | 42.8±4.0 | 25.1±3.9 mm | 9.2±2.1 mm | 7.8±1.7 mm | - |
| Kooreman et al. [16] | 31 (31) | 19±1 | 2.9±0.2 cm/m | - | - | - | 61±9 g/$m^2$ |
| McClean et al.[22] | 1668 (358) | 12.6±0.6 | 43.4(41.7-45.1) mm | 25.4(24.8-26.0) mm | 7.4(7.1-7.8) mm | 7.2(6.6-7.8) mm | 98.2(84.6-111.8) g |
| Pelà et al. [156] | - | - | - | - | - | - | - |
| Rodriguez-Lopez et al. [88] | - | - | - | - | - | - | - |
| Rundqvist et al. [86] | 27 (11) | 15.4 (13-19) | 26 (22-37) mm/$m^2$ | - | 3.1 (2.5-4.9) mm/$m^2$ | 4.0 (3.2-4.9) mm/$m^2$ | 45 (37-73) g/$m^2$ |
| Simsek et al. [82] | 20 (0) | 16.4±1.8 | 46.7±4.7 mm | 29.3±4.3 mm | 9.4±0.9 mm | 9.4±1.3 mm | 88±14 g/$m^2$ |
| Zdravkovic et al. [85] | 47 (0) | 12.85±0.86 | 35.68±2.54 mm/$(m^2)^{0.5}$ | 20.75±2.30 mm/$(m^2)^{0.5}$ | 6.53±0.81 mm/$(m^2)^{0.5}$ | 6.46±0.80 mm/$(m^2)^{0.5}$ | 92.84±18.29 g/$m^2$ |

* $p < .05$
NR – not recorded