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VENTRICULAR AND VALVULAR REMODELING ASSOCIATED WITH THE ATHLETE'S HEART: THE ADDED VALUE OF ADVANCED ECHOCARDIOGRAPHIC TECHNIQUES

Ph.D. Thesis

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DOI:10.14753/SE.2023.2808

TABLE OF CONTENTS

DOI:10.14753/SE.2023.2808

DOI:10.14753/SE.2023.2808

DOI:10.14753/SE.2023.2808

List of abbreviations

2D – two-dimensional

2DE – 2D echocardiography

3D – three dimensional

3DE – 3D echocardiography

ACHWR – annulus height to commissural width ratio

ANOVA – analysis of variance

A-P diameter – anteroposterior diameter

ARVC – arrhythmogenic right ventricular cardiomyopathy

AV – atrioventricular

BMI – body mass index

BSA – body surface area

BW – body weight

cMR – cardiac magnetic resonance imaging

CMWI – constructive myocardial work index

CO – cardiac output

CPET – cardiopulmonary exercise testing

DBP – diastolic blood pressure

dP/dt_{max} – the maximal slope of left ventricular systolic pressure increment

dP/dt_{min} – the maximal slope of left ventricular diastolic pressure decrement

E_a – arterial elastance

EACVI – European Association of Cardiovascular Imaging

EAPC – European Association of Preventive Cardiology

ECG – electrocardiography

EDVi – end-diastolic volume index

EF – ejection fraction

ESC – European Society of Cardiology

ESPVR – end-systolic pressure-volume relationship

ESVi – end-systolic volume index

F_{Ath} – female athlete group

F_{Co} – female control group

F_{Ex} – female exercised group

FR – functional regurgitation

FWLS – free wall longitudinal strain

GCS – global circumferential strain

GLS – global longitudinal strain

GMWI – global myocardial work index

HCM – hypertrophic cardiomyopathy

HR – heart rate

LA – left atrium

LA active EF – LA active emptying fraction

LA passive EF – LA passive emptying fraction

LA total EF – LA total emptying fraction

LAVi max – LA maximal volume index

LAVi min – LA minimal volume index

LAVi preA – LA preA wave (at the onset of atrial contraction) volume index

LV – left ventricle

M – mass

MA – mitral annulus

M_{Ath} – male athlete group

M_{Co} – male control group

M_{Ex} – male exercised group

Mi – mass index

MR – mitral regurgitation

MV – mitral valve

MW – myocardial work

MWE – myocardial work efficiency

OLS – ordinary least squares

PM-AL diameter – posteromedial-anterolateral diameter

PRSW – preload recruitable stroke work

P-V – pressure-volume

RA – right atrium

RA active EF – RA active emptying fraction

RA passive EF – RA passive emptying fraction

RA total EF – RA total emptying fraction

RAVi max – RA maximal volume index

RAVi min – RA minimal volume index

RAVi preA – RA preA wave (at the onset of atrial contraction) volume index

ROI – region of interest

RV – right ventricle

SBP – systolic blood pressure

SCD – sudden cardiac death

STE – speckle-tracking echocardiography

SV – stroke volume

SVi – stroke volume index

TA – tricuspid annulus

TAPSE – tricuspid annular plane systolic excursion

TR – tricuspid regurgitation

TTE – transthoracic echocardiography

TV – tricuspid valve

VCW – vena contracta width

VO_2 – peak oxygen uptake

VO_2/kg – peak oxygen uptake indexed to body weight

WMWI – wasted myocardial work index

σED – meridional end-diastolic wall stress

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1. Introduction

1.1. Sports cardiology – the emergence of an independent sub-specialty

"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health." Over the last few decades, the ever-growing scientific interest in exercise physiology and cardiopulmonary health resulted in numerous studies proving that regular physical activity prevents cardiovascular and non-cardiovascular diseases (1). Although the principle behind the teachings of Hippocrates has indubitably withstood time, novel results of systematic research have revealed alarming findings about the possible adverse/harmful consequences of vigorous training, which is most often seen in the field of competitive, elite athleticism (1, 2). The exponential increase in the numbers of both professional and recreational athletes and the observations in exercise physiology prompted the recognition of the need for a systematic guide to help optimize and maintain healthy cardiovascular status. Thus sports cardiology was brought to life. Nowadays, sports cardiology encompasses several different sub-specialties within the field of heart- and vascular medicine, including cardiovascular imaging, electrophysiology, rehabilitation, and even experimental cardiology, and focuses on clinical issues pertaining to sports participants such as pre-participation screening, prevention of sudden cardiac death (SCD) or the differentiation of physiological remodeling from cardiomyopathies (3). However, despite the significant advances in sports cardiology over recent time, there is still a substantial need for research to advance knowledge and clinical care.

1.1.1. The importance of sports: well-being benefits of physical activity

One of the cornerstones since the early era of medicine is the recommendation of physical exercise as a means of maintaining not only physical but mental health (4). Today, based on intense scientific research, several medical societies recommend a certain quantity and quality of exercise to preserve cardiorespiratory, musculoskeletal, and neuromotor fitness giving evidence-based guidance for prescribing exercise (5-8). According to current guidelines, physical activity could reduce the risk of several adverse outcomes irrespective of age, sex, or potential presence of comorbidities, showing a dose-effect relationship between exercise and cardiovascular and all-cause mortality, reducing the risks of adverse events by 20-30% compared to sedentary people (6, 9-11). Nevertheless,

studies have suggested a U-shaped relationship between training volume and cardiac morbidity, where the greatest benefits on cardiovascular status are derived from the recommended amount of exercise, and increasing training volume might not enhance those beneficial effects; in fact, it may have adverse impact on some individuals (12). As stated in the *2020 European Society of Cardiology (ESC) Guidelines on sports cardiology and exercise in patients with cardiovascular disease* the recommended amount of exercise that healthy adults of all ages should perform is a minimum of 150 minutes of moderate intensity endurance training in 5 days or 75 minutes of vigorous exercise in 3 days per week, and additional benefits could be derived by doubling to 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity aerobic exercise per week (6, 9). Vast evidence shows that regular physical activity could decrease blood pressure, has a lowering effect on blood cholesterol levels and could enhance the expression of anti-atherogenic factors and potentially lower the incidence of several types of cancer (13). Furthermore, on top of reducing the risks of and/or improving many diseases and conditions, data suggests that physical activity lengthens life expectancy as well (14). Besides all the benefits on physical health, sport participation have been associated with improved cognitive performance and mental health. Studies have previously reported better cognitive and school performance among children with higher fitness (15, 16). Physical activity has also been linked to improvements in mood and creativity even after a single session and has positive effects on mental well-being by reducing psychological distress and helping people to cope with stress more effectively (17, 18). While the health benefits of regular exercise seem to be indisputable, the overall effects and adaptive cardiac changes arising from competitive training are much more controversial.

1.1.2. Physiological and pathophysiological cardiac remodeling in response to exercise

During high-intensity exercise the cardiovascular system is exposed to significant hemodynamic demands that could vary in different sports disciplines. Generally, cardiac output (CO) could increase 5- to 6-fold during maximal exercise effort, and as CO is determined by stroke volume (SV) and heart rate (HR), substantial increment in SV and especially in HR are required to cope with such a surge in workload. Therefore, complex structural and functional cardiac adaptative mechanisms are observed in athletes in order

to further enhance peak performance and to endure subsequent hemodynamic changes. This exercise-induced cardiac remodeling, commonly referred to as the athlete's heart, was described in one of the first cornerstone studies by Morganroth et al (19). Dynamic or isotonic exercise (e.g. endurance training) results in a sustained elevation in CO, thus a pronounced dilation of all four cardiac chambers can be observed primarily due to volume load. On the other hand static or isometric exercise (e.g. strength training) is characterized by increased peripheral vascular resistance and normal or slightly elevated CO, thus it imposes mainly pressure load due to the increase in systolic and diastolic blood pressure that ultimately could manifest in increased left ventricular (LV) mass (LV M) (19-21). While the classical concept of Morganroth et al. is based on a dichotomous classification of exercise types, most sports cannot be categorized as solely static or dynamic, but rather described with a proportion of each components as suggested by Mitchell et al.; or defined as sport disciplines (skill, power, mixed, endurance) according to the recommendations of current guidelines (6, 22). Furthermore, beyond the structural remodeling, the athlete's heart also relies on functional adaptation that leads to enhanced myocardial contractility. While the results of echocardiographic assessment in terms of cardiac function are ambiguous, several recent publications have presented evidence of reduced resting systolic function (23-27). The observed decrease in cardiac function may be attributable to the exercise-induced dilation of the ventricles as less strenuous contraction is required at rest in order to maintain normal stroke volume, whilst ensuring a higher reserve with exercise.

These geometrical and mechanical alterations may considered to be a part of the spectrum of physiological cardiac remodeling in response to exercise, however upon the failure of adaptation or predisposition for cardiac diseases, vigorous training could also impose potential adverse effects on the cardiovascular system. Notably, several clinical studies showed that the risk of SCD in athletes is higher compared to sedentary population: a prospective study enrolling 1 million young participants in Italy found that the incidence of SCD was 2.5 times higher in athletes (28). Another study from the US reported more alarming results: the rate of SCD in professional athletes was 1 person / 3100 persons per year (29). Consequently, research was focused on investigating the etiology of SCD: in North America, studies reported that hypertrophic cardiomyopathy (HCM) was one of the most prevalent etiology of SCD in the athlete population (30). Other studies

suggested, that genetic mutations related to arrhythmogenic right ventricular cardiomyopathy (ARVC) was more prevalent in South-Europe (31) and, ARVC was found to be one of the most common cause of SCD in Italy (32). The rationale behind ARVC as an important etiological factor of exercise-associated SCD was underpinned as numerous studies observed right ventricular (RV) alterations in response to training: research had shown that during exercise the right side of the heart is exposed to a disproportionate load compared to the left side, and vigorous training may induce pathological RV damages (33-35). The alterations seen in physiological and pathophysiological adaptations are often overlapping, thus the differentiation of the athlete's heart from cardiovascular conditions has difficulties and created a diagnostic 'grey zone'. In order to ensure the safety of not only professional athletes but those partaking in leisure-time physical activity, a thorough pre-participation screening is highly recommended as per the position paper and the guidelines of the European Society of Cardiology (6, 36).

1.1.3. Challenges in the echocardiographic assessment of the athlete's heart

Several different diagnostic modalities have been established as an integral part of pre-participation screening of athletes with potential predisposition to cardiac diseases. To this day electrocardiography (ECG) holds paramount importance in pre-participation screening as it detects distinct changes and sings of electrical remodeling in the athlete's heart (37). However, over the last decades, transthoracic echocardiography (TTE) and cardiac magnetic resonance (cMR) imaging have become regularly used diagnostic tools as well due to their ability to identify the majority of athletes with cardiomyopathies. Nevertheless, several sporting organization have advocated the use of TTE as part of the pre-participation screening protocol as it is usually widely accessible, non-invasive and relatively cost-effective (36).

Echocardiographic evaluations have the ability to quantify the aforementioned structural and functional remodeling that potentially helps to achieve enhanced CO, and ultimately performance. While this increase in cardiovascular function does not translate directly to athletic performance, as success in professional athleticism is influenced by several other factors, still CO has been shown to be associated with cardiopulmonary exercise testing (CPET)-derived peak oxygen uptake (VO_2/kg) (38). VO_2/kg is known to be dependent on

maximal HR and SV and it is shown to increase by long term endurance training, thus VO_2/kg may be an objective parameter of exercise capacity enabling the quantification of athletic performance. Although data are scarce concerning the relationship between echocardiography derived resting measures and exercise capacity, direct associations between increased biventricular volumes and better athletic performance have been previously reported (24, 38-40). In terms of cardiac function, inverse association was observed between resting LV EF and VO_2/kg (40).

On the other hand conventional two-dimensional (2D) echocardiography (2DE) is not free of limitations. Besides structural changes, one of the most important features of the athlete's heart in terms of echocardiographic evaluation, is its systolic function that adapts to the increased workload leading to enhanced myocardial contractility which cannot be fully grasped by ejection fraction (EF). Myocardial contractility is the intrinsic ability of the myocardium to generate force and to shorten independently of afterload and preload with fixed heart rates. The gold standard method of investigating contractility is by invasive hemodynamic assessment: pressure-volume (P-V) analysis is one of the most accurate approach for examining ventricular function independently of the changes in loading conditions, thus it is widely used in experimental studies. P-V analysis is performed using a pressure-conductance microcatheter and various hemodynamic indices can be assessed such as the maximal slope of LV systolic pressure increment (dP/dt_{max}), and diastolic pressure decrement (dP/dt_{min}), whereas with the transient occlusion of the inferior vena cava during the procedure, preload recruitable stroke work (PRSW) and the slope of the LV end-systolic P–V relationship (ESPVR, according to the parabolic curvilinear model) can be obtained which is one of the most reliable, load-independent, gold-standard parameter of contractility (41-43). Although these parameters carry invaluable information of systolic function, understandably, these procedures are not suited to be routinely performed in athletes due to their invasive nature.

1.2. Deformation imaging and myocardial work

Indubitably, EF is still a primetime measure of LV systolic function with a well-established diagnostic and prognostic importance and guideline-directed recommendations on its measurement to support every-day clinical decision making (44). However, there are well-known limitations to EF: the biplane method results in a volume-

derived index which relies on geometric assumptions, it may be influenced by the changes of LV geometry, it has a significant load dependency that also leads to suboptimal reproducibility, and ultimately, it does not reflect accurately myocardial contractility (45, 46). Due to the several shortcomings of EF, significant efforts were made to identify more sensitive indices of myocardial contractility enabling a more objective quantification of systolic function.

1.2.1. Global longitudinal strain

Speckle tracking echocardiography (STE) has emerged as a promising new imaging modality. In contrast to conventional echocardiographic techniques, such as tissue doppler imaging, STE utilizes a standard 2D greyscale image and the algorithm uses "speckles" caused by reflections, refraction, and scattering of echo beams. The software defines clusters of speckles (kernels) in the myocardial wall and tracks these speckle patterns frame-by-frame throughout the cardiac cycle in a previously defined region of interest (ROI). The detection of this spatial movement allows the myocardial deformation to be quantified as strain values, which represents the relative change in the length of the ROI measured as percentages and negative values as shortening (47, 48). Myocardial deformation is often described as shortening along 2 major mechanical direction, namely longitudinal, and circumferential. Longitudinal shortening may reflect the function of the longitudinally aligned LV subendocardial myofibers, which have high oxygen demand, are prone to ischemia and they are the most affected by hemodynamic overload, hence the majority of different cardiac diseases deteriorates longitudinal strain first (45). Over the last decade STE-derived global longitudinal strain (GLS) gained momentous clinical importance due to the possibility to detect more subtle changes of myocardial function: compared to conventional functional parameters, GLS had incremental prognostic value in several cardiac diseases (49, 50) Despite the better sensitivity towards cardiac function, results are still inconsistent in terms of exercise induced alterations of resting strain. While enhanced myocardial contractility is an established feature of the athlete's heart, strain values are influenced by loading condition and chamber geometry (47) and such shortcomings may justify its inability to adequately reflect the contractile function during resting conditions (51).

1.2.2. Myocardial work index

Previous studies have observed that although several hemodynamic factors has an impact on GLS, afterload has the most influential effect on myocardial strain. In recent years, focus has shifted towards a promising tool that allowed the non-invasive evaluation of myocardial function. Myocardial work (MW) analysis has the ability to overcome the aforementioned limitations of STE-derived strain by adjusting myocardial deformation to afterload that results in a more accurate assessment of myocardial performance (52-55). In experimental setup, to validate the correlations between MW and contractility, MW indices are obtained from pressure–strain loops: first, STE is performed to assess GLS which is followed by invasive P-V analysis that enables the measurement of gold-standard parameters of contractility (56). Russell et al introduced a novel clinical method for quantifying MW by the analysis of LV pressure-strain loop performed similarly: the integration of STE-derived longitudinal strain with estimated LV pressure curves at rest. However, in this method, the LV pressure curve was derived from non-invasively acquired brachial artery cuff pressure measured on subjects in a resting supine state prior to the echocardiographic evaluation (55). In order to derive MW indices, opening and closure timepoints of the mitral and aortic valves need to be identified that corresponds to four phases: isovolumetric contraction, ejection, isovolumetric relaxation, and diastolic filling (Figure 1). Global MW index (GMWI) represents the area within the pressure-strain loop and calculated by integrating the power over time from mitral valve closure until mitral valve opening. Constructive MW index (CMWI) is defined as the shortening performed in systole and the negative work or lengthening performed during isovolumetric relaxation, in contrast to wasted MW index (WMWI) which quantifies the work that does not contribute to LV ejection during systole. WMWI is derived from the lengthening performed in systole and the shortening in isovolumetric relaxation. Lastly, MW efficiency (MWE) represents the percentage of constructive work over total work and calculated as follows: CMWI/(CMWI + WMWI) (55, 57). Due to its established advantages, MW analysis gained popularity as increasing number of studies has proved that MW indices have the prospect of providing incremental information in various cardiovascular diseases (54, 58-66). Besides pathological conditions, preliminary data also demonstrated the feasibility of MW analysis to assess myocardial systolic

performance in athletes (67), however an in-depth validation is still needed to establish the relationship between MW indices and contractility in terms of the athlete's heart.

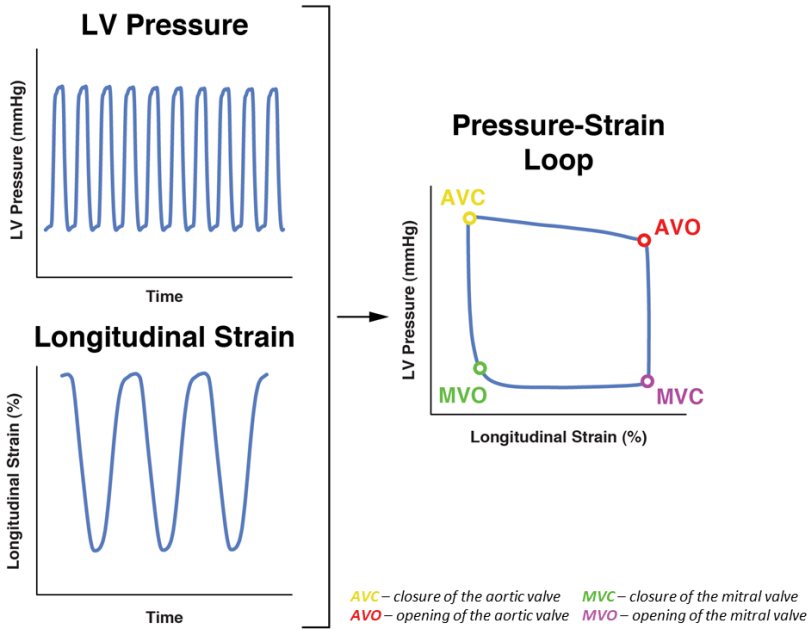

Figure 1. *Myocardial work analysis performed with the integration of speckle-tracking echocardiography-derived global longitudinal strain and LV pressure curves. (Figure was based on illustration from (68))*

1.3. Three-dimensional echocardiography

Echocardiography has become an integral part of cardiovascular medicine and evolved tremendously since its first clinical applications in the 1950s (69). Even to this day, conventional 2DE is still considered to be one of the most valuable imaging approach of everyday clinical practice. However, major limitations have to be acknowledged with regards to 2D imaging: all cardiac features are complex, three-dimensional (3D) structures, therefore imaging techniques that are limited to few tomographic planes and reliant on geometric assumptions cannot adequately characterize actual 3D morphology and function. The emergence of 3D echocardiography (3DE) over 25 years ago represented a significant step in the evolution of cardiovascular ultrasound techniques (70) and overcame several shortcomings of 2D assessment. With the advancements in computational and transducer technologies, real-time 3D acquisitions and the visualization of cardiac structures from virtually any viewpoint became available. One of the first important step was the development of fully sampled matrix-array transducers: these transducers are composed of approximately 3000 simultaneously active

piezoelectric elements and their operating frequencies range from 2 to 4 MHz (transthoracic) and 5 to 7 MHz (transesophageal) (71). These elements are arranged in rows and columns to form a rectangular grid (matrix configuration) and their firing within the matrix generates a scan line (axial or y direction, x or azimuthal direction, elevation or z direction) that allows to acquire volumetric pyramid of data (72). 3DE data acquisition can be performed by 3 different methods: multiplane imaging, real-time and ECG-gated multibeat acquisition. With the multiplane imaging method several 2D views can be acquired at a high frame rate using different plane orientations. The real-time method obtains multiple pyramidal volumes per second in a single heartbeat, whereas multibeat imaging provides images of higher temporal resolution with acquiring a number of ECG-gated narrow volumes over several consecutive heartbeats that are then stitched together to build up a larger final pyramidal data set (71, 72). The post-processing analysis of the acquired 3D datasets allows the quantification of relevant parameters using vendor-specific or vendor-independent software packages that are extensively validated (73-75). Current software solutions are providing automated or semiautomated border detection that may require the user to define few relevant anatomic landmarks, or perform manual corrections if necessary, thus offering a solution that gathers high quality data of 3D morphology and function of the heart, without excessive time strains (Figure 2).

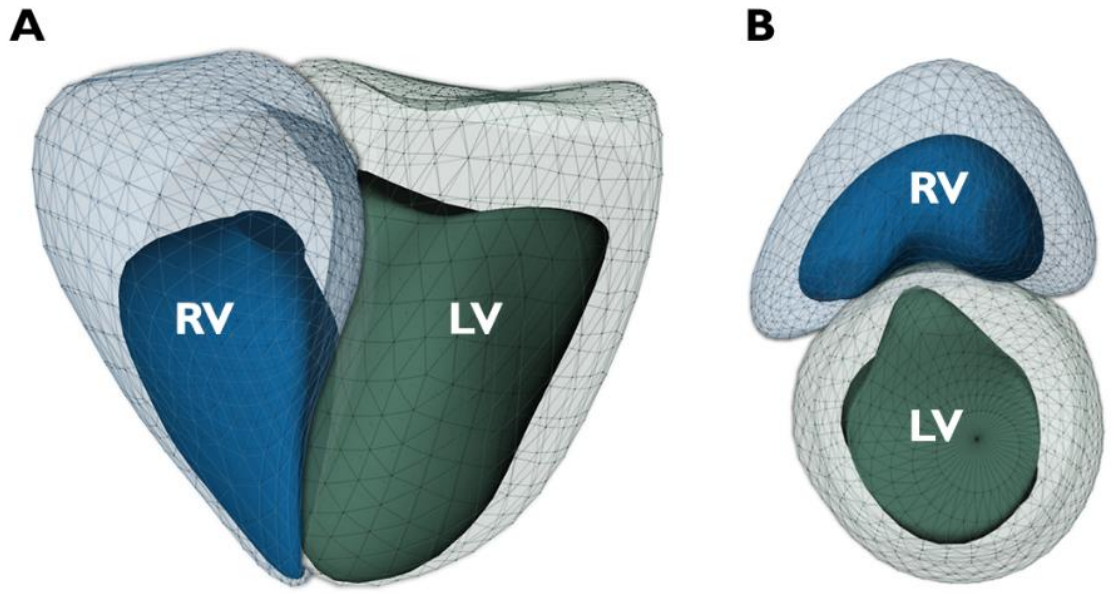

Figure 2. *3D model reconstruction of left (LV) and right ventricles (RV) obtained from 3D echocardiographic datasets. A – long axis view. B – short axis view. (Own work)*

1.3.1. Assessment of the left ventricle

Assessing LV morphology and function is a fundamental part in every echocardiographic protocol as the measurements of LV volumes, mass or function provides significant diagnostic and prognostic power (76). Compared to 2D imaging, 3D quantification of the LV offers incremental value in diagnostic accuracy and more precise risk stratification in several cardiac diseases. 3D volumetric parameters have been extensively validated against cMR and consistently showed better correlation and less underestimation compared to 2DE-derived geometry measures (77, 78). Contrary to other echocardiographic techniques, 3DE can directly measure myocardial volume and quantify LV mass (LV M), however the errors of muscle mass estimation are far from negligible: it is likely underestimated compared to cMR. Furthermore, 3DE provides more accurate quantification of LV EF, free of geometrical assumptions, LV foreshortening, and several studies proved its robust prognostic value of predicting adverse outcomes in several cardiac diseases (79, 80). Of note, beyond its prognostic significance, Rodriguez-Zanella et al demonstrated that 3DE-derived LV EF improved risk prediction in patients with LV dysfunction, and might help identify patients misclassified using 2D LV EF (81). These advantages of 3DE-derived measures, including 3D deformation, became especially important in the screening of athletes as they are often presented with significant chamber dilation and altered resting systolic function, thus hampering the differentiation of physiological adaptation from pathophysiological states.

1.3.2. Overcoming the limitations of conventional right ventricular measurements

Although the echocardiographic assessment of the RV morphology and function is included in everyday clinical practice, most of the acquired parameters consist of simple linear measurements with limited ability to portray the complex anatomy of the RV. The distinct myofiber architecture corresponds to the RV mechanics as RV global pump function is the cumulative result of three main mechanism: (1) shortening along the longitudinal axis, (2) the “bellows effect” referring to inward (radial) motion of the RV free wall, (3) anteroposterior shortening (82). Nevertheless, the added prognostic role of RV motion components have previously been demonstrated highlighting their incremental value (83). Furthermore, studies have shown exercise-induced alterations by

separate quantification of RV longitudinal and radial function: a relative dominance in the longitudinal shortening along with decreased radial function was observed among athletes (23). However, the routinely measured conventional parameters, such as tricuspid annular plane systolic excursion (TAPSE), or free wall longitudinal strain (FWLS) refer only to the longitudinal mechanics of the RV neglecting the other motion components. Therefore, 3DE evaluation of the RV is essential for a comprehensive volumetric and functional assessment that can go beyond the longitudinal component (84). 3DE-derived RV EF is a well-established, reproducible parameter which could overcome several shortcomings of conventional 2D RV indices (74). Of note, a recent meta-analysis from our research group indeed demonstrated the superior prognostic value of 3D RV EF compared with conventional 2D parameters, and RV EF might further support the risk stratification of patients (85). Although the 3D deformation of the athlete's heart is scarcely characterized, especially in terms RV, it may help to better understand the associations between resting cardiac function and athletic capacity.

1.3.3. Evaluation of the mitral complex and the tricuspid apparatus

3DE has also significantly contributed to understand the complex anatomy and mechanics of both mitral (MA) and tricuspid annulus (TA). 2DE is not suitable to provide accurate data about their shape and function due to its inability to visualize the mitral (MV) and the tricuspid valve (TV) in its entirety. Both MA and TA are forming a fibrous continuity between ventricular and atrial myocardium and leaflet tissues and have non-planar geometry: MA is referred to as a hyperbolic paraboloid and often likened to a saddle shape, whereas TA has an elliptical asymmetric structure (86). The cyclic changes in the atrioventricular (AV) valves' shape are contributing to lessening the strain on the leaflets during systole and optimizing coaptation throughout the corresponding phase of the cardiac cycle (87, 88). Previous studies have also described the dynamics of the MA: first annular contraction in protosystole followed by annular folding (during LV contraction the MA folds from early- to mid-systole increasing its non-planarity), then during late systole in relation to atrial and ventricular filling and emptying it gradually expands to its diastolic state (86, 89, 90). In healthy MV, the MA is quite flexible and is significantly influenced by the LV as during systole the closure of the MV is a result of the interaction between closing forces and opposite tethering forces. While the former is related to transmitral pressure gradient, the latter is determined by LV systolic pressure (91).

Concerning the TV, the TA dilates asymmetrically due to the relatively fixed nature of the septal leaflet, still it is rather dynamic and changes significantly with loading conditions and even with the cardiac cycle: during ventricular end-systole/early diastole and atrial systole the TA becomes larger, whereas smaller in ventricular systole (92, 93). The coaptation of TV is located at annular level with overlapping leaflets (>5mm in length) providing a coaptational reserve to ensure efficient closure (94). These mechanisms are pivotal to preserve valvular competence, however various cardiac conditions could lead to the imbalance of tethering and closing forces resulting in valvular insufficiency. The pathophysiology of functional mitral (MR) and tricuspid regurgitation (TR) shares similarities: the displacement of papillary muscles lead to leaflet tethering and malcoaptation, whereas annular dilation results in changes of annular geometry and dynamics (95). Although in functional regurgitation (FR) both of these characteristics can be present, the former rather refers to the ventricular type of FR, where the papillary displacement and subsequent leaflet tethering are secondary to ventricular remodeling, whereas the latter describes atrial FR with a more pronounced annular enlargement and flattening secondary to atrial dilation (95). Although degenerative etiologies of regurgitation, such as myxomatous valve diseases (i.e. valve prolapse, Barlow disease, fibroelastic deficiency) are rare, distinct changes was observed in the AV structures: the annuli and leaflets are enlarged and flattened, and showed different, a more blunted annular dynamics (88). 3DE and dedicated available softwares for both MV and TV have offered a solution to accurately characterize the valvular geometry by quantifying the annulus with parameters such as 3D area, area fraction, perimeter, transverse diameters, and nonplanar angle or annulus height to commissural width ratio (ACHWR; both used to describe the annular saddle shape) and quantifying the leaflets with measuring leaflet lengths, areas, or tenting height, area and volume (89, 96). Consequently, numerous studies investigated the distinctive structural and functional alterations of valvular diseases using 3DE, however less is known about the exercise-induced remodeling of the AV structures in athletes. Nevertheless, functional regurgitation is reported frequently among athletes (97), thus the 3D assessment of valves would be of high clinical importance.

2. Objectives

2.1. Investigation of the correlation between myocardial work indices and load-independent metrics of contractility in a rat model of athlete's heart and the characterization of the association between myocardial work and exercise capacity among elite athletes

Although both EF and GLS are sensitive parameters of LV systolic function, they are significantly influenced by multiple factors, such as loading conditions and heart rate. Conversely, MW is less dependent on loading conditions, therefore we may hypothesize that it better reflects cardiac contractility, and thus, it might be a robust resting marker of the athlete's heart. Accordingly, we sought to investigate the correlation between MW and the invasively measured myocardial contractility in a rat model of athlete's heart. We also aimed to evaluate the MW of elite athletes and explore its association with aerobic capacity.

2.2. Characterization of biventricular morphology and function using 3D echocardiography and investigation of the correlations between cardiac remodeling and peak exercise capacity

While LV adaptation to regular, intense exercise has been thoroughly studied, data concerning the RV mechanical changes and their continuum with athletic performance are scarce. The aim of this study was to characterize biventricular morphology and function and their relation to sex, age, and sports classes in a large cohort of elite athletes using 3D echocardiography and to investigate the correlations between cardiac remodeling and peak exercise capacity.

2.3. Characterization of the geometry of mitral (MA) and tricuspid (TA) annuli in elite athletes using 3D echocardiography

A balanced dilation of the cardiac chambers is a characteristic and unequivocal feature of an athlete's heart. Although ventricular and atrial dilation can significantly affect atrioventricular annular geometry and related valvular competency, less is known about the exercise-induced alterations in the shape of the MA and TA in elite athletes. Thus, our study aimed to characterize the geometry of MA and TA in elite athletes compared with healthy, sedentary volunteers using 3D echocardiography.

3. Results

3.1. Investigation of the correlation between myocardial work indices and load-independent metrics of contractility in a rat model of athlete's heart and the characterization of the association between myocardial work and exercise capacity among elite athletes

3.1.1. Experimental investigations

Young adult (57–61 days old) male (n = 16) and female (n = 16) Wistar rats (Charles River Laboratories, Sulzfeld, Germany) were included in the current study (68). After acclimatization, the rats were divided into four experimental groups: male control (M_{Co}, n = 8), male exercised (M_{Ex}, n = 8), female control (F_{Co}, n = 8), and female exercised groups (F_{Ex}, n = 8). Rats of the exercised male and female groups were exposed to 200 min/day swimming, 5 days/week for 12 weeks to induce physiological hypertrophy, as previously described by our research group (43). The study protocol was approved by the Ethical Committee for Animal Experimentation of Semmelweis University (Approval No. PEI/001/2374-4/2015).

3.1.1.1. Conventional echocardiography-derived parameters

Both the M_{Ex} and F_{Ex} groups showed the characteristic echocardiographic features of exercise-induced myocardial hypertrophy. Exercised animals exhibited increased wall thickness values and higher LV mass compared to controls in both sexes. The extent of relative LV hypertrophy was more pronounced in female animals than males (+20 to 25% vs. +10 to 15% increase in calculated LV mass) (Figure 3) (68).

3.1.1.2. Invasive hemodynamic parameters

Basic hemodynamic parameters did not differ between the control and exercised groups (68). Markedly increased values of ESPVR (the load-independent index of contractility) were found in the exercised groups compared to control animals. The presence of these adaptive changes was independent of sex (Figure 3).

3.1.1.3. Myocardial work analysis in the rat model of athlete's heart

GLS was significantly increased in the exercised groups compared to controls, with female rats having higher strain values than males (Figure 3, Table 1). In addition, GMWI and CMWI showed higher values in exercised animals, with similar sex-related differences as seen in GLS. WMWI and MWE did not differ between the experimental groups (Table 1).

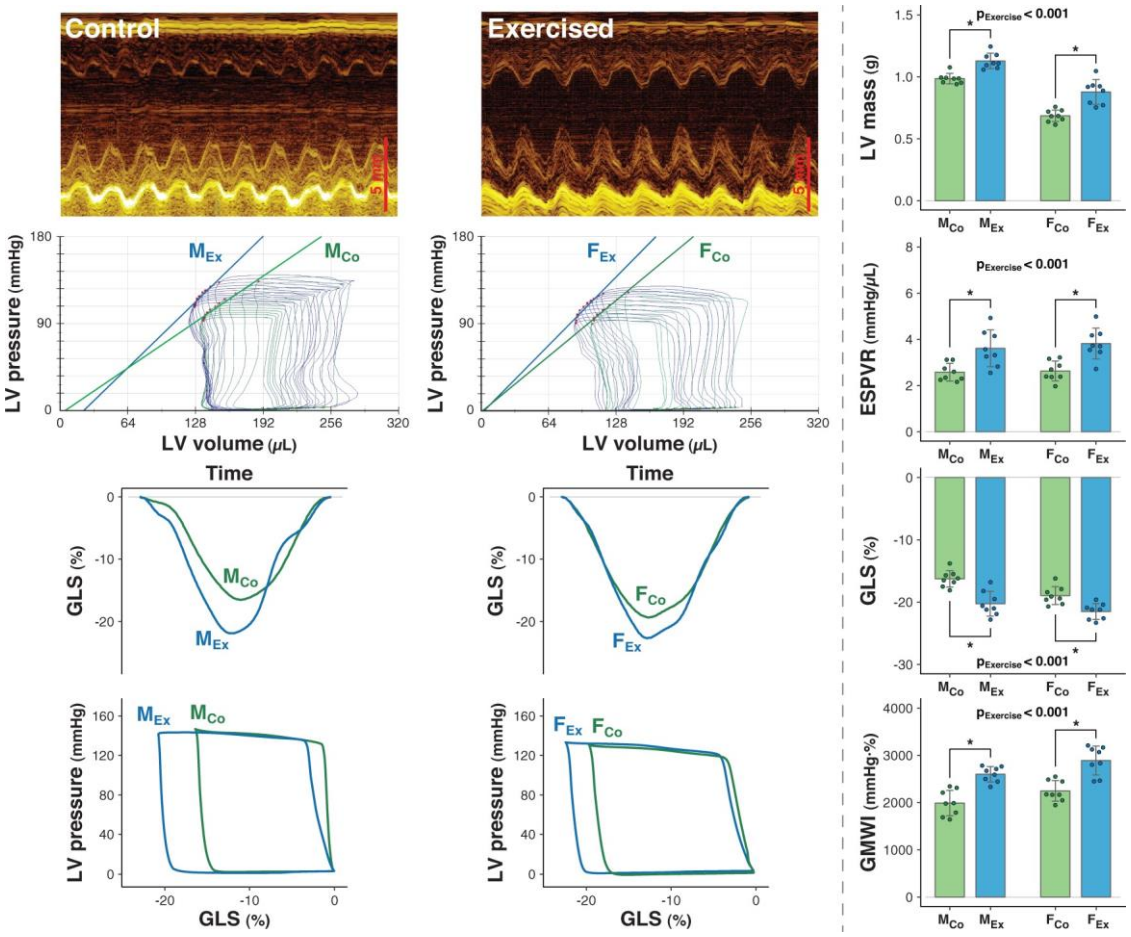

Figure 3. *Exercise-induced structural and functional adaption in the rat model of athlete's heart (68). Left panel illustrates M-mode echocardiographic recordings, pressure-volume loops, strain curves, and pressure-strain loops of representative animals. Right panel depicts the group comparisons of LV mass, ESPVR, GLS, and GMWI. *P < 0.05, Tukey's post hoc test (following two-way analysis of variance with the factors 'Sex' and 'Exercise'). ESPVR, slope of end-systolic pressure-volume relationship;* F_{Co}*, female control group;* F_{Ex}*, female exercised group; GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular;* M_{Co}*, male control group;* M_{Ex}*, male exercised group.*

Table 1. Myocardial work in the rat model of athlete's heart

	M_{Co}	M_{Ex}	F_{Co}	F_{Ex}	p_{Sex}	$p_{Exercise}$	p_{Inter}
GLS (%)	-16.3±1.3	-20.3±2.0*	-19.0±1.4	-21.5±1.3**	0.001	<0.001	0.195
GMWI (mmHg·%)	1989±268	2600±163*	2248±220	2890±305**	0.004	<0.001	0.859
CMWI (mmHg·%)	2341±290	2915±211*	2550±261	3214±364**	0.018	<0.001	0.658
WMWI (mmHg·%)	11±8	5±4	10±10	17±9	0.085	0.796	0.029
MWE (%)	98±1	99±1	98±1	98±1	0.275	0.519	0.065

*Values are mean ± SD. ∗ $P < 0.05$ vs. M_{Co}, ** $P < 0.05$ vs. F_{Co}. Statistical test: two-way analysis of variance (ANOVA) with the factors 'Sex' and 'Exercise'. The p-value for sex-exercise interaction (p_{Inter}) was also calculated. CMWI, constructive myocardial work index; F_{Co}, female control group; F_{Ex}, female exercised group; GLS, global longitudinal strain; GMWI, global myocardial work index; M_{Co}, male control group; M_{Ex}, male exercised group; MWE, myocardial work efficiency; WMWI, wasted myocardial work index.*

3.1.1.4. Correlation of contractility with myocardial work indices

GLS showed a strong correlation with ESPVR in the pooled animal cohort ($r = -0.716$, $P < 0.001$). According to our experimental data, MW indices are robustly correlated with LV contractility: both GMWI and CMWI demonstrated strong positive correlation with ESPVR ($r = 0.764$ and $r = 0.729$, both $P < 0.001$) (Figure 4).

3.1.1.5. Determinants of global longitudinal strain and myocardial work indices

Ordinary least squares (OLS) analysis was performed to determine the relative importance of five predefined factors [(i) preload (defined as meridional end-diastolic wall stress, σED), (ii) afterload (defined as arterial elastance, E_a), (iii) LV contractility (defined as ESPVR), (iv) exercise training, and (v) sex] that were assumed to substantially influence the values of GLS, GMWI, and CMWI (68). This analysis revealed that GLS was predominantly determined by sex and afterload, whereas the major determinants of GMWI and CMWI were rather contractility and exercise (Figure 4).

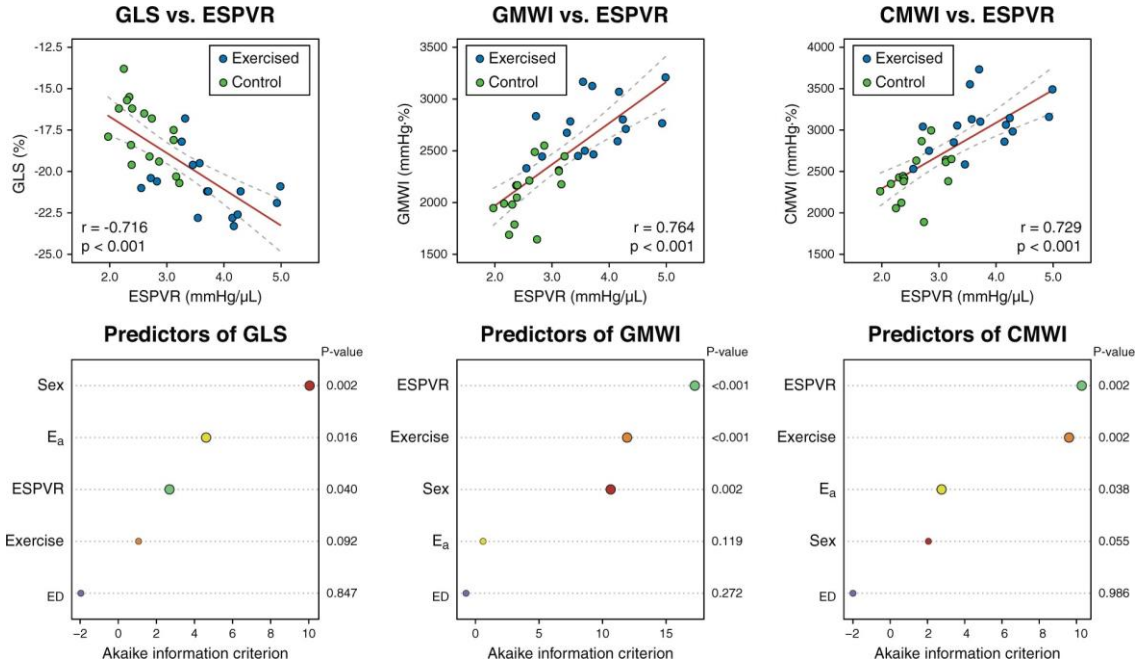

Figure 4. *Correlations between LV contractility and LV deformation parameters in rats (upper panel), predictors of LV deformation parameters assessed using multivariable analysis (lower panel)(68). σED, meridional end-diastolic wall stress; CMWI, constructive myocardial work index; E_a, arterial elastance; ESPVR, slope of end-systolic pressure–volume relationship; F_{Co}, female control group; F_{Ex}, female exercised group; GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular; M_{Co}, male control group; M_{Ex}, male exercised group.*

3.1.2. Human investigations

3.1.2.1. Morphometric and echocardiographic characteristics

The included 20 elite swimmer athletes (10 women and 10 men, members of the national team; the study was approved by the Medical Research Council; ETT-TUKEB No. 13687-0/2011-EKU) had been competitively participating in swimming for 14±5 years, with a current average training duration of 23±4 h per week. Athletes had significantly higher resting systolic blood pressure and lower resting HR compared to control subjects. As expected, higher values of CPET-derived peak oxygen uptake were measured in athletes than in controls (68). In athletes, exercise-induced adaptive changes could be observed in the echocardiographic parameters of cardiac structure and function (Table 2, Figure 5).

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Table 2. Morphometric and 3D echocardiographic characteristics of human athletes and controls

	M_{Co}	M_{Ath}	F_{Co}	F_{Ath}	p_{Sex}	$p_{Exercise}$	p_{Inter}
Age, years	20.6±3.9	21.1±4.5	22.4±0.9	18.6±4.9	0.785	0.183	0.092
Height, cm	177.5±6.4	186.0±6.6*	169.1±4.9	169.2±8.3	<0.001	0.049	0.053
BW, kg	75.0±15.8	80.3±9.7	64.3±11.4	60.2±7.3	<0.001	0.874	0.201
BMI, kg/m^2	23.7±4.1	23.2±2.0	22.5±4.1	21.0±1.4	0.103	0.305	0.605
BSA, m^2	1.92±0.22	2.03±0.15	1.73±0.15	1.68±0.14	<0.001	0.541	0.121
SBP, mmHg	127±13	140±10*	117±7	130±8$^{\#}$	0.001	<0.001	0.974
DBP, mmHg	76±7	80±11	75±6	75±7	0.211	0.413	0.390
HR, 1/min	76±13	62±16	73±12	63±11	0.750	0.007	0.645
VO_2/kg, mL/min/kg	47.0±4.8	58.6±4.2*	37.6±5.1	51.8±2.8$^{\#}$	<0.001	<0.001	0.344
3D LV EDVi, mL/m^2	61.4±12.4	91.1±17.7*	59.1±11.3	75.8±4.3$^{\#}$	0.030	<0.001	0.106
3D LV ESVi, mL/m^2	24.4±5.7	41.1±10.9*	23.6±5.8	32.0±4.0$^{\#}$	0.033	<0.001	0.073
3D LV SVi, mL/m^2	37.0± 7.1	49.9±7.9*	35.5±7.0	43.8±4.6$^{\#}$	0.080	<0.001	0.284
3D LV Mi, g/m^2	66.0±11.8	88.4±16.3*	65.9±8.9	78.5±11.7	0.217	<0.001	0.219
3D LV EF, %	60.3±2.7	55.0±4.8	60.2±5.3	57.7±4.7	0.370	0.010	0.328
3D RV EDVi, mL/m^2	63.1±9.4	93.6±14.4*	54.8±6.6	79.1±7.4$^{\#}$	0.001	<0.001	0.333
3D RV ESVi, mL/m^2	26.0±4.7	44.7±9.1*	22.8±3.3	34.7±4.6$^{\#}$	0.001	<0.001	0.077
3D RV SVi, mL/m^2	37.1±5.5	48.8±6.8*	32.0±4.5	44.3±4.9$^{\#}$	0.009	<0.001	0.864
3D RV EF, %	58.9±3.2	52.5±3.9*	58.4±3.8	56.1±3.6$^{\#}$	0.184	0.001	0.082

Values are mean ± SD. $^{*}p$ <0.05 vs. M_{Co}, $^{\#}p$ <0.05 vs. F_{Co}. Statistical test: two-way analysis of variance (ANOVA) with the factors 'Sex' and 'Exercise'. The p-value for sex-exercise interaction (p_{Inter}) was also calculated. BMI, body mass index; BSA, body surface area; BW, body weight; DBP, diastolic blood pressure; EDVi, end-diastolic volume index, EF, ejection fraction; ESVi, end-systolic volume index; F_{Ath}, female athlete group; F_{Co}, female control group; HR, heart rate at rest; fraction; LV, left ventricular; M_{Ath}, male athlete group; M_{Co}, male control group; Mi, mass index; RV, right ventricular; SBP, systolic blood pressure; SVi, stroke volume index VO_2/kg, peak oxygen uptake

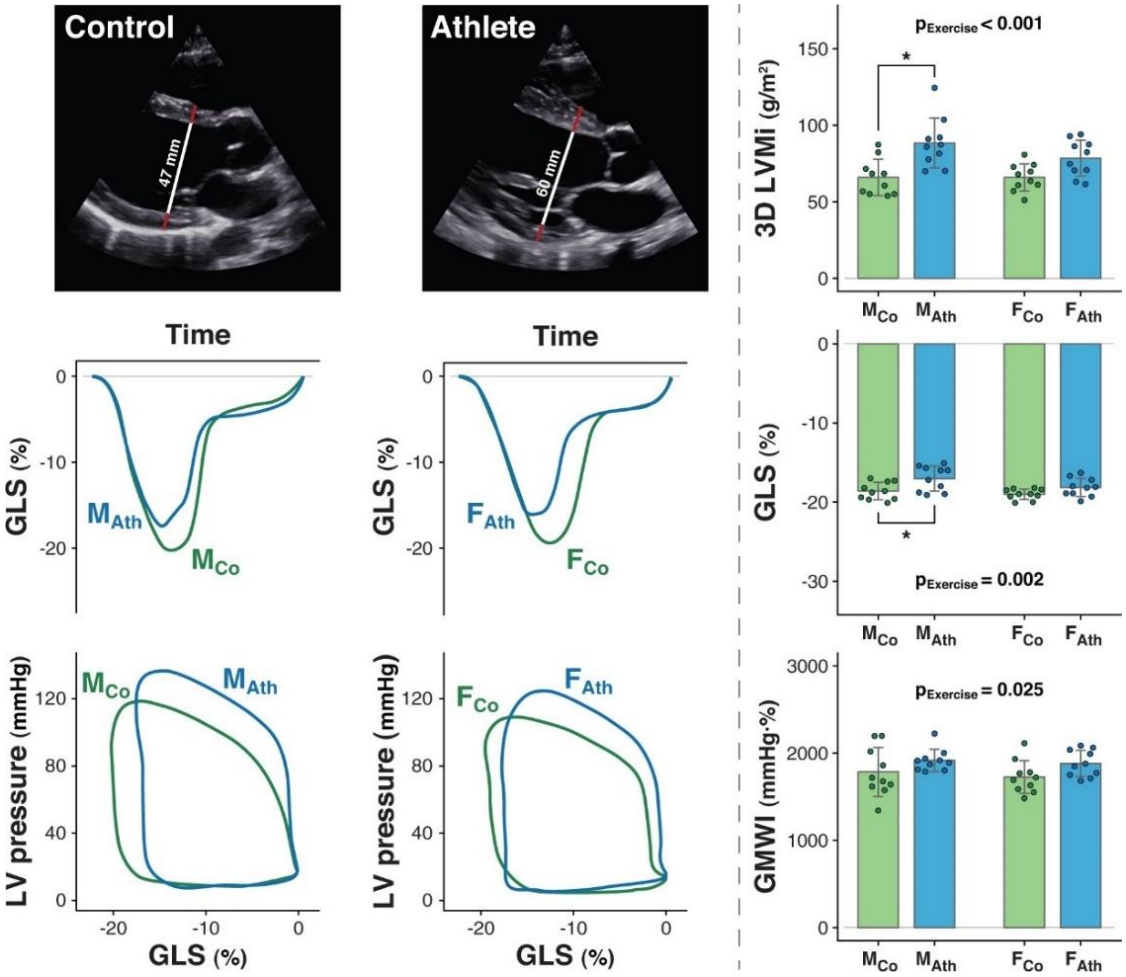

Figure 5. *Exercise-induced structural and functional adaptation in human athletes (68). Left panel illustrates 2D echocardiographic images, strain curves, and pressure-strain loops of representative athletes and control subjects. Right panel depicts the group comparisons of LVMi, GLS, and GMWI. *p<0.05, Tukey's post hoc test (following two-way analysis of variance with the factors 'Sex' and 'Exercise'). GMWI, global myocardial work index; GLS, global longitudinal strain; F_{Ath}, female athlete group; F_{Co}, female control group; LV, left ventricular; LVMi, left ventricular mass index; M_{Co}, male control group, M_{Ath}, male athlete group.*

3.1.2.2. Myocardial work analysis in elite athletes

Regular exercise training resulted in the reduction of GLS ($P_{Exercise}$ = 0.002), and sex was observed to have a slight impact on GLS (P_{Sex} = 0.046) (Table 3, Figure 5). In contrast, exercise training was associated with higher values of GMWI ($P_{Exercise}$ = 0.025) and CMWI ($P_{Exercise}$ = 0.004), and sex did not have a significant effect on their values (P_{Sex} = 0.460 and P_{Sex} = 0.297, respectively) (Table 3, Figure 5). WMWI and MWE did not differ between athletes and controls (Table 3).

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Table 3. Myocardial work in human athletes and controls

	M_{Co}	M_{Ath}	F_{Co}	F_{Ath}	p_{Sex}	$p_{Exercise}$	p_{Inter}
GLS (%)	-18.6±1.1	-17.0±1.6*	-19.0±0.7	-18.2±1.2	0.046	0.002	0.344
GMWI (mmHg·%)	1784±280	1916±127	1726±187	1882±149	0.460	0.025	0.846
CMWI (mmHg·%)	2038±253	2187±164	1954±136	2151±134	0.297	0.004	0.676
WMWI (mmHg·%)	66±30	90±27	62±26	64±47	0.170	0.220	0.312
MWE (%)	97±1	96±1	97±1	97±2	0.240	0.451	0.246

*Values are mean ± SD. * P < 0.05 vs. M_{Co}, ** P < 0.05 vs. F_{Co}. Statistical test: two-way analysis of variance (ANOVA) with the factors 'Sex' and 'Exercise'. The P-value for sex-exercise interaction (P_{Inter}) was also calculated. CMWI, constructive myocardial work index; F_{Ath}, female athlete group; F_{Co}, female control group; GLS, global longitudinal strain; GMWI, global myocardial work index; M_{Ath}, male athlete group; M_{Co}, male control group; MWE, myocardial work efficiency; WMWI, wasted myocardial work index.*

3.1.2.3. Correlation of LV functional parameters with peak oxygen uptake

In the pooled study cohort, LV EF and GLS correlated weakly to moderately with VO_2/kg (r = -0.341, P = 0.032 and r = 0.494, P = 0.001, Figure 6). Both GMWI and CMWI exhibited moderate positive correlation with CPET-derived VO_2/kg (r = 0.527 and r = 0.582, both P < 0.001, Figure 6). Correlations of similar strength were observed in the subgroups containing males or females exclusively (68).

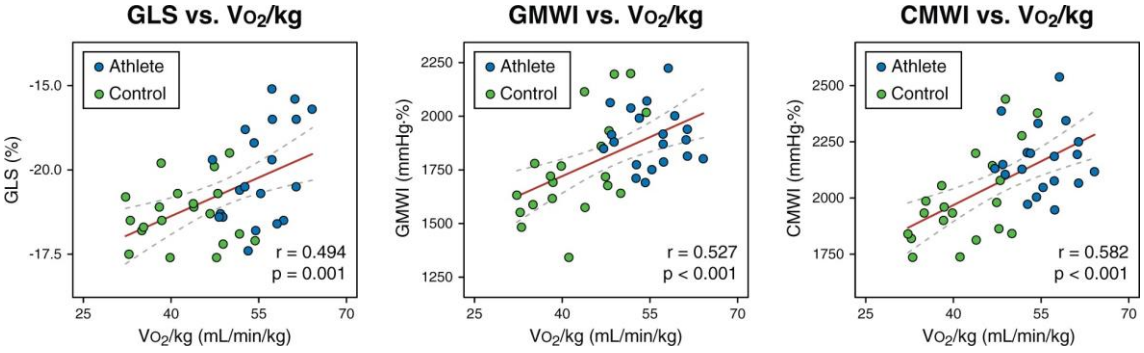

Figure 6. *Correlations between peak oxygen uptake and left ventricular deformation parameters in human athletes (68). CMWI, constructive myocardial work index; GLS, global longitudinal strain; GMWI, global myocardial work index; VO_2/kg, peak oxygen uptake.*

3.2. Characterization of biventricular morphology and function using 3D echocardiography and investigation of the correlations between cardiac remodeling and peak exercise capacity

3.2.1. Athletes versus sedentary volunteers

Basic anthropometric, hemodynamic data, and training-specific characteristics of the athlete and control groups are summarized in Table 4 (in accordance with the Declaration of Helsinki and approved by the Medical Research Council (ETT-TUKEB No. 13687-0/2011-EKU). Most of the athletes participated in mixed and endurance classes of sports, predominantly water polo (34.8%), soccer (30.6%), and swimming (13.3%); however, other types of sports, such as power and skill, were represented as well in our cohort of athletes. Athletes presented with higher values of height, weight, and body surface area (BSA) compared with the sedentary control group. Athletes also demonstrated significantly higher resting systolic blood pressures and lower diastolic blood pressures and heart rates than controls. Our athletes have been participating in competitive sports for an average of 12 years with an average training duration of 15 hours/week at the time of the echocardiographic evaluation. The athlete group's CPET-derived peak exercise capacity significantly exceeded the control population's (Table 4).

Conventional 2DE parameters of athletes and controls showed results as seen in previous studies with regards to the athlete's heart (26). Detailed 3D echocardiographic characteristics of athletes and controls are summarized in Table 5. As expected, there were significant differences between the athlete and the control group concerning LV and RV morphological and functional parameters. Athletes had significantly higher LV and RV end-diastolic (EDVi) and end-systolic volume index (ESVi) values. Similarly, LV mass index (Mi), LV stroke volume index (SVi), and RV SVi values were higher in athletes compared with controls. In athletes, LV EF, LV GLS, LV global circumferential strain (GCS) along with RV EF, RV GCS showed significantly decreased resting values, in contrast to RV GLS, which did not show difference compared with controls (Table 5). The aforementioned results remained the same when comparing male athletes to male controls and female athletes to female controls. Similarly, adolescent athletes (irrespective of sex) already presented with the same pattern of exercise-induced cardiac remodeling as seen in the pooled athlete population when compared to controls (26).

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Table 4. Baseline and training-specific characteristics of athlete and control groups

	Athletes (n=422)	Controls (n=55)	p
Baseline characteristics			
Age (years)	20.1±5.8	20.1±3.2	0.939
Male, n (%)	295 (69.9)	31 (56.4)	0.061
Height (cm)	177.9±10.6	171.1±9.5	<0.001
Weight (kg)	72.6±14.7	65.2±13.2	<0.001
BSA (m^2)	1.9±0.2	1.8±0.2	<0.001
SBP (mmHg)	131.9±14.8	123.6±12.5	<0.001
DBP (mmHg)	74.5±9.8	78.2±9.8	0.009
HR (bpm)	67.9±12.5	78.9±15.1	<0.001
Training-specific characteristics			
Type of sport			
• **Mixed, n (%)**	293 (69)	-	
• **Endurance, n (%)**	88 (21)	-	
• **Power, n (%)**	33 (8)	-	
• **Skill, n (%)**	8 (2)	-	
Competitive training since (years)	11.9±5.6	-	
Training time (h/week)	15.4±7.3	-	
VO_2 (L/min)	3.8±0.9	2.9±0.8	<0.001
VO_2/kg (mL/kg/min)	52.7±7.7	44.9±7.3	<0.001

Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; VO_2, peak oxygen uptake; VO_2/kg, peak oxygen uptake indexed to body weight

Table 5. Three-dimensional echocardiographic data of athlete and control groups

	Athletes (n=422)	Controls (n=55)	p
LEFT VENTRICLE			
LV EDVi (mL/m^2)	81.3±13.2	62.2±11.4	<0.001
LV ESVi (mL/m^2)	35.3±7.3	24.3±5.5	<0.001
LV SVi (mL/m^2)	45.9±7.5	37.9±7.2	<0.001
LV Mi (g/m^2)	86.7±15.1	66.0±12.0	<0.001
LV EF (%)	56.7±4.2	61.0±4.5	<0.001
LV GLS (%)	-19.2±2.3	-21.2±2.0	<0.001
LV GCS (%)	-27.7±3.0	-31.0±3.5	<0.001
RIGHT VENTRICLE			
RV EDVi (mL/m^2)	81.6±14.3	62.7±11.2	<0.001
RV ESVi (mL/m^2)	36.7±8.7	25.7±5.3	<0.001
RV SVi (mL/m^2)	44.9±7.3	37.0±7.4	<0.001
RV EF (%)	55.3±4.8	58.9±4.7	<0.001
RV GLS (%)	-21.8±3.4	-22.2±3.6	0.447
RV GCS (%)	-20.9±4.4	-24.5±4.5	<0.001

Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricle; Mi, mass index; RV, right ventricle; SVi, stroke volume index

We have also compared the exercise-induced relative decreases of LV GLS, GCS, and RV GLS and GCS. Left ventricular GLS (average decrease of 10%) and LV GCS (11%) showed a similar, balanced decrease. Meanwhile, the relative decrease of RV GCS (15%) exceeded the decrement in RV GLS (2%, $P < 0.001$) (Figure 7).

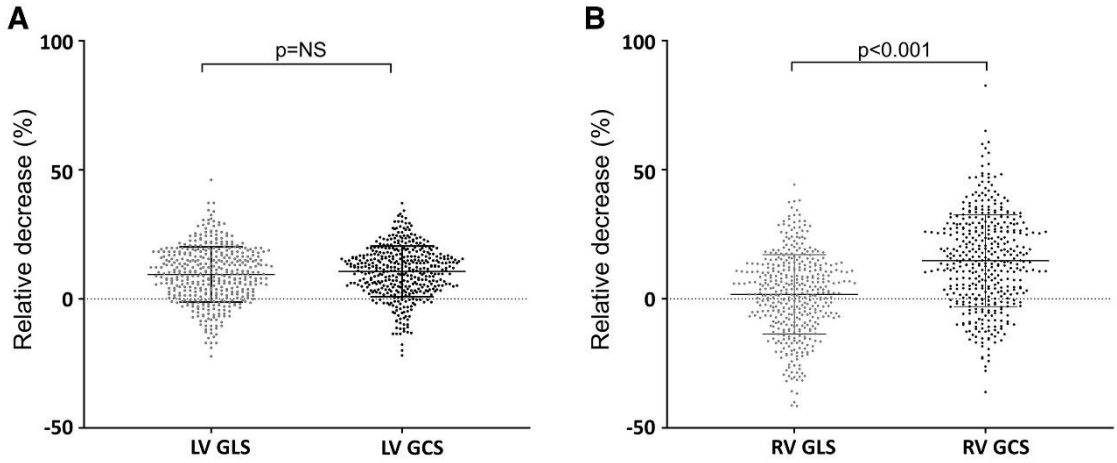

Figure 7. *Comparison of the exercise-induced relative decreases of the left ventricular (LV) global longitudinal (GLS) and global circumferential strain (GCS) – (A) and the right ventricular (RV) GLS and GCS – (B) in the athlete cohort (26). 3D LV GLS and LV GCS (P = NS) showed a similar exercise-induced relative decrease; however, the decrement in RV GCS was disproportionately larger compared with RV GLS (P < 0.001). NS, nonsignificant.*

3.2.2. Sex-specific differences in athletes

We have compared male (n = 295) and female (n = 127) athletes based on training-specific characteristics and 3D echocardiographic data (26). The results are shown in Table 6. There was no significant age difference between the two groups. Male athletes have been participating in competitive sports for longer periods of time; however, females had longer average weekly training duration. Male athletes also showed higher values in CPET-derived peak exercise capacity compared with women. Regarding the 3D echocardiographic results, distinct morphological and functional differences were observed between male and female athletes. Male sex was associated with higher LV and RV EDVi and ESVi. Similarly, LV Mi, LV SVi, and RV SVi values were higher among male athletes compared with females. In male athletes, LV EF, LV GLS, LV GCS along with RV EF, and RV GCS showed significantly decreased resting values, in contrast to RV GLS, which did not differ compared with females (Table 6).

Table 6. Comparison of male and female athletes based on training-specific characteristics and 3D echocardiographic data

	Male athletes (n=295)	Female athletes (n=127)	p
Age (years)	19.8±6.1	20.7±5.1	0.144
Type of sport			
● **Mixed, n (%)**	217 (74.1)	76 (25.9)	-
● **Endurance, n (%)**	53 (60.2)	35 (39.8)	-
● **Power, n (%)**	21 (63.6)	12 (36.4)	-
● **Skill, n (%)**	4 (50)	4 (50)	-
Competitive training since (years)	12.3±5.9	10.9±4.9	0.026
Training time (h/week)	13.5±6.3	19.9±7.6	<0.001
VO_2/kg (mL/kg/min)	55.2±7.1	46.8±5.7	<0.001
LEFT VENTRICLE			
LV EDVi (mL/m^2)	84.3±13.1	74.3±10.5	<0.001
LV ESVi (mL/m^2)	37.0±7.2	31.3±5.9	<0.001
LV SVi (mL/m^2)	47.2±7.6	43.0±6.5	<0.001
LV Mi (g/m^2)	89.8±15.2	79.4±11.9	<0.001
LV EF (%)	56.2±4.0	57.9±4.4	<0.001
LV GLS (%)	-18.9±2.3	-19.8±2.1	<0.001
LV GCS (%)	-27.4±2.9	-28.3±3.3	0.006
RIGHT VENTRICLE			
RV EDVi (mL/m^2)	84.7±14.6	73.6±12.1	<0.001
RV ESVi (mL/m^2)	38.7±8.8	31.9±7.2	<0.001
RV SVi (mL/m^2)	46.1±7.7	41.7±6.7	<0.001
RV EF (%)	54.6±4.6	56.9±4.8	<0.001
RV GLS (%)	-21.7±3.5	-22.1±3.3	0.243
RV GCS (%)	-20.4±4.1	-22.0±4.7	0.001

Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricle; Mi, mass index; RV, right ventricle; SVi, stroke volume index; VO_2/kg, peak oxygen uptake indexed to body weight

3.2.3. Adult versus adolescent athletes

We have also compared adult (>18 years of age, n = 207) and adolescent (<18 years of age, n = 215) athletes based on training-specific characteristics and 3D echocardiographic data (Table 7) (26). Adolescent athletes had an average training duration of 12 h/week. In comparison, adult athletes had an average training duration of 19 h/week. Despite the differences in the training regimes of the two age groups, adolescent athletes' CPET-derived peak exercise capacity significantly exceeded the adult populations'. Adolescent athletes had significantly lower LV EDVi and ESVi and LV Mi values compared with

adult athletes; however, LV SVi did not differ between the two age groups. Interestingly, all RV volumes were comparable in the pooled adult vs. adolescent athlete groups; however, if the two sexes were compared, only female adolescents showed similar volumes to adult female athletes (26). In adolescents, LV EF, LV GLS, and GCS showed higher resting values compared with adults (Table 7). In contrast, RV EF and RV GCS did not differ between adults and adolescents, while RV GLS was significantly higher in adolescents compared with adult athletes (Table 7).

Table 7. Comparison of adolescent and adult athletes based on training-specific characteristics and 3D echocardiographic data

	Adolescent athletes (n=215)	**Adult athletes (n=207)**	**p**
Age (years)	15.8±1.4	24.5±5.2	<0.001
Male, n (%)	169 (78.6)	126 (60.9)	<0.001
Type of sport			
● **Mixed, n (%)**	180 (61.4)	113 (38.6)	-
● **Endurance, n (%)**	26 (29.5)	62 (70.5)	-
● **Power, n (%)**	3 (9.1)	30 (90.9)	-
● **Skill, n (%)**	6 (75)	2 (25)	-
Competitive training since (years)	8.4±3.0	15.5±5.5	<0.001
Training time (h/week)	12.3±6.1	18.6±7.2	<0.001
VO_2/kg (mL/kg/min)	54.4±6.9	50.9±8.2	<0.001
LEFT VENTRICLE			
LV EDVi (mL/m^2)	80.0±13.0	82.6±13.3	0.040
LV ESVi (mL/m^2)	34.2±7.2	36.4±7.4	0.003
LV SVi (mL/m^2)	45.7±7.3	46.2±7.7	0.418
LV Mi (g/m^2)	83.8±13.5	89.6±16.1	<0.001
LV EF (%)	57.3±3.9	56.1±4.4	0.002
LV GLS (%)	-19.6±2.1	-18.8±2.3	<0.001
LV GCS (%)	-28.0±2.9	-27.4±3.1	0.035
RIGHT VENTRICLE			
RV EDVi (mL/m^2)	80.2±15.2	82.6±14.3	0.104
RV ESVi (mL/m^2)	36.1±8.8	37.2±9.0	0.198
RV SVi (mL/m^2)	44.2±7.9	45.4±7.4	0.098
RV EF (%)	55.3±4.5	55.3±5.1	0.965
RV GLS (%)	-22.3±3.4	-21.3±3.4	0.003
RV GCS (%)	-20.6±4.2	-21.1±4.5	0.195

Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricle; Mi, mass index; RV, right ventricle; SVi, stroke volume index; VO_2/kg, peak oxygen uptake indexed to body weight

3.2.4. Differences among sports classes

We have compared the athlete population categorized by different sport disciplines (Table 8) (26). The subgroups consisted of athletes participating in mixed (n = 293), endurance (n = 88), power (n = 33), and skill (n = 8) sport classes, which classification was based on the relative isometric and isotonic components of exercise according to the recommendations of the European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI); however, we excluded skill discipline from further analysis due to the very low number of subjects in this subgroup (22). Power athletes have been competing for the longest time with an average of 17 years, while endurance athletes had significantly longer training durations with an average of 21 h/week. Endurance athletes also exceeded the other groups in terms of peak exercise capacity. Concerning the 3D echocardiographic analysis, LV EDVi and ESVi were comparable between the study groups; however, LV SVi and LV Mi were significantly lower in power athletes than in mixed and endurance athletes. Interestingly, RV EDVi and RV ESVi were the highest in endurance athletes, while power athletes had lower values of RV EDVi, ESVi, and RV SVi compared with the other groups. In terms of LV function, power athletes demonstrated lower resting values of LV GLS and GCS compared with mixed and endurance athletes. In contrast, resting values of RV EF, RV GLS, and GCS were the lowest in endurance athletes, while power athletes demonstrated the highest resting values of RV GCS compared with the other groups (Table 8).

Table 8. Comparison of the athlete population categorized by different sport disciplines

	Mixed (n=293)	Endurance (n=88)	Power (n=33)	Overall p
Age (years)	18.8±4.9$^{§\#}$	22.6±6.7$^{*\#}$	25.2±5.9§*	<0.001
Male, n (%)	217 (74.1)§	53 (60.2)*	21 (63.6)	0.031
Competitive training since (years)	10.8±5.1$^{§\#}$	14.0±5.6$^{*\#}$	16.6±6.2§*	<0.001
Training time (h/week)	13.8±7.1§	21.1±6.3$^{*\#}$	15.3±3.9§	<0.001
VO_2/kg (mL/kg/min)	52.7±7.3$^{§\#}$	55.4±7.8$^{*\#}$	45.7±7.3§*	<0.001
LEFT VENTRICLE				
LV EDVi (mL/m^2)	81.7±12.6	82.5±15.3	78.1±10.9	0.257
LV ESVi (mL/m^2)	35.3±6.9	36.2±8.8	35.3±5.6	0.579
LV SVi (mL/m^2)	46.4±7.4$^{\#}$	46.3±8.2$^{\#}$	42.8±6.1§*	0.034
LV Mi (g/m^2)	87.4±14.7$^{\#}$	88.7±16.9$^{\#}$	78.5±9.2§*	0.002
LV EF (%)	56.9±4.1$^{\#}$	56.3±5.0	54.9±2.9*	0.024
LV GLS (%)	-19.3±2.0$^{\#}$	-19.2±2.5$^{\#}$	-17.7±2.9§*	0.001
LV GCS (%)	-27.8±2.9$^{\#}$	-27.7±3.5$^{\#}$	-26.4±2.4§*	0.035
RIGHT VENTRICLE				
RV EDVi (mL/m^2)	81.5±13.9$^{§\#}$	85.1±16.8$^{*\#}$	73.6±13.6§*	0.001
RV ESVi (mL/m^2)	36.4±8.2$^{§\#}$	39.5±10.3$^{*\#}$	32.1±8.3§*	<0.001
RV SVi (mL/m^2)	45.1±7.4$^{\#}$	45.6±8.3$^{\#}$	41.5±6.8§*	0.022
RV EF (%)	55.5±4.7§	53.9±5.0$^{*\#}$	56.7±4.7§	0.004
RV GLS (%)	-22.2±3.4§	-20.7±3.1*	-21.5±3.5	0.001
RV GCS (%)	-20.7±4.3$^{\#}$	-20.3±4.1$^{\#}$	-22.5±5.2§*	0.042

*Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). * p < 0.05 vs. Mixed, # p < 0.05 vs. Power, § p < 0.05 vs. Endurance; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricle; Mi, mass index; RV, right ventricle; SVi, stroke volume index; VO_2/kg, peak oxygen uptake indexed to body weight*

3.2.5. Associations of resting echocardiographic parameters with exercise capacity

Univariable correlations between 3D echocardiography-derived parameters and VO_2/kg were assessed using our entire study population. LV volumes, such as LV EDVi (r = 0.457, P < 0.001), LV ESVi (r = 0.427, P < 0.001), and LV SVi (r = 0.389, P < 0.001) as well as LV Mi (r = 0.397, P < 0.001) correlated significantly with VO_2/kg. Left ventricular functional parameters, namely, LV EF (r = -0.184, P < 0.001), LV GLS (r = 0.198, P < 0.001), and LV GCS (r = 0.169, P < 0.001) showed a weaker inverse correlation with peak exercise capacity. Concerning the right heart, RV EDVi (r = 0.477, P < 0.001), RV ESVi (r = 0.449, P < 0.001), and RV SVi (r = 0.409, P < 0.001) showed significant correlations with VO_2/kg. Right ventricular EF (r = -0.223, P < 0.001) and RV GCS (r =

0.221, P < 0.001) had inverse correlations, but RV GLS (r = 0.018, P = 0.688) did not correlate with VO_2/kg.

We have performed multivariable linear regression analysis (using ordinary least squares) to determine the predictors of VO_2/kg among the 3D echocardiographic LV and RV parameters (26). Right ventricular EDVi was found to be the strongest independent predictor of VO_2/kg, followed by RV GCS and LV EDVi. The other parameters (LV GLS, LV GCS, LV Mi, and RV GLS) were not significant predictors of peak exercise capacity (Figure 8).

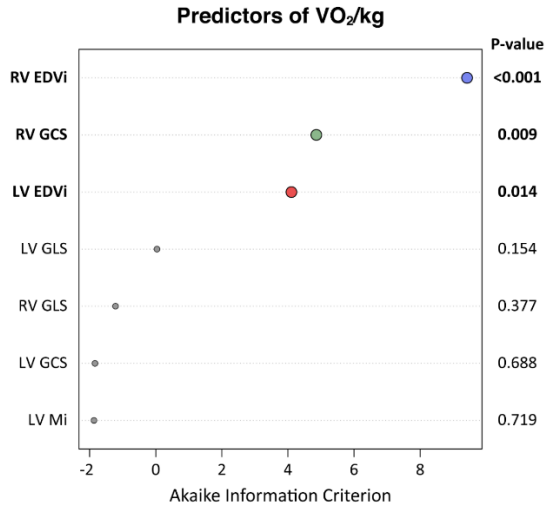

Figure 8. *Multivariable linear regression analysis (using ordinary least squares) to determine the predictors of VO_2/kg in the entire study cohort (athletes and controls, n = 477) (26).*

3.3. Characterization of the geometry of mitral (MA) and tricuspid (TA) annuli in elite athletes using 3D echocardiography

3.3.1. Demographic and echocardiographic data

Four hundred and twenty-five healthy athletes were identified with a previous echocardiographic examination with both left heart- and right heart-focused 3D datasets. From this cohort, 42 (9.9%) athletes presented with at least mild MR. Eight athletes were excluded due to either suboptimal image quality for MA quantification (n=6) or noncompatible image source vendor (n=2). Thus, 34 athletes (male/female: 26/8) formed

the final study population (MR athlete group). Furthermore, 34 age-matched athletes (non-MR athlete group) and 34 healthy, sedentary individuals (control group) with the same sex distribution (male/female: 26/8) were selected from our database (Figure 9; Table 9). This study was in accordance with the Declaration of Helsinki and approved by the Medical Research Council (ETT-TUKEB No. 13687-0/2011-EKU.

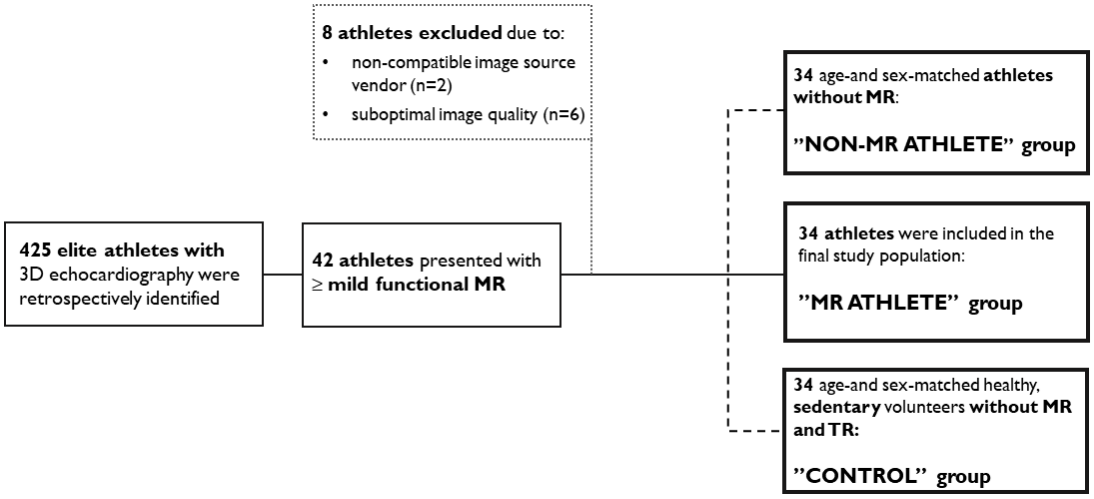

Figure 9*. Flowchart for the identification of the study groups. MR, mitral regurgitation; TR, tricuspid regurgitation. (Figure was based on illustration from (25))*

Basic anthropometric, hemodynamic, and training specific data of the study groups are summarized in Table 9. Our athlete populations consisted of mixed or endurance-trained individuals, predominantly soccer players (28%), water polo players (28%), and swimmers (25%). Athletes had a higher height, weight, and lower resting heart rate than the sedentary control group. Athletes without MR demonstrated significantly higher systolic blood pressure compared with the other two groups. Athletes have been participating in competitive sports for an average of 15 years; at the time of the echocardiographic investigation, they trained an average of 17 h/week. BSA, HR, competitive years, weekly training hours, and CPET-derived peak exercise capacity did not differ between the two athlete groups (Table 9).

Table 9. Baseline and training specific characteristics of athlete and control groups

	MR athletes (n=34)	NON-MR athletes (n=34)	Controls (n=34)	Overall p
Baseline characteristics				
Age (years)	24.0 ± 7.3	22.5 ± 5.0	23.9±6.4	0.449
Male, n (%)	26 (76.5)	26 (76.5)	26 (76.5)	1.000
Height (cm)	180.0±13.1*	182.1±10.5*	173.7±7.6§#	0.003
Weight (kg)	76.2±17.7	77.9±16.0*	70.8±14.8#	0.043
BSA (m 2)	1.9±0.3	2.0±0.2*	1.8±0.2#	0.043
SBP (mmHg)	128.4±14.7#	137.7±13.3§*	123.8±14.8#	<0.001
DBP (mmHg)	76.3±9.1#	81.1±9.6§	76.8±9.0	0.031
HR (bpm)	62.4±10.5*	67.3±12.0*	78.2±12.7§#	<0.001
Training specific characteristics				
Since (years)	14.8±6.1	14.9±5.4	-	0.903
Training time (h/week)	17.1±7.4	16.9±8.1	-	0.915
VO_2 (L/min)	4.0±1.0	4.0±0.9	-	0.902
VO_2/kg (mL/kg/min)	52.8±6.5	51.6±8.7	-	0.512

*Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). * p < 0.05 vs. CONTROLS, # p < 0.05 vs. NON-MR athletes, § p < 0.05 vs. MR athletes. BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; MR, mitral regurgitation; SBP, systolic blood pressure; VO_2, peak oxygen uptake; VO_2/kg, peak oxygen uptake indexed to body weight*

Conventional 2D parameters showed similar differences as suggested in previous results in terms of athlete's heart (25). Detailed 3D echocardiographic parameters are shown in Table 10. As expected, there were significant differences between the athlete groups and the control group concerning LV and RV morphological and functional parameters. LV and RV EDVi and ESVi were significantly higher in the athletes compared with controls; on the other hand, these did not differ between the MR and non-MR athlete groups. LV Mi, LV SVi, and RV SVi values were the highest in the athlete group with MR compared with non-MR and control groups. LV EF, GLS, GCS, and RV EF showed significantly decreased resting values in the athletic groups than controls. Notably, LV GLS was higher in the MR athlete group compared with the non-MR group. 3D left (LA) and right atrial (RA) maximal volume indices (LAVi max and RAVi max) were higher among athletes with MR, even compared with non-MR athletes. In terms of LA reservoir and contractile function, there was no difference between the groups; however, LA passive EF referring to conduit function was significantly lower in the MR athlete group compared with controls. Although RA contractile function was similar, athlete groups presented with

lower RA reservoir and conduit function. Moreover, RA total emptying fraction was significantly lower in the MR athlete group compared with non-MR athletes. (Table 10).

Table 10. 3D echocardiographic parameters of athlete and control groups

	MR athletes (n=34)	NON-MR athletes (n=34)	Controls (n=34)	Overall p
Left ventricular parameters				
LV EDVi (mL/m²)	85.5±17.2*	78.5±11.8*	60.9±12.1§#	<0.001
LV ESVi (mL/m²)	37.7±10.5*	35.7±7.8*	24.7±5.7§#	<0.001
LV SVi (mL/m²)	47.8±8.0*#	42.8±5.5§*	36.2±7.3§#	<0.001
LV Mi (g/m²)	89.4±16.7*#	81.9±12.6§*	64.9±10.0§#	<0.001
LV EF (%)	56.4±4.8*	54.8±4.5*	59.5±3.8§#	<0.001
LV GLS (%)	-19.4±2.4*#	-18.3±2.3§*	-20.6±2.1§#	<0.001
LV GCS (%)	-27.6±3.2*	-26.6±2.9*	-30.0±2.8§#	<0.001
Left atrial parameters				
LAVi max (mL/m²)	37.1±7.1*#	31.9±6.2§*	24.7±6.9§#	<0.001
LAVi min (mL/m²)	15.3±4.3*	13.5±4.5*	9.6±3.7§#	<0.001
LAVi preA (mL/m²)	23.6±5.9*#	19.2±4.1§*	14.6±4.8§#	<0.001
LA total EF (%)	58.9±7.5	59.1±5.9	61.2±7.9	0.361
LA passive EF (%)	36.7±7.9*	39.6±6.6	40.8±7.5§	0.041
LA active EF (%)	35.0±9.7	29.9±14.4	34.4±11.4	0.167
Right ventricular parameters				
RV EDVi (mL/m²)	84.9±16.7*	79.1±13.1*	61.2±10.6§#	<0.001
RV ESVi (mL/m²)	38.0±9.5*	35.9±8.5*	25.1±5.0§#	<0.001
RV SVi (mL/m²)	46.9±8.4*#	43.2±6.2§*	36.1±6.7§#	<0.001
RV EF (%)	55.5±4.0*	55.1±4.8*	58.9±4.2§#	<0.001
Right atrial parameters				
RAVi max (mL/m²)	42.0±9.7*#	35.1±7.1§*	26.7±6.2§#	<0.001
RAVi min (mL/m²)	20.7±6.4*#	16.0±4.7§*	10.5±3.3§#	<0.001
RAVi preA (mL/m²)	28.3±7.6*#	22.5±5.1§*	15.3±4.1§#	<0.001
RA total EF (%)	50.9±8.2*#	55.3±8.8§*	60.2±10.1§#	<0.001
RA passive EF (%)	32.9±8.1*	36.0±7.0*	42.7±10.0§#	<0.001
RA active EF (%)	27.0±8.2	28.8±10.6	30.8±10.6	0.296

*Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). * p < 0.05 vs. CONTROLS, # p < 0.05 vs. NON-MR athletes, § p < 0.05 vs. MR athletes. EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; GCS, global circumferential strain; GLS, global longitudinal strain; LA, left atrium; LA active EF, LA active emptying fraction; LA passive EF, LA passive emptying fraction; LA total EF, LA total emptying fraction; LAVi max, left atrial maximal volume index; LAVi min, left atrial minimal volume index; LAVi preA, left atrial preA wave volume index; LV, left ventricle; Mi, mass index; MR, mitral regurgitation; RA, right atrium; RA active EF, RA active emptying fraction; RA passive EF, RA passive emptying fraction; RA total EF, RA total emptying fraction; RAVi max, right atrial maximal volume index; RAVi min, right atrial minimal volume index; RAVi preA, right atrial preA wave volume index; RV, right ventricle; SVi, stroke volume index*

In the MR athlete group, all individuals presented with mild MR, and no moderate regurgitation was established (vena contracta width (VCW): 0.22 ± 0.07 cm). Interestingly, 74% of athletes with MR also had mild TR (VCW: 0.19 ± 0.07 cm). In the non-MR group, 9% of athletes presented with mild TR (VCW: 0.12 ± 0.04 cm).

We have compared the exercise-induced relative dilation of the LV, the LA, and the MA in the overall athlete cohort. Although the relative increase in LV EDVi and LAVi max was comparable, the MA 3D area index's increment was disproportionately higher, with an average enlargement of over 60%. Concerning the right heart, the relative increase in the 3D TA area index was significantly higher than in RV EDVi but showed no difference compared with RAVi max. The increment in RAVi max was higher compared with RV EDVi (Figure 10). We investigated the relative geometrical changes in female athletes (n=16) separately and found that the increment in LAVi max ($46 \pm 33\%$) was significantly higher compared with LV EDVi ($32 \pm 21\%$) but was still lower than MA 3D area index ($61 \pm 30\%$, overall $P < 0.001$). In terms of the right heart, the increment in TA 3D area index ($35 \pm 25\%$) was similar to RV EDVi ($35 \pm 25\%$), but both were lower compared with RAVi max ($49 \pm 45\%$, overall $P < 0.001$).

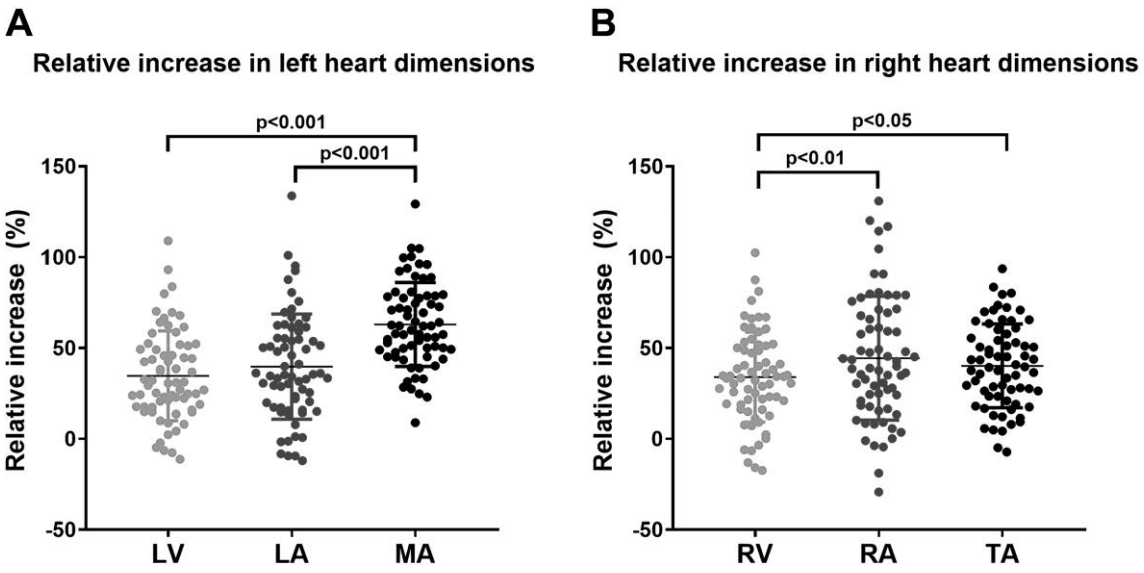

Figure 10. *Comparison of the exercise-induced dilation of the left ventricle (LV), the left atrium (LA), and the mitral annulus (MA) (A) and the right ventricle (RV), the right atrium (RA), and the tricuspid annulus (TA) (B) (25). Three-dimensional (3D) MA area index showed a disproportionate increment compared with both LV and LA volume indices (n = 68, overall P < 0.001). The relative increase in the 3D TA area index was significantly higher compared with RV volume index (n = 68, overall P < 0.01).*

3.3.2. 3D echocardiographic quantification of the mitral annulus

The three groups differed significantly from each other with regard to all of the parameters (3D and 2D area indices, perimeter, anteroposterior, posteromedial-anterolateral, commissural diameters, intertrigonal distance) describing the size of the MA, as athletes having MR had significantly higher values even compared with athletes without MR (Table 11; Figure 11). The athlete groups had higher annulus height and less obtuse mitral-aortic angle. Athletes without MR had a more pronounced MA saddle shape, as suggested by the significantly less obtuse nonplanar angle and higher annulus height to commissural width ratio (AHCWR, Figure 11). Interestingly, athletes with MR were rather similar in this regard to sedentary controls. Sphericity, annular excursion, and MA area fraction did not differ between the athlete groups. Anterior leaflet length and area were significantly higher in the MR athletes even compared with non-MR athletes; however, posterior leaflet length and area did not show a difference between the two athlete groups. The anterior leaflet angle was significantly lower in the MR athlete group compared with non-MR athletes. Tenting height, area, and volume indices were higher in both athlete groups compared with the control group (Table 11; Figure 11).

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Table 11. Mitral valve quantification of athlete and control groups

	MR athletes (n=34)	NON-MR athletes (n=34)	Controls (n=34)	Overall p
ANNULUS				
Annulus 3D area index (cm^2/m^2)	8.2±1.0*#	7.2±1.0§*	4.7±0.6§#	<0.001
Annulus 2D area index (cm^2/m^2)	7.3±0.9*#	6.4±0.9§*	4.2±0.6§#	<0.001
Annulus perimeter (cm)	14.2±1.2*#	13.6±1.1§*	10.6±0.9§#	<0.001
A-P diameter (cm)	3.6±0.4*#	3.4±0.4§*	2.7±0.4§#	<0.001
PM-AL diameter (cm)	4.5±0.4*#	4.3±0.4§*	3.4±0.3§#	<0.001
Commissural diameter (cm)	4.5±0.4*#	4.2±0.4§*	3.4±0.3§#	<0.001
Inter-trigonal distance (cm)	3.3±0.6*#	2.9±0.4§*	2.4±0.4§#	<0.001
Sphericity index	0.8±0.1	0.8±0.1	0.8±0.1	0.312
Annulus height (mm)	9.6±2.8*	10.5±2.1*	7.2±2.0§#	<0.001
Non-planar angle (°)	128.9±16.9#	116.0±21.4§*	131.1±13.8#	<0.001
Mitral annular excursion (mm)	12.9±2.0*	12.2±2.1	11.3±2.1§	0.009
Annulus (2D) area fraction (%)	-4.8±6.5	-2.5±3.9	-4.1±9.0	0.371
Mitral-aortic angle (°)	140.4±13.1*	138.1±12.1*	147.1±11.6§#	0.011
AHCWR (%)	21.8±6.8#	25.2±5.6§*	21.6±6.7#	0.036
LEAFLETS				
Anterior leaflet area index (cm^2/m^2)	4.4±0.9*#	3.4±0.5§*	2.5±0.4§#	<0.001
Posterior leaflet area index (cm^2/m^2)	4.2±0.8*	4.3±0.8*	2.6±0.5§#	<0.001
Anterior leaflet length (cm)	2.7±0.3*#	2.5±0.3§*	2.0±0.3§#	<0.001
Posterior leaflet length (cm)	1.7±0.3*	1.8±0.4*	1.4±0.3§#	<0.001
Anterior leaflet angle (°)	23.9±4.6#	26.3±6.0§	25.1±4.8	0.043
Posterior leaflet angle (°)	39.5±9.9	39.6±7.6	40.6±10.2	0.948
Tenting height (cm)	1.0±0.2*	1.0±0.2*	0.8±0.2§#	<0.001
Tenting area index (cm^2/m^2)	1.2±0.3*	1.2±0.3*	0.8±0.2§#	<0.001
Tenting volume index (mL/m^2)	2.0±0.6*	1.8±0.6*	0.9±0.3§#	<0.001

*Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). * p < 0.05 vs. CONTROLS, # p < 0.05 vs. NON-MR athletes, § p < 0.05 vs. MR athletes; AHCWR, annulus height to commissural width ratio; A-P diameter, anteroposterior diameter; MR, mitral regurgitation; PM-AL diameter, posteromedial-anterolateral diameter*

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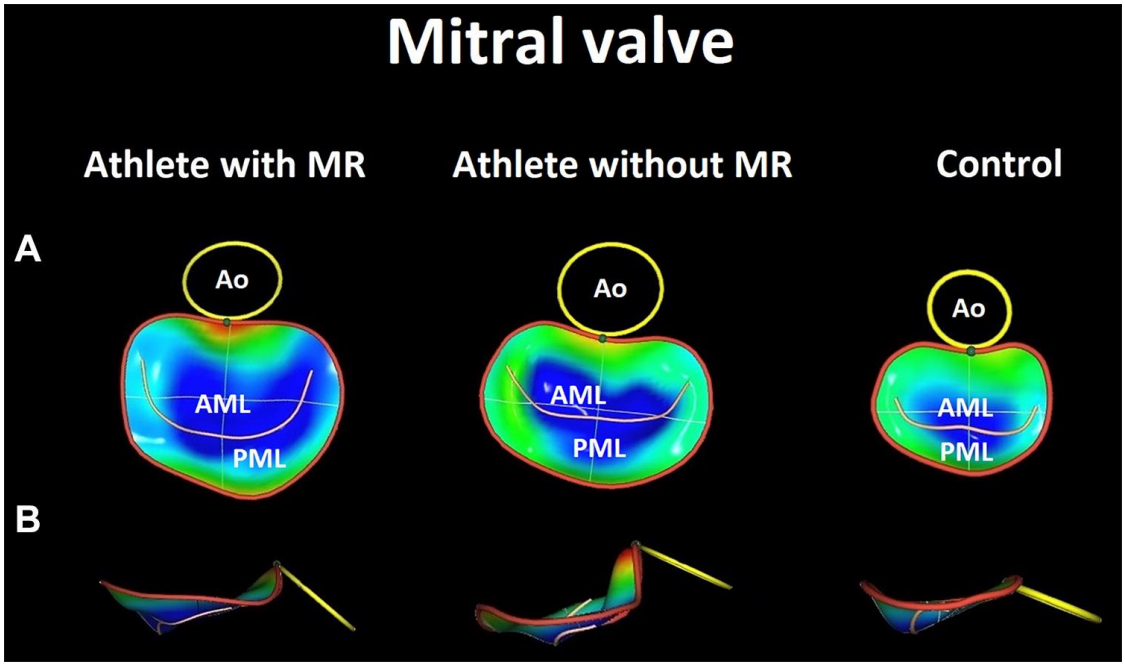

Figure 11. *3D mitral annular reconstructions of athletes with and without mitral regurgitation (MR) and a healthy sedentary volunteer (control; representative cases) (25). The impact of regular exercise training is represented by the larger dimensions of the mitral annulus in athletes; however, athletes presented with MR even had a larger annular size. Athletes without MR had a more pronounced saddle shape, whereas athletes with MR and controls did not differ in this regard. See details in the text. A: surgeon's view. B: side view of the mitral annulus. More blueish hues represent more tenting of the mitral valve leaflets. AML, anterior mitral valve leaflet; Ao, aortic annulus; PML, posterior mitral valve leaflet.*

3.3.3. 3D echocardiographic quantification of the tricuspid valve

Interestingly, athletes with MR had also significantly enlarged TA, as shown by 3D and 2D area indices, four-chamber view diameters, and minor axis diameters compared with both non-MR athletes and controls (Table 12 and Figure 12). TA perimeter, two-chamber view diameters, and major axis diameters were comparable between athlete groups but still larger than controls. TA sphericity, area fraction, and systolic excursion were similar between groups. Maximal tenting height and tenting volume index were significantly higher in the athlete groups compared with the sedentary controls (Table 12; Figure 12).

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Table 12. Tricuspid valve quantification of athlete and control groups

	MR athletes (n=34)	NON-MR athletes (n=34)	Controls (n=34)	Overall p
ANNULUS				
Annulus 3D area index (cm^2/m^2)	7.2±1.1$^{*\#}$	6.5±1.1§*	5.0±0.8$^{\S\#}$	<0.001
Annulus 2D area index (cm^2/m^2)	7.1±1.1$^{*\#}$	6.4±1.1§*	4.9±0.8$^{\S\#}$	<0.001
Annulus (2D) area fraction (%)	15.2±4.4	15.4±4.0	16.1±4.2	0.622
Annulus perimeter (cm)	13.3±1.2*	12.9±1.2*	10.8±0.8$^{\S\#}$	<0.001
4-chamber diameter (cm)	4.1±0.3$^{*\#}$	3.8±0.4§*	3.2±0.3$^{\S\#}$	<0.001
2-chamber diameter (cm)	4.1±0.4*	4.0±0.4*	3.2±0.4$^{\S\#}$	<0.001
Major axis (cm)	4.4±0.5*	4.3±0.5*	3.6±0.3$^{\S\#}$	<0.001
Minor axis (cm)	3.9±0.4$^{*\#}$	3.7±0.3§*	3.1±0.3$^{\S\#}$	<0.001
Sphericity index	0.9±0.1	0.9±0.1	0.9±0.1	0.712
Excursion (cm)	1.6±0.2	1.5±0.3	1.5±0.3	0.370
LEAFLETS				
Max tenting height (cm)	0.9±0.1*	1.0±0.2*	0.7±0.1$^{\S\#}$	<0.001
Tenting volume index (mL/m^2)	2.1±0.5*	2.0±0.6*	1.0±0.3$^{\S\#}$	<0.001

*Continuous variables are presented as means ± SD, categorical variables are reported as frequencies (%). * p < 0.05 vs. CONTROLS, # p < 0.05 vs. NON-MR athletes, § p < 0.05 vs. MR athletes. MR, mitral regurgitation*

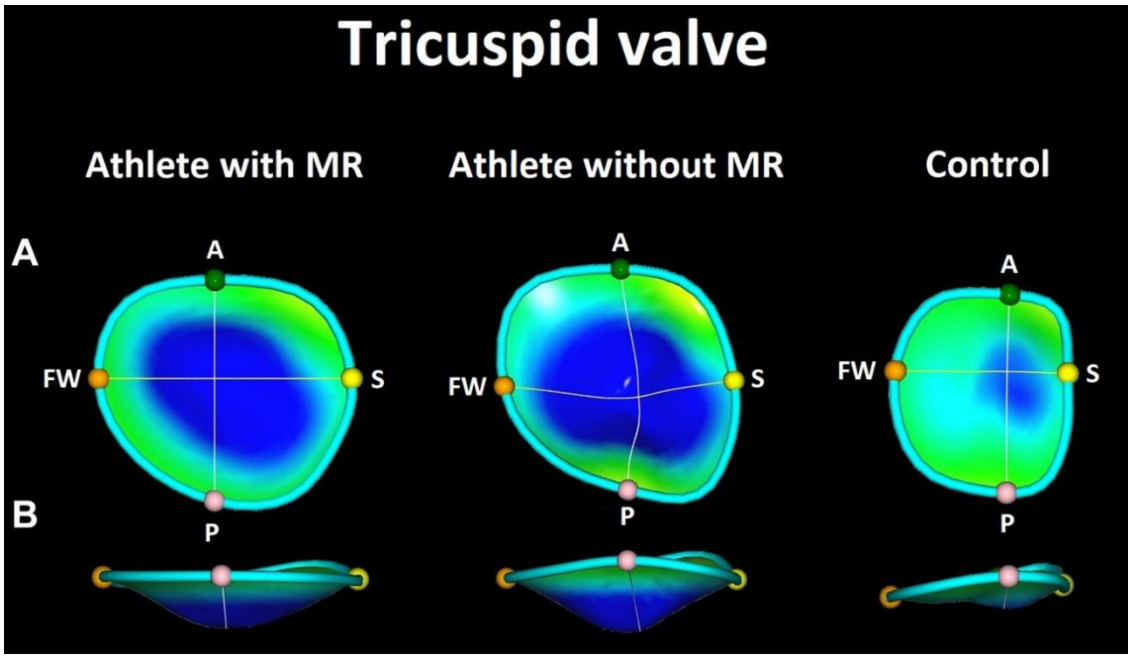

Figure 12. *3D tricuspid annular reconstructions of athletes with and without mitral regurgitation (MR) and a healthy sedentary volunteer (control; representative cases)(25). The impact of regular exercise training is represented by the larger dimensions of the tricuspid annulus in athletes; however, athletes presented with MR even had a larger annular size. See details in the text. A: surgeon's view. B: side view of the tricuspid annulus. More blueish hues represent more tenting of the tricuspid valve leaflets. A, anterior; FW, free wall; P, posterior; S, septal reference points.*

3.3.4. Relationships between cardiac chamber morphology and exercise capacity

In the pooled population (n = 102), MA 3D area index correlated with LV EDVi ($r = 0.704$, $P < 0.001$), LV Mi ($r = 0.657$, $P < 0.001$), and LAVi max ($r = 0.719$, $P < 0.001$), whereas TA 3D area index correlated with RV EDVi ($r = 0.643$, $P < 0.001$) and RAVi max ($r = 0.741$, $P < 0.001$). MA tenting volume index correlated with LV EDVi ($r = 0.673$, $P < 0.001$), whereas TA tenting volume index correlated with RV EDVi ($r = 0.617$, $P < 0.001$). Furthermore, in athletes (n = 68), MA and TA 3D area index correlated with VO_2/kg (MA: $r = 0.443$, $P < 0.001$; TA: $r = 0.423$, $P < 0.01$). Multivariate linear regression models were built to identify independent determinants of MA and TA 3D area index in athletes. In the first model (comprising age, sex, LV EDVi, LAVi max, and VO_2/kg), LAVi max and VO_2/kg were found to be independent determinants of MA 3D area index, with a cumulative R value of 0.681 ($P < 0.001$; Table 13). In a second model (comprising age, sex, RV EDVi, RAVi max, and VO_2/kg), RAVi max was the only independent predictor of TA 3D area index, with a cumulative R value of 0.648 ($P < 0.001$; Table 13).

Table 13. Multivariable linear regression analysis: independent determinants of mitral annular 3D area index and tricuspid annular 3D area index in athletes (n=68)

Covariate		β	P
MA 3D area index			
Age		0.153	0.124
Gender		0.156	0.124
LAVi max		**0.398**	**0.001**
LV EDVi		0.200	0.131
VO_2/kg		**0.260**	**0.033**
Cumulative R	0.681		
Standard error	1.13		
Cumulative P	0.000001		
TA 3D area index			
Age		-0.04	0.719
Gender		0.117	0.299
RAVi max		**0.543**	**<0.001**
RV EDVi		0.013	0.932
VO_2/kg		0.221	0.108
Cumulative R	0.648		
Standard error	1.188		
Cumulative P	0.000005		

EDVi, end-diastolic volume index; LAVi max, left atrial maximal volume index; LV, left ventricle; RAVi max, right atrial maximal volume index; MA, mitral annulus; RV, right ventricle, TA, tricuspid annulus; VO_2/kg, peak oxygen uptake indexed to body weight

4. Discussion

4.1. Investigation of the correlation between myocardial work indices and load-independent metrics of contractility in a rat model of athlete's heart and the characterization of the association between myocardial work and exercise capacity among elite athletes

Animal models enable the profound and standardized investigation of cardiac function and hemodynamics using both invasive and non-invasive techniques. Our current investigation was based on a previously validated and established rat model of athlete's heart (43). Our previous studies revealed that LV strain parameters could accurately monitor the changes in the systolic function during both the development and the regression of exercise-induced hypertrophy, and these metrics also exhibited good correlations with load-independent measures of LV contractility (42, 51). While strain parameters were able to describe LV inotropic state, there is an immense body of evidence about their load-dependency (47, 98), which represents an obvious issue in athletes as HR and loading conditions vary significantly during exercise-induced adaptations or even after a single exercise session (99, 100). Considering our experiments, GLS and MW indices suggested enhanced systolic performance in swim-trained rats that was also confirmed by their robust correlations with the invasively measured contractile function (Figure 4). Nevertheless, it is important to emphasize that indicators of preload (σED) and afterload (E_a) did not considerably affect GMWI in contrast to GLS (Figure 4). From another point of view, ESPVR was found to be the strongest determinant of both GMWI and CMWI, while it played a less dominant role in determining GLS (Figure 4). These findings imply the superiority of GMWI and CMWI over conventional functional parameters in the characterization of the contractile function of the athlete's heart.

Furthermore, the aforementioned favorable features of MW analysis could be translated to clinical sports cardiology as in clinical settings, MW indices are easily obtainable by a commercially available and validated software: after assessing GLS the software automatically generates the pressure–strain loops and the corresponding metrics using blood pressures measured by a simple brachial cuff. In our cohort of elite swimmers we observed, that despite the slightly reduced GLS, both GMWI and CMWI were significantly higher than the control group, implying enhanced systolic performance even

during resting conditions. Thus, MW analysis may be a meaningful addition to the everyday clinical practice, as LV EF and GLS can be reduced in athletes prohibiting the confident exclusion of overlapping cardiac disorders with athlete's heart (20, 21, 101). Importantly, MW indices correlated moderately with CPET-derived VO_2/kg, justifying that supernormal values of GMWI and CMWI measured during resting conditions indicate better performance during exercise. Of note, a significant correlation between peak oxygen uptake and GMWI was observed previously in pathological conditions as well, such as in heart failure patients (102) or hypertensive patients (103). Furthermore, our results coincide with the results of a recently published study, which reported that GLS was reduced in endurance athletes compared to control subjects, whereas WMWI and MWE were comparable between the two groups (67). Based on our findings, GMWI and CMWI (the parameters showing strong correlations with LV contractility in the experimental setting) were found to be supernormal in athletes at rest. Thus, our experimental and clinical findings endorse the utilization of MW analysis in the evaluation of the athlete's heart as MW indices reflect LV contractility in a less load-dependent manner and are markers of exercise capacity.

Although MW parameters implied supernormal systolic function in exercised rats as well as in human athletes, there are apparent dissimilarities in the underlying factors of this phenomenon between these two settings. Considering the rat model of athlete's heart, GLS was higher compared to control animals with female rats having higher strain values than males, whereas LV pressures were remained similar in both sexes. Furthermore, the multivariable analysis revealed that GLS was predominantly determined by sex, whereas it had less influence on the values of GMWI and CMWI. Therefore, the increase in GMWI and CMWI was mainly attributable to the enhancement of myocardial deformation. The relatively less pronounced exercise-induced LV dilation and the anesthesia (during the echocardiographic examination) generated a physiological set-up that could diminish the differences between the experimental groups with regards to LV geometry, preload, and afterload (104). Thus, GLS will be supernormal in the exercised rats and will adequately reflect the increased LV contractility (42, 51). On the other hand, the exercise-induced cardiovascular adaptation of human swimmer athletes is different in two pivotal aspects. First, unlike in the rat model, swimming resulted in the marked dilation of the LV (in both sexes, although males had larger volumes compared to females). Therefore, the decrease

in GLS and the consequent uncoupling between myocardial deformation and contractility are partially attributable to the alterations in the LV geometry: in the case of LV dilation, less strenuous myocardial deformation is sufficient to generate a normal stroke volume (47). Second, similarly to our findings, it has been previously reported that elite swimmer athletes often present with elevated resting systolic blood pressure due to vascular remodeling and altered sympatho-adrenergic regulation (105). Thus, measuring preserved or even elevated values of GMWI and CMWI can be expected, as the increase in LV pressures might countervail the reduction of GLS. Nevertheless, the calculation of MW by interpreting LV deformation in the context of instantaneous LV pressure can overcome these differences between the rat model and human athletes; hence MW parameters seem to be universal and reliable markers of the LV systolic function in this scenario.

4.2. Characterization of biventricular morphology and function using 3D echocardiography and investigation of the correlations between cardiac remodeling and peak exercise capacity

Numerous publications, including the above-discussed study, have established the 'conventional' exercise-induced alterations in elite athletes, namely the increased LV volumes and mass, and recently, similar changes were demonstrated concerning the RV as well (23, 24). In this study we have utilized 3DE as it offers better agreement with gold-standard cMR imaging compared with conventional 2DE measurements and confirmed the above-mentioned phenomena (106).

Although adaptation is generally similar in male and female athletes sex may impact cardiac remodeling as previous studies have shown that male athletes have greater absolute cardiac dimensions (24, 107, 108). Similarly, in our findings male athletes had significantly higher LV and RV volumes and LV mass, however, it is important to emphasize, that in female athletes all the features of the exercise-induced remodeling are present when compared with sedentary female controls. As expected, adult athletes participated in competitive sports for a longer period, thus larger LV volumes and mass was observed. Still, despite the higher absolute training load of adults, the RV volumes were comparable between adolescent and adult athletes. These findings suggest that the right heart remodeling precedes its left counterpart with significant dilation even at a younger age and especially, in females. Furthermore, endurance athletes are often

described as having the most extensive but balanced dilation of all four cardiac chambers (109), however, a recent publication, suggested that the RV undergoes a disproportionate remodeling compared with the LV which resonated with our findings (34).

The direct association between increased biventricular volumes and enhanced athletic performance was previously investigated (38-40), and it was also confirmed by our findings as LV and RV volumes significantly correlate with peak exercise capacity; however, RV EDVi was found to be the strongest independent predictor among other volumetric or functional parameters.

Although 3DE offers a promising approach in determining resting systolic function, recent publications have presented conflicting results with LV EF values ranging from supernormal or normal to even reduced (20, 21, 27), which might be attributable to the significant heterogeneity of the athlete populations. According to our findings, resting values of LV and RV EF were mildly but significantly reduced compared with sedentary controls. Regarding the associations between resting systolic functions and exercise capacity, similarly to La Gerche et al. (40), our data showed significant inverse correlations between 3D echocardiography-derived LV and RV EF and VO_2/kg. Furthermore, although 3D STE derived GLS is also a well-established marker of systolic function, still studies have provided inconsistent data of resting strain values in athletes. The geometric adaptation along with the load-dependency of GLS justifies its shortcomings, namely that it cannot reflect the contractile state during resting conditions (51), despite the established increase in the myocardial contractility observed in the athlete's heart. Importantly, the deterioration of LV longitudinal vs. circumferential shortening is often dissociated in different pathological conditions; thus, this balanced decrease may rather point at a physiologic process (110). Power athletes showed the lowest resting values compared with the other sports classes. This may be explained by the different training profile of these athletes: a mainly static exercise regime imposes significant pressure load on the LV, which manifests in reduced LV deformation. Correlations of decreased LV deformation with higher systolic blood pressure and increased LV mass were previously reported in power athletes (111, 112).

Regarding the RV mechanical pattern, we face a knowledge gap, since RV circumferential shortening has been scarcely investigated in athletes, although it has been demonstrated in healthy individuals that non-longitudinal motion components largely

contribute to global RV pump function (84). Our study demonstrated that the athlete's heart is characterized by a disproportionate decrease in RV GCS compared with RV GLS. 3D-based RV GLS was similar between athletes and controls in this study which is particularly interesting since the decrease of LV longitudinal shortening would imply a parallel decrease in RV longitudinal shortening. In pathological conditions (such as left-heart diseases), due to the change in the function of the interventricular septum and myofiber arrangement, such a decrease in LV and subsequent RV longitudinal shortening is compensated with an increase in RV radial (circumferential) shortening (83). However, in the context of the athlete's heart, circumferential shortening is decreased along with maintained or even supernormal longitudinal shortening, which was also confirmed by a recent meta-analysis (113). This may be explained by the myofiber meshwork transitioning into a more advantageous (more oblique) orientation that will result in the aforementioned mechanical pattern, despite the significant chamber dilation. Of note, similar changes in myofiber orientation may be present concerning the LV and its twist and untwist mechanics (114). A supernormal RV longitudinal shortening may also support right atrial filling by enhancing venous return in systole, which can serve as an advantageous component of cardiac function, especially during exercise. Although these alterations may support effective systolic and diastolic ventricular function during significant hemodynamic demands arising from intense exercise, the deterioration of RV circumferential shortening (especially at the basal free wall segments) is an established early marker of pressure overload-induced wall stress in various cardiac pathologies (115, 116). Furthermore, during vigorous exercise, the right side of the heart is exposed to a disproportionate increase of afterload, which can potentially manifest in adverse RV remodeling (35, 117). Notably, La Gerche et al. demonstrated an acute reduction in RV function after an endurance race, suggesting that RV function may be more profoundly affected by endurance training (33). In our cohort, athletes competing in endurance sport disciplines presented with the lowest values of RV EF, RV GLS, and also RV GCS. Still, we found a significant inverse correlation between RV GCS and peak exercise capacity, moreover, RV GCS was an independent predictor of fitness by multivariable linear regression.

4.3. Characterization of the geometry of mitral (MA) and tricuspid (TA) annuli in elite athletes using 3D echocardiography

Although the ventricular myocardium's dynamic adaptation is definitely the most widely known aspect of the athlete's heart, alterations of the interconnected valvular apparatus should not be overlooked. During intense exercise, the AV valves have to support an adequate diastolic filling while also keeping their systolic competency to maintain the "one-way" circulation in the face of a wide range of intracardiac pressures and ventricular outputs (114). Coinciding with our results, it was previously shown that athletes have significantly higher MA linear diameters than sedentary controls. Moreover, a more pronounced MA enlargement exists in athletes presenting with MR (97). Although FR rarely exceed the mild degree in athletes, a higher overall prevalence of MR and TR is reported in the literature (97). In our cohort, the majority of athletes with functional MR had concomitant TR, and interestingly, this MR group was presented with higher TA dimensions as well, which could imply that athletes prone to more excessive dilation of the MA are susceptible to a more pronounced TA remodeling. Of note it has been suggested that alterations in TA geometry can be present even in the case of degenerative processes affecting the MA primarily (118). The MV apparatus also shows a distinct change in shape when comparing the two athlete groups: although in athletes with MR, the parameters describing the MA saddle shape, namely AHCWR and nonplanar angle showed comparable values with sedentary controls, increased AHCWR and a less obtuse nonplanar angle were found in athletes without MR. This indicates a more pronounced MA saddle shape in the non-MR group, which is, according to our knowledge, a unique finding across the spectrum of physiological or pathophysiological alterations of the MA (89). Although the anatomical advantages of this phenomenon are still not completely clear, it may serve as an adaptive change to maintain proper coaptation during different exercise levels when chamber geometry and intracardiac pressures continuously change. The MA nonplanarity of athletes presented with MR did not significantly differ from sedentary controls, suggesting that in this population, the mild regurgitation may originate at least partially from the "insufficient" geometrical adaptation of the MA to regular, intense exercise. Furthermore, while the posterior leaflet area did not differ, the anterior leaflet area was significantly higher in athletes with MR compared with those without. It has been shown that mechanical stretch by papillary muscle displacement can induce

leaflet hyperplasia (119), however as the enlargement of the leaflets is usually proportional in pathological states, the asymmetrical growth of the mitral valve leaflets may be a specific manifestation of this "adverse" athletic adaptation accompanied by MR. Interestingly, athletes with MR showed tendentially higher LV volumes; significantly higher LV GLS, LAVi max, and RAVi max; and significantly lower RA total emptying fraction than athletes with no MR. While such mild MR (observed during resting conditions) cannot pose a hemodynamically relevant stimulus, these findings can also be seen pathological LV volume overload (120, 121). These finding may be explained by 1) an athlete with a predisposition to a more pronounced exercise-induced chamber dilation may also be more prone to higher MA dimensions and a consequential MR, and 2) there is an inherent anatomical cause of the MR that may significantly increase during exercise, resulting in more excessive cardiac remodeling, thus creating a classical "chicken or the egg" dilemma.

According to our results, MA and TA areas showed at least moderate correlations with the corresponding ventricular and atrial volumes, confirming these exercise-induced dilatative processes' interconnected nature. We also demonstrated an increase in the tenting volumes of both AV valves related to the ventricular volumes. Thus, a mixed type of functional MR and TR could be established in our cohort, showing the characteristics of both atrial and ventricular FR. MA and TA 3D areas also correlated with exercise performance; and regarding the MA, VO_2/kg was even found to be an independent determinant, supporting that the AV annular dilation is still one of the adaptive aspects exercise-induced cardiac alterations. Furthermore, atrial volumes were independent determinants of annular areas, whereas ventricular volumes were not, resonating with recent publications showing that the RA dilation is the major determinant of TA size in patients with atrial fibrillation and/or functional TR which warrants further studies to establish the (patho)physiological link between exercise-induced cardiac remodeling, functional valvular regurgitation, and, eventually, occurrence of atrial fibrillation (122, 123).

4.4. Limitations

Several limitations have to be acknowledged regarding the above-discussed studies in general. First and foremost we utilized echocardiography in all of our studies. Although

echocardiography is not the gold-standard imaging modality for measuring cardiac chamber volumes and function, still it is considered to be an accurate and reproducible method. Nevertheless, all the post-processing software are extensively validated against cMR (106, 124). Second, these are single-center, retrospective, cross-sectional studies with a limited number of cases performing only resting echocardiographic measurements. Longitudinal data would help to better understand the progression/regression dynamics of the established alterations and the potential occurrence of clinical adverse events in athletes. Further studies are also needed to provide data on 3D chamber mechanics during exercise and different phases of training (conditioning/deconditioning). However, the utilization of advanced echocardiographic techniques along with a same-day CPET elevates the value of our studies. Third, our athlete populations falls into a relatively younger age group, therefore the distinct characteristics of exercise-induced remodeling in different age groups (i.e. master athletes) remain unknown. In our first study, we involved only swim-trained rats and elite swimmer athletes, thus, the generalizability of our results to other sport disciplines remains to be clarified in future investigations. In this study, cardiac contractility was measured directly only in the rat model but not in humans, and in rats, echocardiography and P–V analysis were performed under anesthesia, which might influence parameters dependent on the autonomic nervous system, such as HR and pressure values. Although in humans STE was performed in images acquired from apical views, whereas in the rat model, GLS was assessed from the parasternal long-axis view, evidence suggests that the insonation angle has only a modest effect on the measurement of GLS. In our second study, although we enrolled athletes from all four types of sports classes, the distribution of mixed, endurance, power, and skill athletes was imbalanced. On the other hand, we were also able to enroll a large number of female and also adolescent athletes, who are rather underrepresented in contemporary literature to this day. Furthermore, atrial volumes were quantified by 2D and not 3D echocardiography as currently no vendor independent 3D solution is available. Lastly in our third study, beyond the above-mentioned limitations, it should be addressed that 3DE quantification of the mitral valve is primarily designed for transesophageal images (where spatial and temporal resolutions are higher); however, athletes generally have exceptionally good acoustic windows, and data have shown that results derived from transthoracic and transesophageal approaches are rather interchangeable (73).

5. Conclusions

In our first study, we comprehensively investigated the role of STE-derived MW in the functional evaluation of the athlete's heart. Our study provided experimental data by performing both non-invasive (STE) and invasive (P–V analysis) measurements in a rodent model of exercise-induced LV hypertrophy. Additionally, human data from elite athletes were obtained by advanced echocardiography and functional testing (CPET). Parameters based on MW analysis were able to accurately reflect LV contractility in a rat model of exercise-induced LV hypertrophy and it was able to capture the supernormal LV systolic performance of human athletes even during resting conditions. Moreover, our results confirmed that MW is less dependent on loading conditions and sex-related differences, which further endorses the widespread utilization of this novel, non-invasive technique in the evaluation of the athlete's heart.

In our second study, by 3D echocardiographic assessment, we were able to thoroughly characterize the exercise-induced adaptation of biventricular morphology and systolic function and its relation to age, sex, sports classes, and peak exercise capacity. According to our finding, regular, intense physical exercise resulted in significant and specific changes in biventricular morphology and function. Resting LV and RV EFs were lower compared with sedentary controls. Concerning the LV, there was a balanced decrease in longitudinal and circumferential shortening; however, RV circumferential shortening showed a disproportionate decrement. These changes were associated with a better exercise capacity measured by CPET. Therefore, in the case of the athlete's heart, the worse is the resting ventricular function, the better is the exercise capacity.

Regarding the third study, we have shown that beyond the dilation of the cardiac chambers, atrioventricular annuli may undergo a disproportionate remodeling in response to regular, intense exercise training. Athletic valvular adaptation is characterized by both annular enlargement and increased leaflet tenting of both the mitral and tricuspid valves. There are also specific differences in MA geometry between athletes presented with or without functional MR.

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6. Summary

Regular, intense exercise imposes significant hemodynamic demand on the heart, resulting in complex structural and functional cardiac adaptation known as the athlete's heart. However, the vast majority of current studies focuses solely on the LV, while the adaptive changes of the RV, and the exercise-induced alterations of the AV annuli are scarcely investigated. Furthermore, conventional echocardiographic measures are not able to fully capture the distinct changes in cardiac mechanics, which may lead to the ambiguous interpretation of resting echocardiograms hampering the confident differentiation between physiological remodeling and pathological processes.

Our research group was able to validate the correlation between STE-derived MW and the invasively measured myocardial contractility in a rat model of athlete's heart. GMWI precisely reflected LV contractility in a rodent model, whereas assessing MW in elite athletes showed a supernormal systolic performance in human athletes even at rest. Furthermore, MW indices was found to be less dependent on loading conditions, thus MW analysis should be utilized in the evaluation of the athlete's heart.

We have also characterized biventricular morphology and function in a large cohort of elite athletes using 3DE. Beyond the larger biventricular volumes of athletes compared to controls, we found that adults athletes had larger LV volumes compared with adolescent athletes, however, RV volumes remained similar. Endurance athletes had the largest RV volumes compared with other sports. Athlete's heart was characterized by a distinct mechanical pattern, as resting LV mechanics showed a balanced decrement in GLS and GCS, whereas in the RV, GCS decreased disproportionately compared to GLS. The geometrical and mechanical features of the RV showed significant associations with athletic performance. By examining a smaller cohort of these athletes presented with or without MR, we were able to demonstrate the exercise-induced remodeling of the AV annuli comprising a disproportionate dilation of both TA and MA and increased leaflet tenting of both valves. Furthermore, a more pronounced saddle shape of the MA was shown to be a marked feature of athletes without MR.

In summary, our findings emphasize that advanced echocardiographic techniques, MW analysis, speckle-tracking and 3D echocardiography in particular, bear significant added value in the assessment of ventricular and valvular remodeling associated with the athlete's heart.

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   **Alexandra Fábián, MD and Bálint K. Lakatos, MD are joint first authors.*
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