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

Ph.D. Thesis

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# 1. INTRODUCTION

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

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. 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 that focuses on pre-participation screening, prevention of sudden cardiac death (SCD) or the differentiation of physiological remodeling from cardiomyopathies. However, there is still a substantial need for research to advance knowledge and clinical care.

### 1.1.1. Physiological and pathophysiological cardiac remodeling in response to exercise

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. Furthermore, data suggests that physical activity lengthens life expectancy as well. 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.

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. 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, is commonly referred to as the athlete’s heart. Furthermore, the athlete’s heart also relies on functional adaptation that leads to enhanced myocardial contractility.

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. Arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypertrophic cardiomyopathy (HCM) were found to be prevalent etiologies of SCD in the athlete population. Research has 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 right ventricular (RV) damage. 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 creates a diagnostic 'grey zone'. In order to ensure the safety of not only professional athletes but those partaking in leisure-time physical activity, thorough pre-participation screening is highly recommended.

### *1.2. Echocardiographic assessment of the athlete's heart*

Over the last decades, two-dimensional (2D) transthoracic echocardiography (TTE) and cardiac magnetic resonance (cMR) imaging have become regularly used diagnostic tools and, 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. However, due to the complexity and three-dimensional (3D) nature of all cardiac features, conventional 2D echocardiography-derived measures oftentimes cannot adequately characterize subtle changes in cardiac morphology and function. The emergence of advanced techniques, such as deformation imaging and 3D echocardiography, offers more accurate and detailed quantification of ventricular structure and function in terms of athlete's heart (Figure 1).

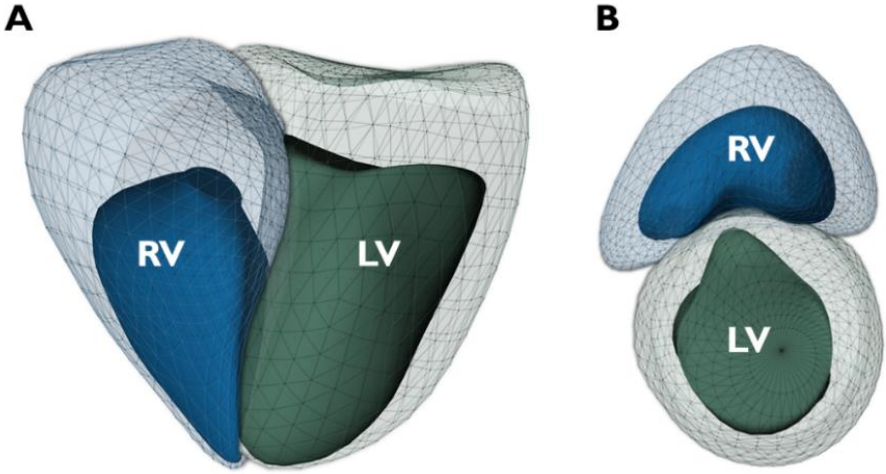

***Figure 1**. 3D model reconstruction of left (LV) and right ventricles (RV) obtained from 3D echocardiographic datasets. A – long axis view. B – short axis view.*

## 2. OBJECTIVES

### 2.1. Investigation of the correlation between myocardial work (MW) 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 ejection fraction (EF) and global longitudinal strain (GLS) are sensitive parameters of left ventricular (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 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 annuli (TA) in elite athletes using 3D echocardiography

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. METHODS

## *3.1. Experimental groups and study design in the rat model of athlete's heart*

### 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. 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.

After completing the 12-week training program, echocardiographic parameters of LV morphology and function were assessed using a Vivid i ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a 13 MHz linear transducer (12 L-RS, GE Vingmed Ultrasound, Horten, Norway). Beyond the conventional echocardiographic protocol, 2D loops dedicated to speckle-tracking echocardiography (STE) were obtained from the parasternal long-axis view. Speckle-tracking analysis was performed in accordance with our internal protocol.

Following the echocardiographic examination, LV pressure-volume (P–V) analysis was performed using a 2-Fr pressure-conductance microcatheter (SPR-838, Millar Instruments, Houston, TX, USA) according to our previously established protocol. We assessed several haemodynamic parameters: LV end-systolic pressure (LVESP), LV end-diastolic pressure (LVEDP), stroke volume (SV). With the transient occlusion of the inferior vena cava, we obtained the slope of the LV end-systolic P–V relationship (ESPVR) that represents a load-independent, gold-standard parameter of contractility. Arterial elastance (Ea) was calculated as LVESP/SV. From the haemodynamic and echocardiographic measurements, meridional end-diastolic wall stress (σED) was estimated to characterize preload.

In MW analysis, we followed the principles published previously by Russell et al. To assess MW in rats, GLS curves and invasive LV pressure recordings were exported and analyzed; then, pressure–strain loops were plotted using our custom-made software (implemented in C#). Global MW index (GMWI) was computed by integrating the power over time from mitral valve closure until mitral valve opening. Constructive MW index (CMWI) is defined as the work generated by the shortening during systole and lengthening during isovolumetric relaxation.

### 3.1.2. Human investigations

In our current study, 20 elite swimmer athletes (10 women and 10 men, members of the national team) were selected from the database of our complex sports cardiology screening program. The participants gave written informed consent before entering the program. All examinations were performed during the in-competition phase and ≥24 h following the last training session.

After a 5-min rest period, brachial artery cuff pressure was measured for each subject while lying in the left lateral decubitus position preceding the echocardiographic examination. Echocardiographic acquisitions were obtained using a Vivid E95 ultrasound system equipped with a 4Vc-D transducer (GE Vingmed Ultrasound, Horten, Norway). Beyond the conventional echocardiographic protocol, ECG-gated full-volume 3D datasets reconstructed from four cardiac cycles optimized for the LV or the right ventricle (RV) were obtained from apical view with a minimum volume rate of 25 volumes/sec for further offline analysis. Datasets focused on the left heart were processed using a commercially available software solution (4D LV-Analysis 3, TomTec I maging, Unterschleissheim, Germany), and LV end-diastolic volume index (LVEDVi), end-systolic volume index (LV ESVi), and LV mass index (LV Mi) were measured. To characterize global LV function, 3D ejection fraction (LV EF) was also computed. The 3D model of the RV was reconstructed from RV-focused 3D datasets using a dedicated software solution (4D RV-Function 2, TomTec Imaging, Unterschleissheim, Germany), and 3D RV EDVi, RV ESVi, RV EF, and 2D free-wall longitudinal strains were quantified as well.

After the echocardiographic examination, all athletes underwent cardiopulmonary exercise testing (CPET; as described in detail below) to quantify peak oxygen uptake ($VO_2$ and $VO_2$/kg). Twenty healthy, age- and sex-matched sedentary healthy volunteers (no previous participation in intensive training, <3 h of exercise/week) were selected from our existing database and served as the control group.

MW analysis was performed using the dedicated module of a commercially available software (AFI, EchoPAC v203, GE Healthcare, Chicago, IL, USA).

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

Healthy, competitive, elite athletes were retrospectively identified (n = 425) from our centre's complex sports cardiology screening programme; the majority of them (n = 304) are members of the national teams in the corresponding age group. 3D echocardiography and then CPET was performed on all athletes on the same day. An age- and sex-matched healthy, sedentary population (<3 h of exercise/week) served as the control group. These individuals also underwent the aforementioned screening protocol, including CPET. All participants provided written, informed consent to the study procedures

Beyond conventional echocardiographic examination, ECG-gated full-volume 3D datasets reconstructed from four cardiac cycles optimized for the left or right heart were obtained for further analysis on a separate workstation. 3D datasets focused on the left heart were processed using semi-automated, commercially available software (4D LV-Analysis 3, TomTec Imaging, Unterschleissheim, Germany). We determined LV EDVi, ESVi, stroke volume index (SVi), and LV Mi. To assess global LV function, EF, 3D GLS, and 3D global circumferential strain (GCS) were also calculated. Concerning the right heart, we quantified 3D RV EDVi, ESVi, SVi, and EF as well (4D RV-Function 2, TomTec Imaging). 3D RV GLS and GCS were calculated using the ReVISION software package (Argus Cognitive, Inc., Lebanon, NH, USA).

Cardiopulmonary exercise testing for peak oxygen uptake ($VO_2$ and $VO_2$/kg) quantification was performed on a treadmill until exhaustion on sport-specific protocols. The volume and composition of the expired gases were analysed breath by breath using an automated cardiopulmonary exercise system (Respiratory Ergostik, Geratherm, Bad Kissingen, Germany). Subjects were encouraged to achieve maximal effort, which was confirmed by respiratory exchange ratio and by reaching the predicted maximal heart rate and a plateau in $VO_2$.

### 3.3. Characterization of the geometry of mitral and tricuspid annuli in elite athletes using 3D echocardiography

We retrospectively identified 425 healthy athletes with 3D transthoracic echocardiographic datasets available for detailed analysis of the left and right hearts. From this cohort, 42 (9.9%) athletes presented with at least mild mitral regurgitation (MR). Eight athletes were excluded due to either suboptimal image quality for MA quantification (n = 6) or non-compatible 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, <3 h of exercise/week) with the same sex distribution (male/female: 26/8) were selected from our database.

The echocardiographic examinations were performed on a commercially available ultrasound system (E95, 4Vc-D probe, GE Vingmed Ultrasound, Horten, Norway), as described in the previous section.

MR was graded based on the measurement of vena contracta width (VCW). Mild MR was defined as having a measurable vena contracta but with a width of <0.3 cm as per current guidelines. Non-MR" was defined as an absolutely not or just barely detectable jet, no flow convergence, and not having measurable vena contracta with a faint, incomplete, or no continuous-wave Doppler signal. Similarly, tricuspid regurgitation (TR) grading was based on measuring the VCW.

Beyond the previously described 3D echocardiographic protocol, we performed 3D quantification of the left atria (LA), and measured maximal volumes (LAVi). For the 3D quantification of the right atria (RA), we used the same software as for the LA (EchoPAC v204, 4D Auto LAQ, GE) due to the lack of dedicated RA software package. Similarly, we measured maximal volumes of RA (RAVi).

Furthermore, MA and TA were quantified by a commercially available software (EchoPAC v204, 4D Auto MVQ and 4D Auto TVQ, GE). We have reported several annular and leaflet parameters such as 3D MA area, MA perimeter, MA nonplanar angle, MA annulus height to commissural width ratio (ACHWR), MA tenting height, area, and volume; and 3D TA area, TA perimeter, TA major and minor axes, TA maximal tenting height, and tenting volume as well.

### 3.4. Statistics

In the first study, statistical analysis was performed in R (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria), whereas in the other two studies, statistical analysis was performed using dedicated software (StatSoft Statistica, v12, Tulsa, OK, USA). Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are reported as frequencies and percentages. After verifying the normal distribution of each variable using the Shapiro–Wilk test, groups were compared with the unpaired Student’s t-test or Mann–Whitney U test for continuous variables and the $\chi 2$ or Fisher’s exact test for categorical variables, as appropriate. Concerning the first study two-way analysis of variance (ANOVA) with the factors ‘Sex’ and ‘Exercise’ was performed, and the P-value for sex and exercise interaction ($P_{Inter}$) was also calculated. To determine differences between subgroups ($M_{Co}$ vs. $M_{Ex}$/$M_{Ath}$ and $F_{Co}$ vs. FEx/$F_{Ath}$), pairwise comparisons were performed using Tukey’s post hoc test. For multivariable analysis, ordinary least squares (OLS) modelling was used. The importance of each predictor in the OLS models with bootstrapped standard errors was determined with ANOVA using the F statistics and the Akaike information criterion. Concerning the last two studies, the Pearson or Spearman test was computed to assess the correlation between continuous variables. In the second study, LV GLS, LV GCS, RV GLS, and RV GCS, individual values of athletes were normalized to the mean value of the control group to calculate their relative changes. Univariable and multivariable linear regression analysis (using ordinary least squares) were applied to determine the predictors of $VO_2$/kg in the entire study cohort. In the third study, multivariate linear regression analysis was performed in athletes to find independent determinants of MA and TA 3D area index. Concerning LV EDVi, LAVi, 3D MA area, RV EDVi, RAVi, and 3-D TA area indices, individual values of athletes were normalized to the mean value of the control group to calculate their relative increase. In all three studies, a two-sided P-value of <0.05 was considered statistically significant.

# 4. RESULTS

## *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*

### 4.1.1. Experimental investigations

#### 4.1.1.1. Conventional echocardiography-derived parameters

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 2).

#### 4.1.1.2. 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. In addition, GMWI and CMWI showed higher values in exercised animals, with similar sex-related differences as seen in GLS (Figure 2).

#### 4.1.1.3. Correlation of contractility with MW indices and the determinants of GLS and MW indices

GLS showed a strong correlation with ESPVR in the pooled animal cohort. MW indices are robustly correlated with LV contractility: both GMWI and CMWI demonstrated strong positive correlation with ESPVR (Figure 2).

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, Ea), (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. 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 2).

### 4.1.2. Human investigations

#### 4.1.2.1. Echocardiographic characteristics

LV wall thicknesses, relative wall thickness, and 3D LV Mi were significantly higher in athletes compared to controls, implying the presence of exercise-induced LV hypertrophy (Figure 2).

#### 4.1.2.2. Myocardial work analysis in elite athletes

Regular exercise training resulted in the reduction of GLS, and sex was observed to have a slight impact on GLS. In contrast, exercise training was associated with higher values of GMWI and CMWI, and sex did not have a significant effect on their values (Figure 2).

#### 4.1.2.3. Correlation of LV functional parameters with peak oxygen uptake

In the pooled study cohort GLS correlated weakly to moderately with $VO_2$/kg. Both GMWI and CMWI exhibited moderate positive correlation with CPET-derived $VO_2$/kg (Figure 2).

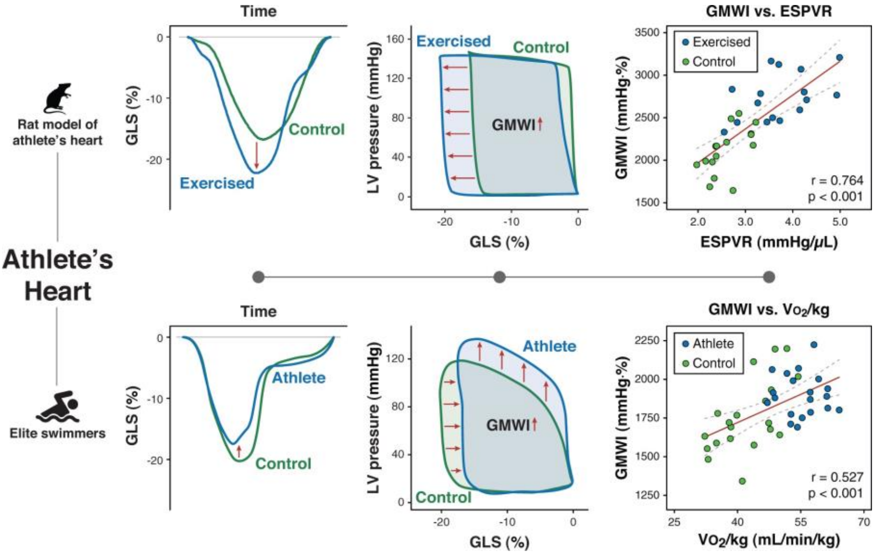

*Figure 2. Exercise-induced changes of myocardial contractility in the rat model of athlete's heart and in human athletes. ESPVR, slope of end-systolic pressure–volume relationship (i.e. the slope of the curve connecting the end-systolic points of the pressure–volume loops recorded during the transient occlusion of inferior vena cava); GLS, global longitudinal strain; GMWI, global myocardial work index; LV, left ventricular; $VO_2$/kg, peak oxygen uptake.*

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

### 4.2.1. Athletes versus sedentary volunteers

Athletes had significantly higher LV and RV EDVi and ESVi values. Similarly, LV Mi, LV and RV SVi values were higher in athletes compared with controls. In athletes, LV EF, LV GLS, LV GCS along with RV EF, RV GCS showed significantly decreased resting values, in contrast to RV GLS, which did not show a difference compared with controls (Figure 3).

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 3)

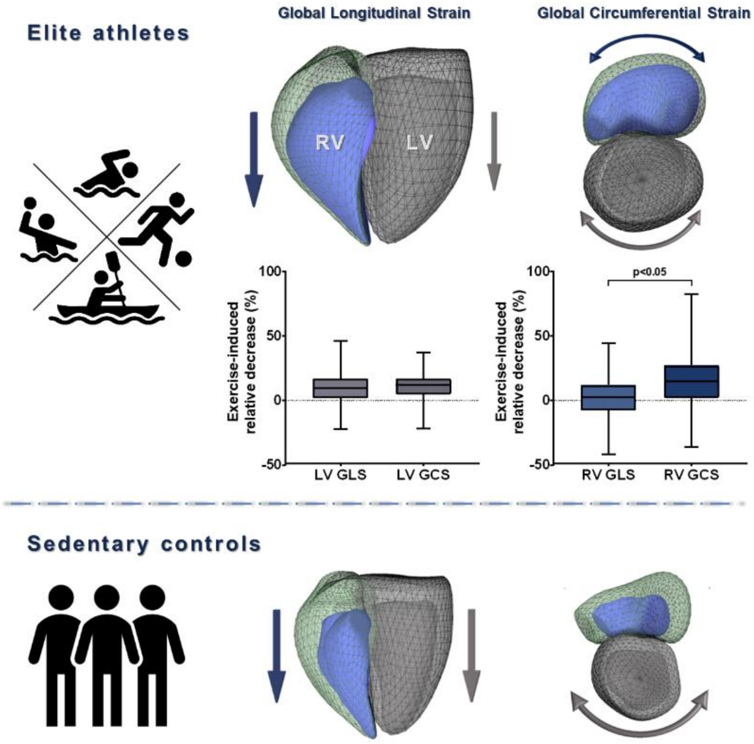

***Figure 3.*** *Exercise-induced alterations in the biventricular mechanical pattern of the athlete's heart assessed by 3D echocardiography. GCS, global circumferential strain; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle*

## 4.3. Characterization of the geometry of mitral and tricuspid annuli in elite athletes using 3D echocardiography

### 4.3.1. Exercise-induced relative dilation of cardiac chambers

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 did not differ compared with RAVi max. The increment in RAVi max was higher compared with RV EDVi (Figure 4).

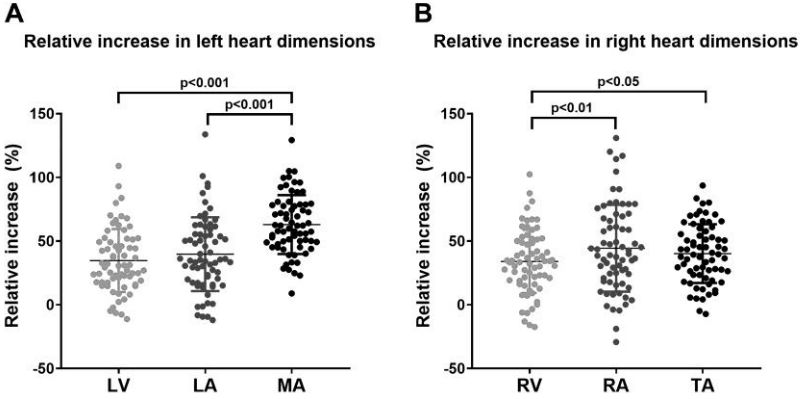

***Figure 4.*** *Comparison of the exercise-induced dilation of the left ventricle (LV), left atria (LA), and the mitral annulus (MA) (A) and the right ventricle (RV), the right atria (RA), and the tricuspid annulus (TA) (B)*

### 4.3.2. 3D echocardiographic quantification of the mitral annulus

The three groups differed significantly concerning all of the parameters (3D and 2D area indices, perimeter, etc.) describing the size of the MA, as athletes having MR had significantly higher values even compared with athletes without MR. 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). Tenting height, area, and volume indices were higher in both athlete groups compared with the control group (Figure 5).

### 4.3.3. 3D echocardiographic quantification of the tricuspid valve

Athletes with MR also had significantly enlarged TA, as shown by 3D and 2D area indices, four-chamber view diameters, and minor axis diameters compared to non-MR athletes and controls. TA perimeter, two-chamber view diameters, and major axis diameters were comparable between athlete groups but still larger than controls. Maximal tenting height and tenting volume index were significantly higher in the athlete groups compared with the sedentary controls (Figure 6).

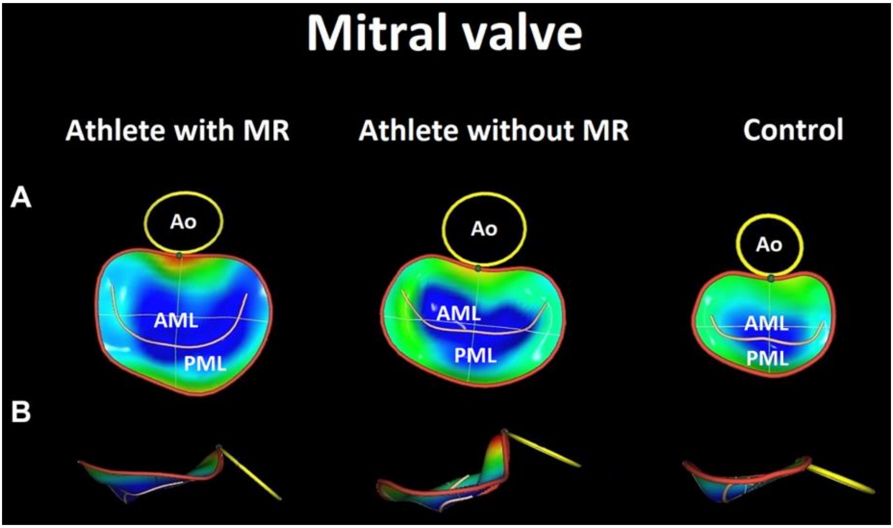

***Figure 5.*** *3D MA reconstructions of athletes with and without MR and a healthy sedentary volunteer (control; representative cases) using 3D echocardiography. A: surgeon's view. B: side view of the mitral annulus. More blueish hues represent more tenting of the mitral valve leaflets. AML, anterior mitral valve leaflet; Ao, aortic annulus; MR, mitral regurgitation PML, posterior mitral valve leaflet.*

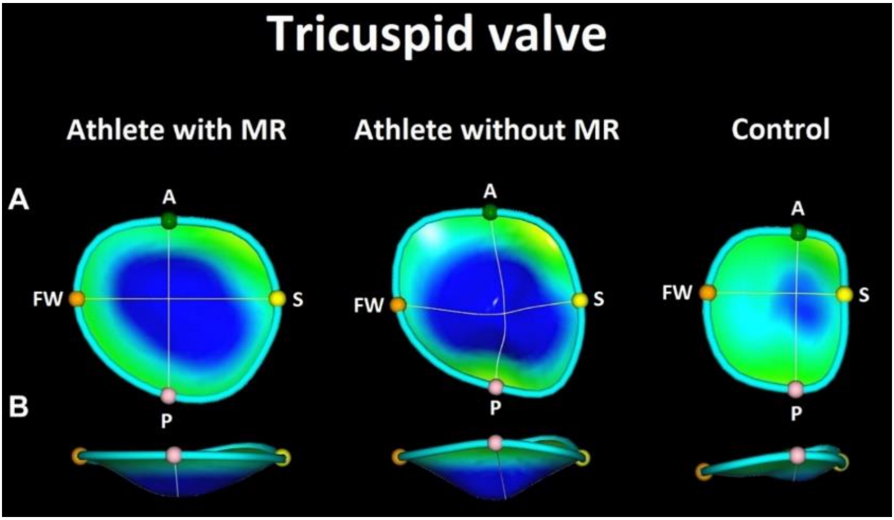

*Figure 6.* *3D TA reconstructions of athletes with and without MR and a healthy sedentary volunteer (control; representative cases) using 3D echocardiography. A: surgeon's view. B: side view of the tricuspid annulus. More blueish hues represent more tenting of the tricuspid valve leaflets. A, anterior; FW, free wall; MR, mitral regurgitation; P, posterior; S, septal reference points.*

## 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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