CHARACTERIZATION OF THE PHYSIOLOGICAL PHENOTYPES OF RIGHT VENTRICULAR CONTRACTION

Ph. D. Thesis

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1. INTRODUCTION

1.1. The right ventricle

The right ventricle (RV) plays a critical role in determining functional status and prognosis across numerous cardiovascular conditions. Unlike the left ventricle (LV), the RV's complex geometry and contraction pattern make its assessment particularly challenging. Historically, its importance was underestimated, yet evidence now highlights its prognostic relevance in diseases such as heart failure (HF), pulmonary hypertension, congenital heart disease, and post-interventional states. RV dysfunction is common, occurring in up to half of patients with HF with reduced LV ejection fraction (EF) and in about one-third with preserved EF. Regardless of LV function, RV dysfunction independently predicts adverse outcomes, including higher hospitalization and mortality rates.

1.1.1. The anatomy and myoarchitecture of the right ventricle

Anatomically, the RV is a thin-walled, crescent-shaped chamber encasing the LV, composed of an inlet, trabeculated apex, and an outflow portion (infundibulum). Its contraction involves multiple fiber orientations: longitudinal subendocardial fibers and circumferential subepicardial fibers, contributing to longitudinal, radial, and anteroposterior motion. These complex fiber interactions underlie the RV's peristaltic contraction and its dependence on LV interaction through ventricular interdependence.

1.1.2. The development and maturational changes of the right ventricle

RV function evolves markedly through life. After birth, as pulmonary vascular resistance decreases, contraction shifts from predominantly radial to longitudinal. With aging, mild increases in pulmonary vascular resistance and decreased myocardial relaxation alter diastolic filling, although systolic function remains preserved.

1.1.3. Contraction pattern of the right ventricle

RV contraction consists of three principal components: (1) longitudinal shortening, represented by tricuspid annular plane systolic excursion (TAPSE); (2) radial inward motion (bellows effect); and (3) anteroposterior shortening due to septal bulging. Each mechanism contributes uniquely to global RV performance.

1.1.4. Echocardiographic assessment of right ventricular function

Echocardiography remains the primary imaging modality for RV assessment, though conventional two-dimensional (2D) parameters—such as TAPSE, fractional area

change (FAC), and tissue Doppler velocities—evaluate only limited motion aspects. Three-dimensional echocardiography (3DE) provides accurate, reproducible quantification of RV volumes and EF, validated against cardiac magnetic resonance imaging. The novel ReVISION method (Right Ventricular Separate wall motIon quantificatiON) further decomposes global RV motion into longitudinal, radial, and anteroposterior components, offering refined insight into RV mechanics beyond traditional indices.

1.2. Knowledge gaps in the understanding of physiological right ventricular function

1.2.1. Lack of normative values in adults and in the young

Reliable normative data are essential for distinguishing physiological from pathological remodeling. However, current guidelines from the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) mainly reflect adult populations, while pediatric and athlete-specific reference ranges remain scarce. The World Alliance of Societies of Echocardiography (WASE) study addressed some of these gaps but did not include children or athletes. Given that young athletes experience both developmental remodeling and intense exercise-induced adaptations, understanding normal RV physiology in this population is vital for distinguishing benign adaptation from early pathology.

1.2.2. Physiological cardiac remodeling in response to exercise – athlete's heart

Athlete's heart is characterized by chamber enlargement and mild EF reduction, primarily reflecting enhanced stroke volume and efficient cardiac output during training. Yet, differentiating these changes from cardiomyopathy remains a diagnostic challenge. Consequently, comprehensive RV evaluation—including 3DE-derived motion analysis—offers potential to improve risk stratification and ensure safe athletic participation.

2. OBJECTIVES

2.1. Quantifying the relative contributions of the longitudinal, radial, and anteroposterior motion components of global right ventricular function and examine their determining factors in a large cohort of healthy adult volunteers using 3D echocardiography

Global right ventricular function is governed by the interplay of multiple motion components that reflect the underlying myofiber architecture. However, the relative contribution of these components remains incompletely characterized. We hypothesize that shortening along the radial and anteroposterior axes holds comparable significance to longitudinal contraction in overall RV performance.

2.2. Quantifying the longitudinal, radial and anteroposterior components of global right ventricular function using 3D echocardiography in a cohort of healthy children and examine maturational changes in these parameters

Recently, 3DE has demonstrated excellent capability in quantifying RV volumes and has been validated against gold-standard imaging modalities in pediatric populations. Building on our initial study, we aimed to investigate the normal contraction patterns of the RV in healthy children.

2.3. The characterization of the right ventricular contraction pattern and its associations with exercise capacity in a large cohort of adolescent athletes using resting three-dimensional echocardiography

Pediatric athletes represent a unique population in which the interpretation of diagnostic findings poses significant clinical challenges; however, there remains a notable lack of data and evidence to guide this process.

3. METHODS

3.1. Quantifying the relative contributions of the longitudinal, radial, and anteroposterior motion components of global right ventricular function and examine their determining factors in a large cohort of healthy adult volunteers using 3D echocardiography

Healthy adults were enrolled at two centers (Semmelweis University, Hungary, and University of Occupational and Environmental Health, Japan). Subjects were recruited from community screenings and hospital staff without known cardiovascular disease. The study was approved by institutional review boards at both centers, and all participants provided written informed consent. Exclusion criteria included BMI $\geq$30 kg/m², cardiovascular risk factors, and poor echocardiographic image quality. The final cohort included 385 adults (balanced by age, sex, and ethnicity).

3.2. Quantifying the longitudinal, radial and anteroposterior components of global right ventricular function using 3D echocardiography in a cohort of healthy children and examine maturational changes in these parameters

Healthy children (<18 years) were enrolled at Boston Children's Hospital (USA) and Semmelweis University (Hungary). At Boston, participants were retrospectively selected from a database of normal 3DE studies, while Semmelweis participants were prospectively recruited from schools. Exclusion criteria eliminated structural or acquired cardiac abnormalities and comorbidities affecting cardiac function. Ethical approval was obtained at both centers; consent was waived in Boston and obtained in Hungary.

3.3. The characterization of the right ventricular contraction pattern and its associations with exercise capacity in a large cohort of adolescent athletes using resting three-dimensional echocardiography

Competitive adolescent athletes (n = 215) were identified from a sports cardiology screening program (ages 10–18 years). Inclusion required available 3DE images. A sedentary, age- and sex-matched control group (n = 38) was also examined. All underwent medical history, ECG, 2D/3D echocardiography, and cardiopulmonary exercise testing (CPET). Written informed consent was obtained from participants or guardians. The study complied with the Declaration of Helsinki.

3.4. Two-Dimensional Echocardiography

Echocardiography was performed using Philips EPIQ 7 and GE Vivid E95 systems, following ASE and EACVI recommendations. Standard 2D parameters—including

LV and RV diameters, wall thicknesses, EF, and strain—were measured. LV volumes were calculated by the area–length method and indexed to body surface area (BSA).

3.5. Three-Dimensional Echocardiography

Beyond conventional imaging, ECG-gated full-volume 3D datasets (four or six cardiac cycles) were obtained for both ventricles. Image quality was verified to minimize stitching artifacts. 3D analyses were performed using TomTec software (4D RV-Function and 4D LV-Analysis). Parameters included EDVi, ESVi, SVi, and EF, normalized to BSA. LV mass index, global longitudinal strain (GLS), global circumferential strain (GCS), and RV free wall longitudinal strain (FWLS) were also calculated.

3.6. Advanced three-dimensional echocardiographic analysis of the right ventricle

RV motion components were quantified using ReVISION software (Argus Cognitive, USA). Exported 3D meshes were automatically aligned to longitudinal, radial, and anteroposterior axes. Motion decomposition provided component-specific EF indices—longitudinal (LEF), radial (REF), and anteroposterior (AEF). Relative contributions were expressed as LEF/RVEF, REF/RVEF, and AEF/RVEF. Because volume changes are multiplicative rather than additive, signed indices (LEF′, REF′, AEF′) were derived to sum to total RVEF. Reproducibility was validated in prior work.
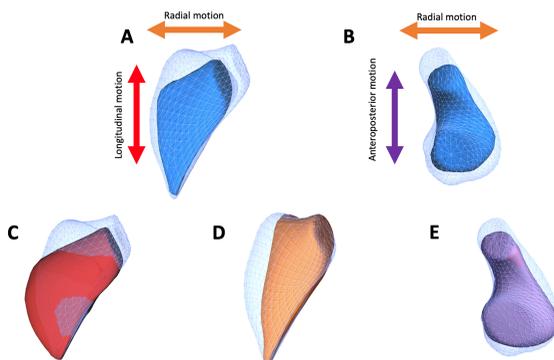

Figure 1. The three different components of right ventricular contraction from a representative subject. In the figure the global motion of the RV is shown from anterior (A) and superior (B) views (blue mesh, RV end-diastolic volume; blue surface, RV end-systolic volume). RV end-systolic meshes can be generated by "locking" the RV motion in two directions, permitting motion in only a single axis and thus revealing the impact of

decomposed contraction components. Thus, the change in ventricular volume attributable to shortening along the longitudinal (C, red surface), radial (D, orange surface) and anteroposterior (E, purple surface) can be separately quantified.

3.7.1. Statistical analysis for quantifying the relative contributions of the longitudinal, radial, and anteroposterior motion components of global right ventricular function in a large cohort of healthy volunteers from two centers using 3D echocardiography

Continuous data were summarized as mean ± SD. Group comparisons used unpaired t tests, correlations Pearson analysis, and age–sex effects two-way ANOVA. Repeated-measures ANOVA assessed motion components, and multiple regression identified independent predictors. Reproducibility was verified in 20 randomly selected cases; $P < 0.05$ was considered significant.

3.7.2. Statistical analysis for describing the relative contributions of longitudinal, radial, and anteroposterior motion components of global right ventricular function in a cohort of healthy children

Continuous data are reported as mean ± SD or median (IQR). Age-related differences were tested using one-way ANOVA or Kruskal–Wallis, and within-group differences in LEF, REF, and AEF with Wilcoxon tests (Bonferroni correction, $p < 0.017$). Sex effects were age-adjusted, and reproducibility was evaluated in 30 cases using ICC; $p < 0.05$ was considered significant.

3.7.3. Statistical analysis for the characterization of the right ventricular contraction pattern and its associations with exercise capacity in a large cohort of adolescent athletes

Effect sizes (Cohen's d) confirmed adequate power (>0.80). Continuous variables are expressed as mean ± SD; normality was tested with Kolmogorov–Smirnov. Between-group comparisons used t or Mann–Whitney tests, correlations Pearson or Spearman; two-sided $P < 0.05$ indicated significance.

3.8. Cardiopulmonary exercise testing

CPET was performed on a treadmill using sport-specific incremental protocols, starting with brief rest and warm-up, followed by continuous uphill running with 1–1.5% slope increases every minute until exhaustion. Expired gases were analyzed breath by breath (Respiratory Ergostik, Geratherm). Maximal effort was defined by subjective exhaustion with RER >1.1 and/or plateauing of VO_2 and HR curves, and peak VO_2/kg was calculated.

4. RESULTS

4.1. *Quantifying the relative contributions of the longitudinal, radial, and anteroposterior motion components of global right ventricular function and investigating their determining factors in a large cohort of healthy volunteers from two centers using 3D echocardiography*

4.1.1. Morphometric and conventional echocardiographic characteristics

The mean age of the enrolled patients was 45±15 years. Men were characterized by significantly higher morphometric parameters, higher systolic and DBP (diastolic blood pressure), and lower HR. Male sex was associated with higher RV basal diameter, RV areas, right atrial volume index (RAVi), and LV volumes and LV mass index. RV FAC and RV FWLS were higher in women, but TAPSE did not differ between sexes. Doppler tissue imaging–derived tricuspid annular velocities and pulmonary artery systolic pressure (PASP) were comparable between men and women.

4.1.2. Three-dimensional right ventricular mechanics of the study group by age categories and sex

Men exhibited higher RV end-diastolic volume index (RVEDVi) and RV end-systolic volume index, whereas RVEF, RV GLS, RV GCS, and RV global area change (GAS) were higher in women. Longitudinal EF index (LEFi), radial EF index (REFi), and anteroposterior EF index (AEFi) revealed no sex-related differences in the relative contributions of motion components. RV volumetric indices, RVEF, RV GLS, RV GAS, and circumferential EF index varied significantly across age groups, but no age–sex interaction was observed. Circumferential motion contributed more than longitudinal shortening in all age categories (P < 0.001). In the pooled population, anteroposterior (49.1±6.8%) and longitudinal shortening (46.6±8.7%) predominated over radial shortening (43.5±10.3%). Longitudinal contribution exceeded radial in younger adults, while LEFi and REFi were comparable in older groups. AEFi exceeded LEFi in the 30–39 and 50–59 age groups and exceeded REFi in all but the 50–59 group. Subjects with low LEFi had preserved RVEF and AEFi but increased REFi, whereas those with low REFi had reduced RVEF but higher LEFi and AEFi, suggesting compensatory mechanisms among motion components (Figure 2).
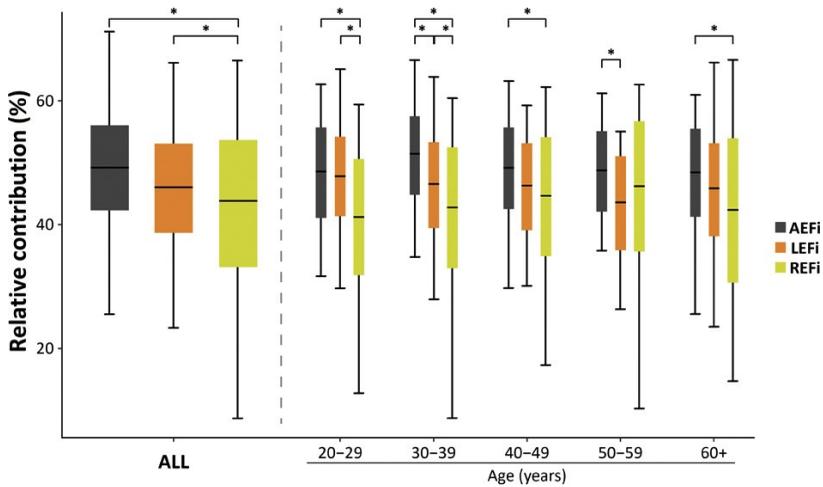
Figure 2. Comparison of the relative contributions of anteroposterior, longitudinal, and radial shortening to global RV function. Individual and mean values of AEFi, LEFi, and REFi are visualized in the pooled population (n = 300) and the different age categories, with statistical comparison among the three motion components. *P <0.05.

4.1.3. Correlations of right ventricular parameters and basic morphometric and demographic parameters

Several RV parameters correlated weakly but significantly with age, BSA, and hemodynamics. Age was inversely associated with RVEDVi, RVEF, RV GLS, LEFi, and RV GAS. BSA correlated negatively with RVEF, RV GLS, LEFi, and AEFi, but positively with RVEDVi and REFi. Systolic blood pressure (SBP) and DBP showed negative correlations with RV GLS and AEFi, while RVEDVi and REFi correlated positively; SBP also correlated negatively with RVEF. HR correlated positively with RVEF, RV GCS, RV GAS, and REFi, and negatively with AEFi. PASP showed no associations in the pooled cohort, but in subjects ≥60 years, weak negative correlations were observed with RVEF and REFi.

4.1.4. Independent predictors of LEFi, REFi and AEFi

Age, BSA, HR, and RVEDVi were independent predictors of LEFi and REFi as well, but all with the opposite effect on the two motion directions. Beyond these variables, LV mass index, LV GLS, and PASP were associated with LEFi in the multivariate analysis. Concerning REFi, RVEF and LVEF were found to be independent predictors. Race, LVEF, and RVEF were independent predictors of AEFi.

4.1.5. Presentation the importance of detailed analysis of right ventricular deformation

We have included three representative cases, all with maintained RVEFs, to highlight the importance of a detailed analysis of RV deformation pattern (Figure 3).
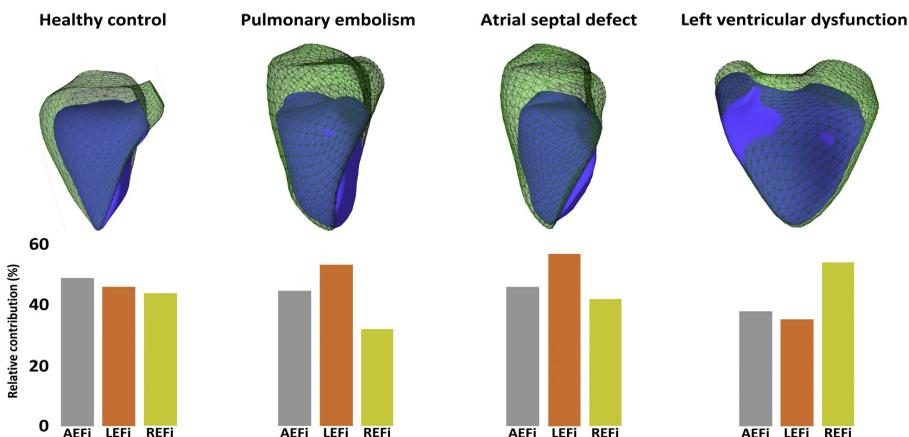

Figure 3. Significant changes in RV deformation pattern with maintained RVEF: representative cases. A healthy subject from our study group (RVEF 62%) demonstrates physiologic RV deformation with more or less equal contribution of the three motion directions. In a patient following massive pulmonary embolism (pressure overload; PASP 57 mm Hg) and maintained global RV function (RVEF 51%), radial motion (REFi) was significantly lower, while anteroposterior shortening (AEFi) remained unchanged, resulting in a higher contribution of longitudinal motion to global function (LEFi). A patient with a hemodynamically significant atrial septal defect (volume overload; Qp/Qs = 1.8) was characterized by hyperdynamic RV function (RVEF 66%). In this case, higher LEFi could be seen, with subsequently lower REFi and AEFi. In a patient with HF with nonischemic dilated cardiomyopathy, severely reduced LV function (LVEF 29%), and maintained RV systolic function (RVEF 48%), LEFi and AEFi were severely reduced, while REFi was relatively increased.

4.2. Describing the relative contributions of longitudinal, radial, and anteroposterior motion components of global right ventricular function in a cohort of healthy children and examining differences in the relative contributions of the 3 components of ejection fraction in children and looking for changes in the contribution of these components as a function of age

4.2.1. Morphometric and demographic characteristics

The study population included 166 subjects (Boston = 76; Semmelweis = 90). The median age of subjects was 13.8 years (IQR 8.6 to 15.3), with a skewed distribution towards the oldest age group (as a consequence of the recruitment strategy at the Semmelweis site). The population was majority male (n = 131, 79%), driven by a male-predominant population recruited at the Semmelweis site (n = 81, 90%) (Table 8).

Table 8. Patient characteristics						
	All (n = 166)	**Infants (n = 13)**	**Toddlers (n = 11)**	**School-Aged (n = 21)**	**(Pre)Teens (n = 121)**	**P-value**
Age, year	13.8 (8.6, 15.3)	0.1 (0.05, 0.1)	3.6 (3.3, 4.1)	6.3 (5.2, 7.9)	14.4 (13.6, 15.7)	<0.001
Female (n(%))	35 (21%)	7 (54%)	5 (45%)	7 (33%)	16 (13%)	
Height, m	1.49±0.38	0.53±0.07	1.00±0.08	1.21±0.11	1.69±0.14	<0.001
Weight, kg	47.7±23.8	4.2±2.0	16.6±3.2	23.3±5.9	59.4±15.3	<0.001
BMI, kg/m²	19.1±3.5	14.3±2.0	16.3±1.4	15.5±1.5	20.5±3.0	<0.001
BSA, m²	1.39±0.54	0.25±0.07	0.68±0.09	0.88±0.14	1.66±0.29	<0.001
SBP, mmHg	117±19	92±14	100±10	100±10	125±16	<0.001
DBP, mmHg	65±12	53±11	53±6	56±8	68±10	<0.001
HR, beats/min	80±20	130±13	89±12	84±14	73±12	

Continuous data are expressed as mean ±SD, with the exception of age which are presented as median (IQR). BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

4.2.2. Conventional echocardiographic parameters
TAPSE increased significantly with age. Most subjects had either no (92, 53%) or trivial (72, 42%) tricuspid regurgitation. There were no differences between groups in terms of RV FAC. Age-related variation in 2D FWLS was present, with the largest absolute values seen in the toddler and school-aged groups.

4.2.3. Three-dimensional echocardiographic analysis of right ventricular size and ejection fraction components

RV volumes, global RVEF, REF, REFi, and longitudinal and circumferential 3D strain parameters differed significantly across age groups. Age-related differences were present for RVEF, REF, REFi, and all RV strain components. No sex-specific differences emerged after age adjustment. Across the cohort, AEFi exceeded the other components, a pattern also observed in the oldest group. In school-aged subjects, AEFi was greater than LEFi, whereas no significant component differences were detected in infants and toddlers (Figure 4).
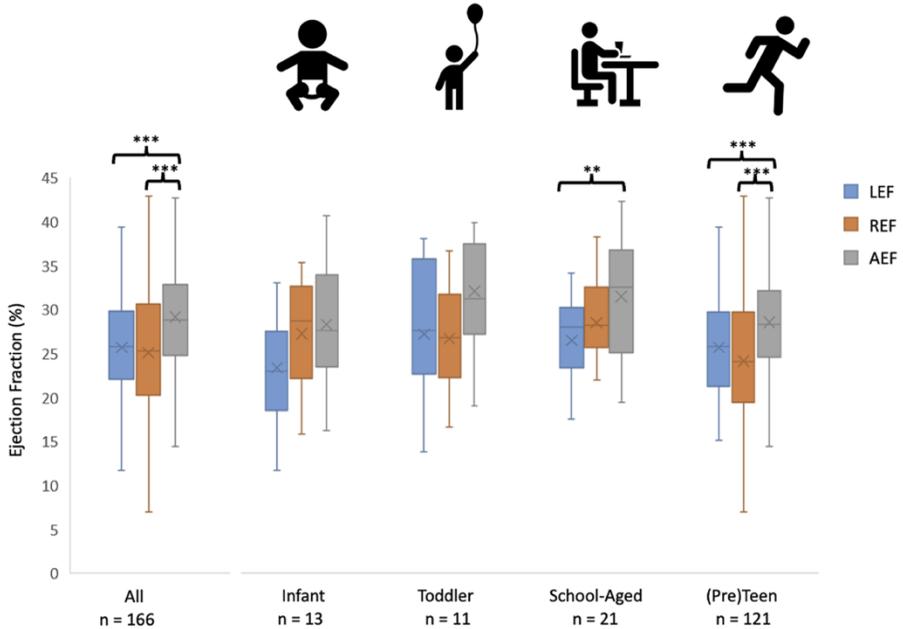

Figure 4. A comparison of the contributions of longitudinal, radial and anteroposterior contraction to global RV function. Individual and mean values of LEF, REF, and AEF are shown in the entire population (leftmost column) as well as the different age categories, with statistical comparison among the three motion components. **p < 0.01, ***p < 0.001.

4.3. The characterization of the right ventricular contraction pattern and its associations with exercise capacity in a large cohort of adolescent athletes using resting three- dimensional echocardiography

4.3.1. Basic demographic, anthropometric and hemodynamic data of the adolescent athletes and control population

Athletes had greater height, BSA, higher resting SBP, and lower HR compared with sedentary controls, while DBP was similar. Most participated in mixed and endurance sports, primarily soccer (46.0%), water polo (33.4%), and swimming (10.2%), with additional representation from power and skill sports. Athletes had engaged in competitive training for 8±3 years (12±6 h/week), and 43.7% were national team members. CPET-derived peak exercise capacity averaged 54 ml/kg/min.

4.3.2. Conventional 2D echocardiographic parameters of athletes and controls

Left ventricular end-diastolic internal diameter, wall thicknesses, and calculated LVMi were significantly higher in athletes compared with controls. Regarding diastolic function, transmitral E-wave velocities were significantly lower in athletes. Systolic, early diastolic and atrial velocities of the mitral septal and lateral annuli were significantly lower in athletes. Concerning the right heart, RV basal diameter was larger, along with RV systolic pressure, which also showed significantly higher values among the athlete population. In athletes, right ventricular FAC and RV FWLS showed decreased resting values.

4.3.3. 3D echocardiographic characteristics of athletes and controls

Athletes showed significantly higher LV and RV EDVi, ESVi, SVi, and LVMi compared with controls. Resting LV and RV EF values were lower in athletes but within the normal range. Regarding RV contraction patterns, REF and AEF were reduced in athletes, while LEF was similar between groups. The relative contribution of radial and anteroposterior components to global RV function was lower in athletes, whereas longitudinal contribution was higher.

4.3.4. Comparison of training-specific characteristics and 3D echocardiographic data in female and male athletes

Male athletes were younger, had longer competitive experience but shorter weekly training hours, and demonstrated higher CPET-derived peak capacity compared with females. Males showed higher LV and RV EDVi, ESVi, SVi, and LVMi. Resting LVEF and RVEF were lower in males, while RV mechanics revealed reduced REF and AEF but higher LEF. Accordingly, the relative contribution of radial and anteroposterior components was lower, and longitudinal contribution higher, in male athletes (Figure 5).
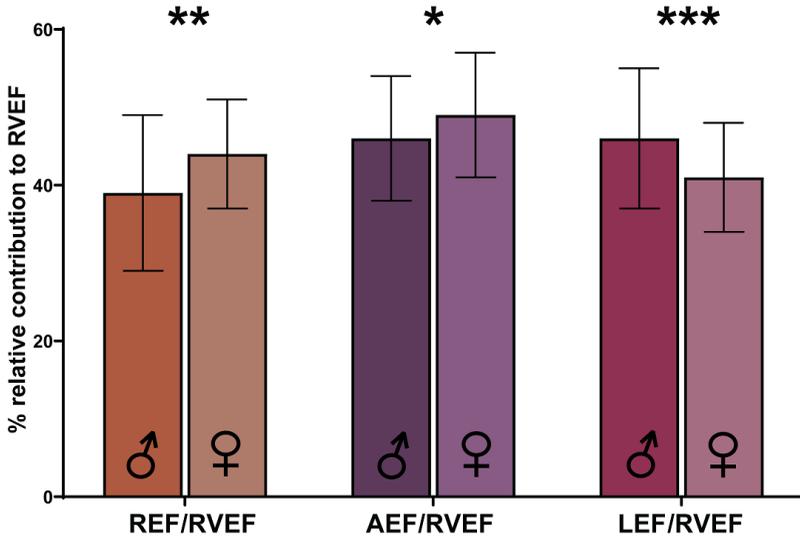
Figure 5. Sex-related differences in right ventricular (RV) contraction pattern in adolescent athletes. Male sex was associated with significantly lower radial contribution to RV ejection fraction (REF/RVEF) as well as anteroposterior shortening (AEF/RVEF), while the contribution of longitudinal shortening (LEF/RVEF) was higher compared to female athletes.

4.3.5. Correlations between 3D echocardiography-derived parameters and VO₂/kg

In athletes, VO_2/kg correlated moderately with LV EDVi, ESVi, SVi, and LVMi, while LV EF showed a weak inverse correlation. For the RV, EDVi, ESVi, and SVi correlated moderately with VO_2/kg, whereas RVEF showed no association. Regarding RV mechanics, LEF/RVEF correlated weakly and positively with VO_2/kg, while AEF/RVEF correlated weakly and inversely.

5.   CONCLUSIONS

In our first study, we demonstrated that the often-overlooked radial and anteroposterior motion components of the RV are as important as longitudinal shortening in determining global RV function in healthy individuals. These findings highlight the value of 3DE in evaluating RV performance. Clinical data indicate that normal values of parameters reflecting only longitudinal motion do not rule out RV dysfunction, just as preserved global RV function can coexist with abnormal longitudinal indices. 3D RVEF captures the integrated contribution of all motion directions, potentially offering superior diagnostic and prognostic utility compared to conventional M-mode or 2D techniques. Even with preserved global function, the proportional contributions of the three components may vary in specific clinical settings (e.g., RV volume or pressure overload, cardiomyopathies, left-sided HF). Thus, further research is needed to determine whether quantifying RV deformation patterns by separating longitudinal, radial, and anteroposterior components enhances the established value of RVEF.

In our second study, we found that analyzing the components of RV contraction in healthy children using 3DE is both feasible and reliable. Within this pediatric cohort, the anteroposterior component consistently exceeded both radial and longitudinal contributions. We also observed age-related changes in global RVEF and in the radial component of RV contraction. These findings support the potential of future 3DE-based investigations in pediatric populations—particularly those with congenital heart disease—to improve the detection of RV dysfunction and aid in evaluating treatment outcomes.

In our third study, we investigated a large cohort of adolescent athletes using advanced echocardiographic techniques alongside CPET. We found that both conventional and emerging features of the athlete's heart—including specific alterations in RV contraction patterns—are already present in pediatric athletes and correlate with peak exercise capacity. Further research using advanced imaging modalities in pediatric populations is warranted to help differentiate the healthy adolescent athlete's heart from rare pathological conditions with overlapping phenotypes.

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