THE ROLE OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY IN THE EVALUATION OF PHYSIOLOGICAL AND PATHOLOGICAL RIGHT VENTRICULAR REMODELING

Ph.D. Thesis

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Budapest
2018

1. INTRODUCTION

The right ventricle (RV) is the heart chamber that receives deoxygenated blood from the right atrium and then pumps it into the pulmonary artery to maintain the pulmonary circulation. Although there is no doubt that the RV is important for normal physiology, the role of the RV in cardiac pathology is frequently underestimated. Currently, there is clear evidence showing that the RV is a strong predictor of outcomes in a range of pathologic conditions, such as RV myocardial infarction, heart failure, pulmonary hypertension, myocarditis, and cardiomyopathies, in addition to heart transplant (HTX) patients.

Echocardiography remains the routine clinical examination of choice to assess RV structure, function and hemodynamics. However, it is complicated to analyze RV dysfunction based on a conventional echocardiographic examination because it is located in an anterior position right behind the sternum and has a complex geometry, prominent trabeculations and a poorly delineated endocardial border. Hence, the myocardial mechanics of the RV are not fully understood. Novel modalities, such as three-dimensional echocardiography (3DE) and speckle-tracking echocardiography can be useful for overcoming these limitations and may provide a better understanding of the mechanical aspects of RV performance under physiological conditions (e.g., in athlete's heart) and the mechanisms underlying cardiac diseases.

'Athlete's heart' is an umbrella term that covers various cardiac effects resulting from regular intense exercise. It is a physiological, benign condition that makes intensive bouts of exercise more well-tolerated in athletes than in non athletes in addition to playing an important physiological role heart adaptations that help a good athlete to become a great one. Athlete's heart has been a topic of great interest for cardiologists for almost two centuries and continues to be a popular topic today.

Distinguishing physiologic from pathologic alterations for athletes can be difficult. A misdiagnosis can be devastating to the athlete with unnecessary interruption of training or elimination from competition. Conversely, a false diagnosis may jeopardize a young life and waive further risk stratification and evaluation of family members for genetic conditions. Nowadays, more and more clinical and also research interest turn toward the adaptation of the RV, because of the awareness to arrhythmogenic cardiomyopathy and the phenomenon of exercise-induced RV dysfunction as well. The aim of the present thesis is to discuss the role of 3DE in the evaluation of RV remodeling, whether it can be utilized to help clinicians in the assessment of physiological and pathological cardiac processes.

2. OBJECTIVES

2.1 Investigation of cardiac remodeling in female athletes induced by different types of exercise training

The vast majority of the literature describes male athlete's heart, and detailed information about physiological cardiac remodeling in female athletes is lacking. We aimed to shed more light on the dichotomous cardiac adaptations observed among elite female competitors who participate in either a more static or a more dynamic sport discipline and to compare them to the results obtained in healthy, sedentary volunteers. Using 3DE, we aimed to characterize both left ventricle (LV) and RV remodeling in these populations.

2.2 Investigation of physiological cardiac remodeling in elite male kayak and canoe athletes

The high-level, mixed-type exercise performed in nature sport disciplines induces distinct alterations in cardiac morphology and function. We have aimed to characterize the cardiac remodeling that occurs in elite kayak and canoe athletes and to compare these results with those obtained in healthy, sedentary volunteers. Using 3DE, we aimed to produce a detailed investigation of both LV and RV remodeling in these populations.

2.3 Determination of RV mechanical patterns in pathological RV remodeling

The complex RV mechanical pattern may shift for a variety of reasons. We sought to investigate a distinct population that exhibits functional remodeling while maintaining the global functions of the RV to evaluate the relative importance of longitudinal and radial wall motions. HTX patients served as an example of the pathological remodeling of the RV with preserved ejection fraction (EF).

3. METHODS

3.1 Study populations

3.1.1. Female athlete's heart

In this single-center study described in the current investigation, three distinct cohorts of different athlete populations were evaluated for athlete's heart. Fifteen elite female athletes competing in the IFBB BikiniFitness category were also enrolled in the study. Furthermore, 15 elite age-matched female waterpolo athletes (all in the national team of the corresponding age category) were invited for voluntary screening between 2016 and 2017. For comparison, 15 age-matched, healthy, non-trained (no previous participation in intensive training, <3 hours of exercise/week) women were investigated. Study participants gave a prior written informed consent to the examinations. In the athletes all of the measurements were performed at least 12 hours after the last athletic training period. The protocol included a detailed medical history and a training regime along with a standard physical examination, blood pressure measurement and 12-lead ECG, and body composition. Subjects showing uncommon echocardiographic and/or ECG changes, suboptimal image quality, and athletes who suspended regular training in the last 6 months were excluded (n=3).

3.1.2. Elite male kayak or canoe athletes

We investigated 11 male kayak or canoe athletes who were competing on an Olympic, World and⁄or National Team. We registered the participants' medical histories and anthropometric data, physical examinations, blood pressure measurements and 12-lead ECG data. The exclusion criteria were any previously known cardiac diseases (except for treated hypertonia), or the presence of a moderate or severe grade valvular disease. For the control group, we invited 10 age-matched, healthy, non-trained volunteers.

3.1.3. HTX recipients

We retrospectively collected echocardiograms obtained in HTX recipients seen from December 2014 to January 2017 and followed-up by our Center. Transthoracic 3D datasets were acquired and found to be suitable for further analysis in 66 individuals. The included patients had already been discharged from an intensive care unit after HTX or had arrived for a regular follow-up visit. The exclusion criteria were (i) hemodynamic instability and/or a need for inotropic agents; (ii) previous rejection ≥ISHLT grade 2R or ≥pAMR2; (iii) a postoperative need for a ventricular assist device; (iv) severe tricuspid insufficiency or any severe valvular disease; (v) non-sinus rhythm on ECG; (vi) a diagnosis of chronic allograft vasculopathy; and (vii) suboptimal 3DE image quality (inadequate visualization of the entire RV endocardial surface inclusive of the RV outflow tract with result confirmed on short-axis planes and/or the presence of stitching artifacts). Finally, 51 patients were entered into the current analysis. An age-and gender-matched control population (n = 30) with normal echocardiographic reports, without any known cardiovascular or other diseases and free from any medication was selected using our existing database of healthy volunteers.

3.2 Methodology

3.2.1 Body composition measurement

Weight and height were measured using validated standard equipment. All participants wore light clothing and were barefoot. Body mass index (BMI) was calculated by dividing the body weight by the squared height. Body surface area (BSA) was calculated using the Mosteller formula:

$$\text{BSA (m}^2\text{)} = \text{(height (cm) x weight (kg)/3600)}^{1/2}.$$

Body composition was assessed by a Bodystat 1500MDD machine (Bodystat Ltd., Douglas, UK). Participants removed all metal and other objects that could interfere with the scan and were then instructed to empty their bladder before the assessment. Each participant was placed in a supine position in the center of the table with their palms down and their arms beside the body. Age, height, weight and gender were entered into the machine before performing the automatic calculations. The fat-free mass index (FFMI) was calculated as the fat-free mass (kg) divided by the square of the height (m^2).

3.2.2 Conventional echocardiography

Tranthoracic echocardiographic examinations were performed with patient in the left lateral decubitus position with continuously registered ECG. Echocardiographic examinations were performed on commercially available ultrasound systems (Philips iE33 or EPIQ 7G, X5-1 and S5-1 transducers, Best, The Netherlands). A standard acquisition protocol consisting of loops from parasternal, apical and subxyphoid views were used according to current guidelines. For post-processing, acquisitions were stored on the TomTec ImageArena platform (TomTec Imaging GmbH, Unterschleissheim, Germany). In the parasternal long-axis view, the interventricular septal (IVSd), LV internal (LVIDd) and LV posterior wall (LVPWd) thicknesses were measured in the end-diastolic frame using the 2D-guided M-mode technique. Relative wall thickness was calculated by 2xLVPWd/LVIDd. We calculated LV mass (LVM) using the Devereux-formula. In A4C view, early (E) and late (A) waves of mitral inflow and the deceleration time of the E wave were measured using pulsed wave spectral Doppler. Mitral annular lateral, septal and tricuspid annular systolic (s'), early diastolic (e') and late diastolic (a') velocities were measured by pulsed wave Doppler on tissue Doppler imaging. LA and RA volumes were measured by the monoplane Simpson's method and indexed to BSA. In an RV-focused apical four-chamber view, the basal and mid-RV diameters and RV length were measured. TAPSE was assessed on an M-mode recording. Valvular diseases were quantified according to current guidelines. Beyond the conventional echocardiographic examination, ECG-gated full-volume 3D datasets were reconstructed from 4 or 6 cardiac cycles optimized for the LV or the RV and were obtained for further analysis on an off-line workstation.

3.2.3 3D echocardiography

The 3D datasets that were focused on the LV were processed by a single experienced operator using semi-automated, commercially available software (4D LV-Analysis 3, TomTec Imaging GmbH, Unterschleissheim, Germany). We determined the end-diastolic (EDVi), end-systolic (ESVi), stroke volume (SVi) and mass (LVMi) indices. Parameters were normalized to BSA. To characterize LV function, EF and deformation parameters, such as GLS and GCS, were also assessed. Off-line analysis of the datasets focused on the RV were performed by the same operator using commercially available software (4D RV-Function 2, TomTec). The algorithm automatically generated an RV endocardial contour that was manually corrected along multiple short- and long-axis planes throughout the entire cardiac cycle. We quantified RV EDVi, ESVi, and SVi normalized to BSA and total EF (TEF). Furthermore, the software automatically measured FAC and free wall longitudinal strain using the 3D dataset. The created 3D model was exported volume-by-volume throughout the cardiac cycle and further analyzed with our custom-made method (Right VentrIcular Separate wall motIon quantificatiON—ReVISION method). Briefly, the wall movements of the exported RV model were decomposed in a vertexbased manner. The volumes of the models accounting for only one direction were calculated at each time frame using the signed tetrahedron method. According to the decomposition of the 3D model's motion along the three orthogonal, anatomically relevant axes, volume loss that could be attributed to longitudinal, radial or anteroposterior wall motions could be separately quantified. Thus, longitudinal (LEF), radial (REF), and anteroposterior (AEF) EFs and their ratios to TEF (LEF/TEF, REF/TEF, AEF/TEF, respectively) could be expressed as a measure of the relative contribution of the given wall motion direction.

3.4 Statistical analyses

All statistical analyses were performed using dedicated software (StatSoft STATISTICA v12, Tulsa, OK, U.S.). Data are presented as the mean ± standard deviation or medians with interquartile range, as appropriate, depending on the distribution of the values. Categorical variables are expressed as a percentage. The Shapiro-Wilk test was used to test normal distributions. Based on the results, unpaired Student's *t*-test or Mann-Whitney *U*-test was used to compare two distinct groups. The Chi-square test was applied to compare categorical variables. One-way ANOVA followed by Fisher's post hoc test was used to compare three distinct groups, and Pearson's or Spearman's test was performed for correlation analyses, as appropriate. Intraobserver and interobserver reproducibility were evaluated using Lin's concordance correlation coefficient.

4. RESULTS

4.1 Investigation of cardiac remodeling induced by different types of exercise training in female athletes

Fitness athletes presented left ventricular end-diastolic, end-systolic and stroke volumes similar to those in healthy, sedentary volunteers. However, waterpolo athletes had higher LV end-diastolic and end-systolic volumes even after indexing to BSA. Correspondingly, LV EF was similar between fitness athletes and controls but lower in waterpolo athletes. LV stroke volume and the stroke volume index were not different between the groups. LVM and the LV mass index (LVMi) were significantly higher in the athlete groups, whereas hypertrophy was more prominent in waterpolo athletes. With regard for geometrical changes, global longitudinal and circumferential strains were lower in waterpolo athletes. Systolic deformation parameters were similar between fitness athletes and controls. Similarly, RV end-diastolic, end-systolic and stroke volumes were all similar between the fitness athletes and controls but were higher in waterpolo athletes. There was no difference in RVEF among the groups. There was no difference in either FAC or free wall longitudinal strain with reference for the similar systolic function of the RV. Regarding the relative contribution of different RV motion directions, we found no difference between fitness athletes and healthy controls (Table 1). However, waterpolo athletes had significantly higher longitudinal contribution to total EF than was observed in controls and a significantly lower radial contribution than was observed in either of the two other groups (Table 1).

Table 1. Comparison of the relative contribution of the different motion directions of the RV among the three study groups.

	Fitness athletes (n=15)	**Waterpolo athletes (n=15)**	**Healthy controls (n=15)**	**ANOVA p**
LEF (%)	25.9±5.3	28.1±3.7	25.3±6.3	0.267
LEF/TEF	0.46±0.07	0.52±0.06§	0.42±0.08*	<0.001
REF (%)	26.3±5.6	19.9±7.4§	32.4±8.6*	<0.001
REF/TEF	0.47±0.09*	0.36±0.10#§	0.53±0.09*	<0.001
AEF (%)	25.1±5.2	22.5±3.9	26.0±6.5	0.213
AEF/TEF	0.44±0.07	0.42±0.07	0.43±0.07	0.633

LEF: longitudinal ejection fraction, REF: radial ejection fraction, AEF: anteroposterior ejection fractions, TEF: total ejection fraction; * significant versus waterpolo athletes, # significant versus fitness athletes, § significant versus controls

In fitness athletes, FFMI was correlated with RV EDV ($r=0.607$, $p<0.05$), RV SV ($r=0.647$, $p<0.05$) and RV length ($r=0.575$, $p<0.05$); in waterpolo athletes, weekly training time was correlated with LV mass ($r=0.527$, $p<0.05$), while training years was correlated with LVMi ($r=0.567$, $p<0.05$).

4.2 Investigation of physiological cardiac remodeling in elite male kayak and canoe athletes

LV end-diastolic, end-systolic and stroke volumes were significantly higher in the athletes than in the control group even after indexing the values to BSA. LV EF was significantly lower in athletes, but its values remained within a normal range. LVM, determined by 3DE, was also higher in top athletes after indexing to BSA but significantly lower than the values obtained via the Devereux formula. GLS (global longitudinal strain) and GCS (global circumferencial strain) were significantly lower in athletes.

Similarly to LV, RV EDV, ESV and SV evaluated by 3DE was also significantly higher in athletes. In athletes, the RV EF was lower than in controls, remaining, however the low-normal range. The FAC calculated using 3DE did not differ between the two groups. Both the septal and the free wall longitudinal strains were lower in athletes.

With regard for the relative contribution of different RV wall motion directions, we found no difference between male athletes and the corresponding controls.

Table 2. Comparison of the different motion directions of the RV between the study groups

	Athletes (n=11)	**Controls (n=10)**	**p**
LEF (%)	21.9±4.9	26.4±3.3	0.100
LEF/TEF	0.42±0.09	0.47±0.06	0.136
REF (%)	21.5±3.7	24.4±4.5	0.134
REF/TEF	0.45±0.09	0.43±0.06	0.556
AEF (%)	20.9±4.8	26.3±3.6	0.052
AEF/TEF	0.43±0.09	0.46±0.08	0.414

LEF: longitudinal ejection fraction, REF: radial ejection fraction, AEF: anteroposterior ejection fraction, TEF: total ejection fraction

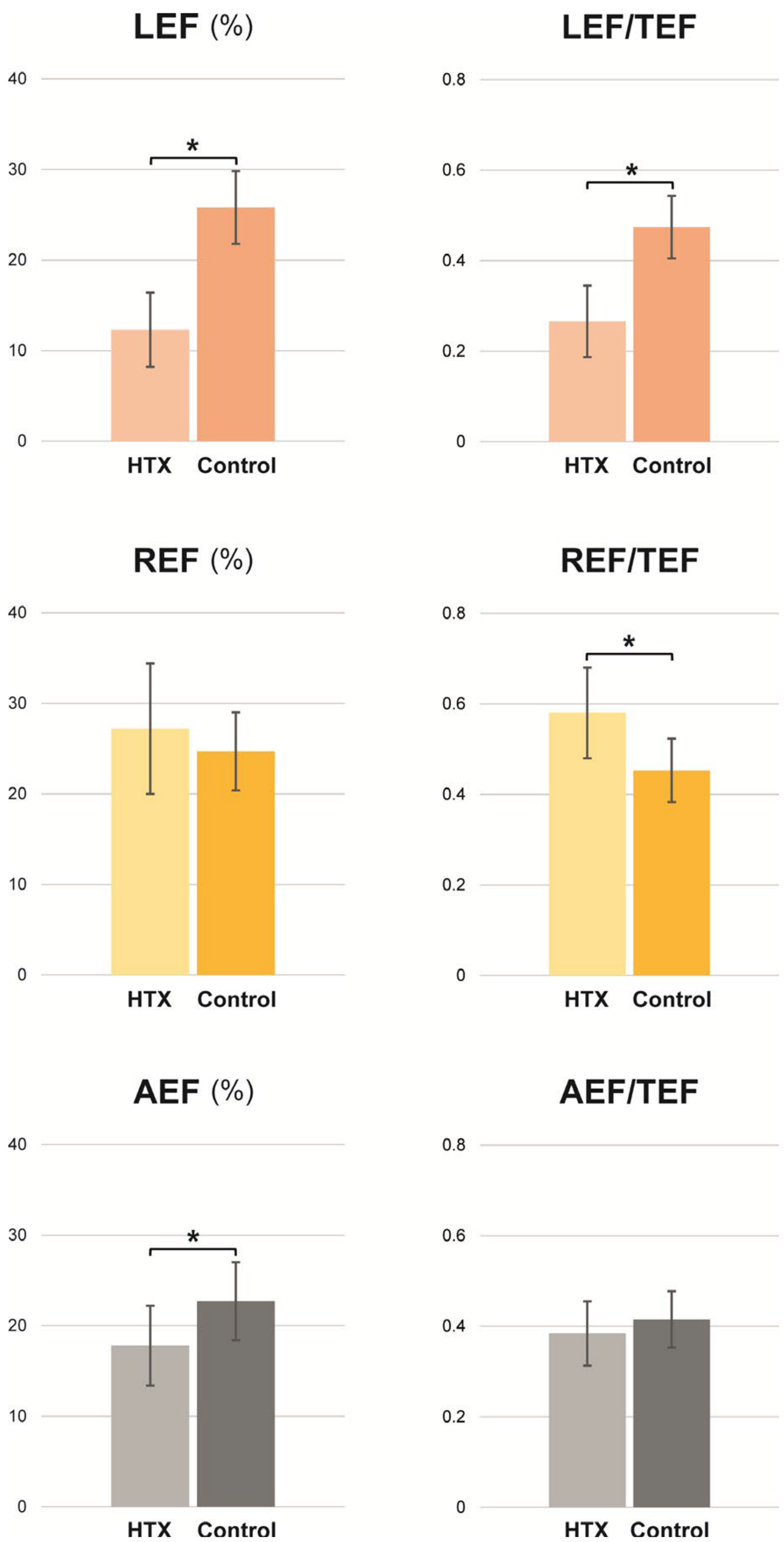
4.3 Determination of the RV mechanical pattern in pathological RV remodeling

LV end-diastolic-, end-systolic volumes, and stroke volume along with their BSA-indexed values showed no difference between the study groups. LV EF and GLS were also similar, excluding the presence of LV systolic dysfunction. There was a trend toward significancein terms of higher LVM in HTX patients.

In terms of conventional linear measurements, the RV mid diameter and length were similar, while its basal diameter was larger in the HTX patients. Measurements referring to longitudinal shortening were consequently lower than those obtained in the control group (TAPSE, s′ by tissue Doppler imaging, free wall and septal longitudinal strain). Nevertheless, FAC, which partly incorporates radial function as assessed on a 2D A4C view, was normal and similar between the HTX patients and healthy volunteers.

There was no significant difference in end-diastolic and end-systolic RV volumes. RV EF was lower in HTX patients. However, it remained within the lower limits of the normal range. Correspondingly, SV and the stroke volume index (SVi) were lower in HTX patients. There were only four patients with moderate tricuspid regurgitation in our HTX group (with severe regurgitation used an exclusion criterion). Pulmonary arterial systolic pressure was higher in the transplanted cohort than in the controls.

Figure 1 shows our results related to the relative contribution of longitudinal, radial, and anteroposterior wall motions to global RV function.



Longitudinal ejection fraction, LEF; radial ejection fraction, REF; anteroposterior ejection fraction, AEF; total right ventricular ejection fraction, TEF; transplant recipients (HTX). *$p < 0.05$

In line with conventional echocardiographic parameters, longitudinal EF and its ratio to TEF was significantly lower in HTX patients compared to healthy controls. However, REF/TEF ratio was significantly higher in HTX patients compared to controls. AEF value alone was lower in HTX patients, and its ratio to TEF was not significantly different from healthy volunteers. In HTX patients, REF/TEF was significantly higher compared to both LEF/TEF and AEF/ TEF (LEF/TEF vs REF/TEF vs AEF/TEF: 0.27± 0.08 vs 0.5±0.10 vs 0.38±0.07, ANOVA, $p<0.0001$), which confirmed the radial wall motion to be dominant determining global RV function after HTX (Figure 1). On the contrary, in healthy volunteers only AEF/TEF ratio was smaller than LEF/TEF, while REF/TEF and LEF/TEF were similar (LEF/TEF vs REF/TEF vs AEF/TEF: 0.47±0.07 vs 0.45±0.07 vs 0.41±0.06, ANOVA, $p=0.0034$). In HTX patients, RV TEF assessed by 3DE correlated with FAC ($r=0.762$, $p<0$ .0001), free wall LS ($r=0.394$, $p=0.018$) and septal LS ($r=0.430$, $p=0.032$); however, TAPSE did not. LEF correlated moderately ($r=0.421$, $p= 0.0023$), while REF strongly with TEF ($r=0.767$, $p<0.0001$) in HTX recipients. We found no association between the perioperative hemodynamic or procedural parameters and the RV functional measurements at follow-up. Similarly, no correlation was established between postoperative sildenafil usage and RV morphology and function. The time elapsed after HTX showed correlation with RV longitudinal function (time vs TAPSE: $r=0.577$, $p<0.0001$; vs free wall LS: $r=0.483$, $p=0.0003$; vs septal LS: $r=0.492$, $p=0.0002$; vs LEF/TEF, $r=0.289$, $p=0.0039$), on the other hand, it had a negative correlation with the dominance of radial contribution (REF/TEF: $r=-0.285$, $p=0.042$).

5. CONCLUSIONS

To the best of our knowledge, our study is the first to characterize female athlete's heart in IFBB BikiniFitness competitors. In our study, we demonstrated that a predominantly static exercise regime induces a mild, concentric-type hypertrophy, while waterpolo athletes exhibited higher ventricular volumes and developed eccentric LV hypertrophy. Fitness athletes presented LV and RV systolic and diastolic functions similar to those in sedentary volunteers. These findings support the applicability of Morganroth's classical hypothesis in the context of female athlete's heart.

Furthermore, kayak and canoe top-level male athletes showed significant LV and RV dilation. LVM was also significantly increased, resulting in concentric LVH. LV and RV function remained lower (EF and longitudinal strain) than that observed in healthy volunteers. Further studies are needed to obtain a deeper understanding of the morphological and functional changes that occur in exercise load, and 3DE can provide valuable assistance in these experiments.

We found that after HTX, the radial motion of the RV free wall compensates for decreased longitudinal shortening to maintain RV EF. Overtime, longitudinal function may recover. Additionally, 3DE may be a useful method in everyday clinical practice for accurately measuring global RV function. If 3D analysis is not available, a detailed 2D echocardiographic assessment is necessary to acquire such measurements, which also refer to the radial motion of the RV. Prospective studies are needed to better characterize the underlying causes of RV functional shifts and determine the potential predictive value of novel RV parameters.

6.1 Publications related to the present thesis

Doronina A, Édes I, Ujvari A, Kántor Z, Lakatos B, Tokodi M, Sydó N, Kiss O, Abramov A, Kovács A, Merkely B.
The female athlete's heart: comparison of cardiac changes induced by different types of exercise training using 3D echocardiography.
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Dominance of free wall radial motion in global right ventricular function of heart transplant recipients.
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