Kleinnibbelink, G, Panhuyzen-Goedkoop, N, Hulshof, HG, van Dijk, A, George, KP, Somauroo, J, Oxborough, D and Thijssen, DHJ

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Exercise Training Induces Left- but not Right-Sided Cardiac Remodelling in Olympic Rowers

Running title: Cardiac remodelling in Olympic rowers
ABSTRACT

Whilst the athlete’s heart has been extensively described, less work has focused on the potential for elite athletes to demonstrate further cardiac remodelling upon an increase in training volume. Moreover, little work explored potential side-specific cardiac remodelling. Therefore, we examined the impact of an increase in training volume across 9-months in elite rowers on left- and right-sided cardiac structure, function and mechanics (i.e. longitudinal, radial and circumferential strain, twist and strain-volume loops). As part of the preparations to the 2012 Olympic Games, twenty-seven elite rowers (26.4±3.7 years, 19 male) underwent echocardiography prior to and post (9-months) an increase in training volume (24 to 30-35h weekly). Training increased left ventricular LV structure, including wall thickness, diameter, volume, mass and LV twist (all p<0.05). Female rowers demonstrated larger adaptation in left ventricular diameter and mass compared to male rowers (both p<0.05). No changes were observed in other measures of left ventricular function in both sexes (all p>0.05). The 9-month intervention showed no change in right ventricular/atrial structure, function or mechanics (all p>0.05). In conclusion, our data revealed that 9-month increased training volume in elite rowers induced left-sided (but not right-sided) structural remodelling, concomitant with an increase in left ventricular twist, with some changes larger in women.

Keywords: athlete’s heart; right ventricle; cardiovascular disease; echocardiography; speckle tracking echocardiography
INTRODUCTION

Exercise training represents a potent stimulus for remodelling of the heart. Recent prospective and long-term intervention studies support the presence of predominant eccentric ventricular adaptation in response to exercise training [1, 2]. In other words, regular exercise training leads to a balanced increase in both volume and mass, whilst function seems largely preserved [1]. Previous work largely focused on either adaptation of the left side or adaptation of the right side of the heart in response to exercise training. As such, there is an important gap in the literature pertaining to the lack of knowledge whether exercise training differentially affects the left versus right ventricle in elite athletes.

Both ventricles receive a similar amount of blood. Due to their distinct geometry and mass, with the right ventricle (RV) being larger in volume but smaller in wall thickness than the left ventricle (LV), both ventricles may be exposed to distinct hemodynamic stimuli, potentially leading to different patterns of adaptation in both structure and function [3]. Indeed, exercise leads to distinctly different changes in afterload for both ventricles, with relatively larger increases in afterload for the RV [4]. This supports the potential for different adaptation between ventricles. Better insight into differences in remodelling between ventricles is highly relevant, especially since previous studies have linked exercise-induced RV cardiomyopathy to high volumes of exercise training in elite athletes [5, 6]. Insight into the potential presence of side-specific physiological remodelling of the heart will also contribute to improved interpretation of pre-participation screening for high-risk cardiovascular conditions associated with sudden cardiac arrest in athletes.

The aim of this study, therefore, was to examine the impact of an increase in volume (across 9-months) in elite rowers on left- and right-sided cardiac structure, function and mechanics (i.e. longitudinal, radial and circumferential strain, twist and strain-volume/area loops). Based on
the higher relative workload for the RV [4], we expect larger structural cardiac adaptation in
the RV (whilst preserving function) compared to the LV in elite rowers. Previous work suggested that sex may differentially affect cardiovascular function during
physiological stimuli [8, 9]. Based on cross-sectional comparisons, similar patterns of cardiac
remodelling have been observed with static and mixed exercise between men and women,
whilst greater LV adaptation may be present in women during dynamic exercise [7, 10].
Therefore, as an explorative aim, we evaluate the impact of sex on the impact of exercise in
elite rowers on left- and right-sided cardiac structure, function and mechanics

METHODS
Study population and study design
In this prospective, longitudinal study, as part of the work-up to the 2012 Olympic Games,
twenty-seven elite level rowers (male and female, all Caucasian) underwent baseline
echocardiography prior to and post (9-months) a planned increase in training volume. Baseline
echocardiograms were performed immediately after the 2011 World Rowing Championships
(i.e. when all athletes were in a highly trained status), and 3 months before the 2012 Olympic
Games. After the baseline echocardiograms, the rowers, both male and female, increased their
training volume gradually from 24 hours to 30-35 hours per week (20% strength, 80% rowing
training consisting of high-intensity interval and endurance training). Height and weight were
obtained before echocardiography was performed (SECA scale and stadiometer, SECA GmbH,
Hamburg, Germany). This study was conducted in accordance to with the ethical standards in
sport and exercise science research and approved by the ethics committee [11].
Echocardiographic measurements

The echocardiographic examinations were performed in the left lateral decubitus position by one highly experienced cardiologist (AvD) using a Vivid-Q ultrasound machine (GE Medical, Horton, Norway), equipped with a 1.5-4 MHz phased array transducer. Heart rate was calculated from a single lead ECG inherent to the ultrasound system. Images were stored in raw digital imaging and communication in medicine (DICOM) format and were exported to an offline workstation (EchoPac, version 113, GE Medical, Horton, Norway). Data-analysis, from three stored cycles, was performed by a single observer with experience in echocardiography (GK) using commercially available software (EchoPac, version 113, GE Medical, Horton, Norway). The echocardiograms were all coded so the observer was blinded for the timing (pre vs. post) and for sex (male vs. female).

Conventional measurements. Cardiac structural and functional measurements were made according to the current guidelines for cardiac chamber quantification [12]. Regarding the left heart, we examined the following structural and functional indices: wall thickness of the septum (IVSd) and posterior wall (PWd), internal cavity diameter at end-diastole (LVIDd), LV mass (LVM), anteroposterior diameter of the left atrium (LA), LA volume by the disk summations technique in apical 4-chamber (A4C) and apical 2-chamber (A2C) view, modified Simpson’s left ventricular ejection fraction (LVEF), tissue Doppler imaging (TDI) of the mitral annulus (s’, e’ and a’) and trans-mitral Doppler (E, A and E/A ratio). Regarding the right heart, following structural and functional indices were determined: basal and mid-cavity end-diastolic diameters, RV end-diastolic area (RVEDA), RV end-systolic area (RVESA), RV outflow tract (RVOT) diameter at the proximal level in the parasternal long-axis (PLAX) and parasternal short-axis (PSAX) view, right atrial (RA) area, RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), TDI of the tricuspid annulus. All LV and RV
structural indices were allometrically scaled to body surface area (BSA) according to the laws of geometric similarity [13].

Mechanics. Images were acquired specifically for speckle tracking. This involved the optimization of frame rates between 40 and 90 frames s\(^{-1}\), depth to ensure adequate imaging of the chamber of interest, a focal zone at mid-cavity to reduce the impact of beam divergence and gain, compression and reject to ensure endocardial delineation.

Ventricular and atrial mechanics. The A4C view was utilized for LV, LA and RA global longitudinal strain and the RV focused view for the RV longitudinal strain. The LV short-axis (SAX) views (basal, mid and apical) were utilized for radial, circumferential strain and twist. Valve closure times were determined from the respective pulsed wave Doppler signals.

For all compartments (LV, LA, RV, RA), the myocardium was manually traced and adjusted so that the region of interest (ROI) incorporated all of the wall thickness, while avoiding the pericardium. The region of interest was divided into six myocardial segments, providing segmental strain curves and a global longitudinal strain curve as an average of all six segments. In order to obtain peak LV circumferential strain, peak LV radial strain and peak apical and basal rotation, a full-thickness ROI of the mid-, basal- and apical-SAX views, which was divided into six segments, was selected. In addition, raw strain values were exported and a cubic spline was applied to normalize for heart rate. This allowed the presentation of temporal strain and rotation across the cardiac cycle.

Strain-volume/area loops. The longitudinal strain-volume/area relationship (for methodology of derivation, see Supplemental I and Oxborough et al. [14]) was assessed using the following parameters: (I) the linear strain-area slope (Sslope) and early strain-area slope during first 5% of volume ejection in systole (ESslope); (II) end-systolic peak longitudinal strain (peak strain); (III) the early linear strain-area slope during first 5% (EDslope) and late linear strain-area slope
(LDslope) during last 5% of volume increase in diastole; and (IV) diastolic uncoupling (i.e.
difference in strain between systole and diastole at any given area), divided into uncoupling
during early (Uncoupling ED) and late diastole (Uncoupling LD) [14, 15].

Statistical analysis

Statistical analyses were performed using SPSS Statistics 24 (SPSS, Inc., Chicago, Illinois).
All parameters were visually inspected for normality and tested with Shapiro-Wilk normality
tests. Continuous variables were reported as mean±SD and categorical variables were
presented as proportions. Paired-Samples T-tests were used to compare echocardiographic
continuous variables between the baseline and follow-up evaluation. Comparison of sex
differences was performed using repeated measurements ANOVA with Bonferroni post hoc
correction for multiple comparisons.

Consistency of intra-observer measurements of selected measurements were verified through
the intra-class correlation coefficient (ICC). Therefore, both echocardiographs of 15 randomly
chosen subjects were analysed by the same operator blinded from earlier results. ICC
coefficients were as follows: RVOT-PLAX 0.96 (0.91-0.98), LVISd 0.91 (0.81-0.96), LVPWd
0.90 (0.80-0.95), LVIDd 0.97 (0.93-0.98), RV basal diameter 0.98 (0.96-0.99), RVEDA 0.98
(0.95-0.99), RA area 0.99 (0.97-0.99), LA volume 0.98 (0.95-0.99). In previous studies, we
showed that strain measurements and both right and left ventricular loops have a good to
excellent inter-observer variability [14-17].

RESULTS

Baseline characteristics
All 27 rowers participated in the 2012 Olympic games. Mean age of the study population was 26.4±3.7 years, consisting of 19 males (70%, 26.3±4.3y) and eight females (30%, 26.6 ±1.9y).

All rowers were Caucasian. Male rowers were significantly taller (193.7±6.6 versus 181.5±8.8 cm, p=0.001), heavier (88.0±12.0 versus 72.9±8.6 kg, p=0.003) and had greater BSA (2.2±0.2 versus 1.9±0.2 m², p=0.002), but had a similar BMI (23.3±2.1 versus 22.2±1.0, p=0.08) compared to female rowers. Weight, body surface area (BSA) and body mass index (BMI) did not significantly change over time (83.9±13.0 to 84.3±13.0 kg, p=0.10; 2.1±0.2 to 2.1±0.2 m², p=0.10; 23.0±1.9 to 23.1±1.9 kg/m², p=0.11, respectively). Resting heart rate was higher at follow-up compared to baseline 54±7 to 58±8 bpm (p=0.02).

Exercise training and cardiac remodelling: comparison between sides

Left ventricle and atrium. There was a significant increase in LV wall thickness, diameter, volume and mass (all p<0.01), which remained significant after correction for BSA (all p<0.05) (Table 1, Figure 1). Similarly, there was a significant increase in LA diameter and volume (both p<0.01), which remained significant after correction for BSA (both p<0.01). Exercise training increased LV twist, whilst no other changes in functional or mechanical indices were found (Table 1, Figure 1-2).

Right ventricle and atrium. We found no significant changes in right ventricular and atrial structure, function and mechanics (Table 2, Figure 1-2).

Exercise training and cardiac remodelling: comparison between sexes

Baseline characteristics. At baseline, female rowers had smaller LV and RV cardiac dimensions compared to male rowers (all p<0.05, Table 1-2), which was not present after
correcting for BSA (all p>0.05). Absolute RVOT dimensions did not differ between sexes (Table 2). Female rowers had a smaller LV mass compared to male rowers (p<0.01), which remained significant after correction for BSA (p<0.05, Table 1). Except for a lower TAPSE and a higher E velocity in female rowers (both p=0.02), no significant differences were found in conventional measurements of left- or right-sided cardiac function (Table 1-2). Female rowers demonstrated significantly higher LV apical circumferential strain, lower peak systolic apical rotation (both p<0.05) and steeper slopes of the left- and right-sided strain-volume/area loop compared to male rowers (LV – Sslope, LDSlope, both p<0.05; RV – Sslope, Eslope, LDSlope, all p<0.05) (Table 1-2, Figure 2).

Training-induced remodelling. Females demonstrated a significantly larger increase in absolute and scaled LV diameter and LV mass compared with male rowers (Table 1, Figure 3). No differences were found between sexes in the right ventricle or atrium (Table 2).

DISCUSSION

The aim of our study was to examine the impact of an increase in volume (across 9-months) in elite rowers on left- and right-sided cardiac structure, function and mechanics. We present the following findings. First, an increased training volume in elite rowers across 9-months resulted in significant structural adaptation of the left ventricle and atrium, with no adaptations observed on the right side. Second, left-sided structural cardiac adaptation was accompanied by an increase in LV twist, but no other left- or right-sided functional adaptations. This highlights the plasticity of the heart for remodelling in response to exercise training, even in elite athletes. Taken together, our results demonstrate cardiac side-, and possibly also sex-specific adaptation, which is relevant for future studies that should acknowledge that cardiac remodelling does not simply follow the same path between and within individuals.
After an increase in training volume across 9-months, the left heart of this cohort of elite rowers showed mild structural (eccentric) adaptation with an increased LV twist, whilst there was no significant remodelling in the right heart. This left-sided structural adaptation is in line with several previous longitudinal training studies including sedentary, moderately- and highly-trained individuals [2, 18-21]. Interestingly, concomitant to left-sided structural adaptation, elite rowers also demonstrated augmented LV twist after the increase in training volume. The higher heart rate post-training may partially explain the increase in twist. However, this seems unlikely since no correlation was found between heart rate and twist (r=0.02, p=0.94). Moreover, other functional parameters (also susceptible for differences in heart rate) did not change over time. Although we found adaptation in functional and structural characteristics, both may demonstrate a distinct pattern and are not similarly present. Indeed, the increase in twist was not correlated with changes in LV cardiac morphology (data not shown). Moreover, Weiner et al. observed that exercise training may initially (i.e. 90 days) lead to increases in LV twist, which subsequently disappeared during the chronic training phase (i.e. 39 months) [22]. Our finding provides some support for this concept, in that an increase in volume of exercise initially resulted in both functional and structural adaptations, where functional changes may ultimately normalize during the chronic phase when volume of exercise remains the same. Future work is required to better understand these time-dependent adaptations in cardiac remodelling.

Despite the disproportionate load on the right versus left ventricle during exercise [4], we found no adaptation of the right ventricle or atrium. This finding contrasts with our hypothesis, but also with others who addressed right-sided cardiac remodelling in elite athletes [23, 24].
D’Ascenzi et al. reported seasonal variation in RV size in a cohort of top-level basketball and volleyball players [23]. Across three consecutive Olympic Games, Aengevaeren et al. noted that RV remodelling occurred between the first two Olympics Games, followed by a plateau during the subsequent 4 years in a heterogeneous group of athletes (n=50, 17 different sports) [24]. These studies, however, are limited by the impact of ageing (i.e. 8-year cycle), large variations in training status across the season, and/or the heterogeneous group of athletes included. The lack of RV remodelling in our study may be explained by achieving a physiological limit for further adaptation prior to the start of the increase in training volume in highly trained rowers due to pericardial constraint. At least, our observations support the presence of distinct remodelling between the left and right side of the athlete’s heart. Future work is required to better understand these differences, specifically focusing on the distinct load placed on both ventricles during exercise, possibly underlying distinct remodelling to (high) volumes of exercise training.

Following the explorative analysis, this study examined the impact of sex on cardiac adaptation to training using a longitudinal design. This design markedly differs from most previous studies that have adopted a cross-sectional design, including a heterogeneous groups of athletes, and generally not using allometric scaling [10, 25-29]. Our data showed larger LV structural adaptation in female rowers, which remained present upon allometric scaling. These distinct adaptations cannot relate to differences in lifetime exposure to elite athlete level training, since both groups do not differ in age (males 26.3±4.3y versus females 26.6±1.9y, p=0.84). Alternative explanations for the distinct remodelling might be hormonal, molecular and/or genetic mechanisms. However, these mechanisms are not fully understood yet and represent topics for future research [7]. Another explanation is the potential for differences in the (absolute and relative) workload of the exercise training between men and women.
Unfortunately, data were not available to compare exercise intensity and workload between groups or individuals. An important limitation is the relatively low sample size for female rowers within this analysis. Nonetheless, our study was sufficiently powered to detect a significant effect between sexes in adaptation. We performed post hoc calculations and found that our study has a statistical power of 0.51-0.64 to detect sex differences in LV mass and LV diameter. At least, our findings highlight the importance for future research to better understand and establish potential sex differences in cardiac adaptation in response to exercise training.

Clinical relevance. The observation of no further adjustment in RV remodelling seems relevant as RV enlargement may overlap with the pathological dilation of the RV in patients with an arrhythmogenic RV cardiomyopathy. Previous studies have related RV remodelling in the already highly trained athlete to potential clinical problems. Our work suggests that even high volumes of exercise does not automatically lead to further remodelling of the RV, despite structural changes in the LV. However, a potential limitation is that subjects followed an individually determined exercise training protocol to increase training volume, which makes it difficult to relate cardiac remodelling to specific determinants of the exercise training protocol and at a cohort level. However, all individuals significantly increased their training volume, highlighting that additional cardiac remodelling is possible upon increases in training volume. Our study may have further clinical relevance, since we specifically explored remodelling in female elite athletes. Participation of females in elite sports has increased significantly over the past decades. Current work on the athlete’s heart, leading to insight into (ab)normal levels of adaptation, largely originate from studies performed in males. Our work supports performing specific studies in women, examining the geometry and potential pathological relevance of the female athlete’s heart.
In conclusion, our data suggest that an increased exercise training volume in elite rowers across 9-months induced side-specific cardiac remodelling. Specifically, we found left-sided (but not right-sided) structural adaptations, with concomitant increase in LV twist in already highly trained rowers. Interestingly, these adaptations were significantly larger in women compared to men, a finding that warrants further exploration in future work. Taken together, our work suggests that examining the athlete’s heart should go beyond the single-sided approach most previous studies adopted, and should explore both left and right-sided adaptation.

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CONFLICT OF INTEREST/DISCLOSURES
The authors have no relationships or conflicts to disclose.
REFERENCES


TABLES LEGENDS

Table 1 – Left heart structural, functional and mechanical echocardiographic parameters observed in male and female elite rowers prior to and post a 9-month increase in training volume

Table 2 – Right heart structural, functional and mechanical echocardiographic parameters observed in male and female elite rowers prior to and post a 9-month increase in training volume
FIGURES LEGENDS

**Figure 1 – Structural and functional cardiac remodelling after 9-months training**

volume increase

Figure 1: Change in right (A-C-E) and left (B-D-F) sided cardiac structure and function in elite rowers (n=27) before (‘Pre’: black bars) and after (‘Post’: grey bars) a 9-month training period. Error bars represent SD. * significantly different from pre (p<0.05).

**Figure 2 – Strain-Area/Volume loops**

Figure 2A: Left and right ventricular strain-volume/area loop in elite rowers before (‘Pre Systolic’: black lines, ‘Pre Diastolic’: black dotted lines) and after (‘Post Systolic’: red lines, ‘Post Diastolic’: red dotted lines) a 9-month training period. 2B: Strain-volume/area loops distributed to sex.

**Figure 3 – Cardiac remodelling distributed to sex**

Figure 3: Change in (A) LV mass index and (B) LV diameter index in elite rowers before (‘Pre’: black bars) and after (‘Post’: grey bars) a 9-month training period distributed to sex. Error bars represent SD.