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Published in:
Scandinavian Cardiovascular Journal

DOI:
[10.3109/14017431.2013.860234](https://doi.org/10.3109/14017431.2013.860234)

2014

[Link to publication](#)

Citation for published version (APA):
Mosén, H., & Steding Ehrenborg, K. (2014). Atrial remodelling is less pronounced in female endurance-trained athletes compared with that in male athletes. *Scandinavian Cardiovascular Journal*, 48(1), 20-26.
<https://doi.org/10.3109/14017431.2013.860234>

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**Atrial remodeling is less pronounced in female endurance trained athletes
compared to male athletes**

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Running head: Atrial volumes in female and male athletes

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ABSTRACT (200 words)

Objectives: Little data exists on atrial adaptation to training in women. Furthermore, data on right atrial (RA) volumes is lacking for both male and female athletes. The objective of this study was therefore to investigate atrial volumes in male and female athletes.

Design: 75 athletes (33 women) and 53 controls (21 women) underwent cardiovascular magnetic resonance imaging. Left atrial (LA) and RA volumes were measured by manual delineation. The atrial appendage was included in the volumes, and pulmonary veins were excluded.

Results: Atrial volumes were larger in athletes compared to controls (males LA 116±19ml versus 93±19ml, RA 166±32ml versus 133±23ml, $p<0.0001$, females LA 90±15ml versus 83±17ml, $p<0.05$, RA 119±24ml versus 108±18ml, $p=0.07$). When normalized for body surface area, atrial volumes remained larger in athletes. However, when normalized for total heart volume (THV) there were no differences between groups except for LA volumes in females where controls had higher LA/THV compared to athletes ($p<0.05$).

Conclusion: Atrial volumes were significantly larger in athletes. Atrial volumes normalized for THV did not differ between athletes and controls indicating a balanced enlargement. There was only a small difference between female controls and female athletes, suggesting that atrial adjustment to training is more modest in women.

Keywords; atrium, physiology, heart, total heart volume

BACKGROUND

Several studies of left and right ventricular volumes in athletes have shown physiological adaptation to training that differs from the pathological remodeling found in diseases such as hypertrophic and dilated cardiomyopathies (1-5). Furthermore, total heart volume (THV) has been shown to increase with long term endurance training, and there is a strong correlation between THV and peak oxygen uptake (VO_2peak) (4). Few studies have investigated the effects on atrial volumes. Using echocardiography and cardiac magnetic resonance imaging (CMR), recent studies have shown increased atrial dimensions and volumes in endurance athletes (6-8). However, studies of atrial adaptation to training in women are scarce and data on the effects on right atrial volumes in both men and women is lacking.

Cut off values for normal atrial remodeling are often presented normalized for body surface area (BSA) (8-12). This form of scaling may be useful in a normal population where atrial volumes vary with BSA (11). However, in an athletic population the atrial volumes are also increased due to training and therefore all volumes normalized for BSA will be higher and often above the limits of normal remodeling (6). We therefore suggest normalizing for THV which takes both BSA and fitness into consideration. This index will give information whether the remodeling is physiologically balanced and may become helpful in differentiation between physiological and pathological remodeling.

Therefore the aim of this paper was to study left and right atrial volumes in healthy male and female elite athletes and healthy control subjects in order to determine a normal range for absolute left and right atrial volumes as well as atrial volumes normalized for THV.

METHODS

This study follows the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Lund, Sweden. All participants provided written informed consent.

Seventy-five athletes; 21 soccer players (9 women), 17 triathletes (6 women), 14 handball players (7 women), 23 swimmers (11 women) and 53 healthy controls (21 women), matched for age and gender, underwent cardiac magnetic resonance imaging (CMR). All athletes were training and competing at national or international level. None of the participants had a history of cardiovascular disease. All test subjects were non-smokers, presented with normal ECG and blood pressure. None of the included subjects used any medications with known cardiovascular effects.

Training intensity and frequency for triathletes, swimmers and healthy controls information was obtained from each individual using standardized protocols. For soccer players and handball players it was obtained from the responsible coach. All athletes were training and competing at the highest national level within their discipline. Male and female triathletes trained endurance on average 11 and 15 hours/week respectively. Both male and female swimmers trained 12 hours/week, male soccer players trained 5-6 hours/week and female soccer players 4-6 hours/week. Male handball players trained endurance on average 3-5 hours/week and female handball players 2-3 hours/week. Furthermore, the sport specific training within each group likely also contributed to their cardiovascular fitness.

Male and female controls were recreationally active approximately two hours/week, *i.e.* not completely sedentary but they spent the major part of their days sitting down.

Both healthy controls and athletes were asked not to participate in any vigorous exercise 48 hours prior to the CMR examination, avoid heavy meals one hour before and not drink coffee, tea or eat chocolate two hours before the examination.

Cardiac Magnetic Resonance Imaging (CMR)

A 1.5-T scanner (Philips Intera CV, Philips, Best, The Netherlands) with a 5-channel cardiac synergy coil was used to scan all subjects in supine position. Images of the heart were acquired using a steady-state free-precession sequence with retrospective ECG triggering (repetition time 2.8 ms, echo time 1.4 ms, flip angle 60°, spatial resolution of 1.4x1.4, temporal resolution typically 30 ms and slice thickness 8 mm with no slice gap). After defining the long axis orientation of the heart, short axis images covering the entire heart from the base of the atria to the apex of the ventricles were obtained.

Volumetric measurements

All volumetric measurements were performed using the software Segment (Segment 1.9; <http://segment.heiberg.se>) (13).

Left atrial (LA) and right atrial (RA) volumes as well as total heart volume (THV) were measured in short axis images using planimetry. The LA and RA volumes were defined as the atrial volume just before the start of the diastolic filling of the ventricles. The endocardial border of the atrium was manually defined. Special care was taken not to include the pulmonary veins. When parts of both the atrium and the ventricle were seen in the same slice, the atrial volume was defined as the volume without muscular myocardium (Figure 1). The atrial appendage was included in the atrial volume. Total heart volume was measured using the same methodology previously described by Carlsson et al. (14).

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (IBM, Chicago, IL, USA) and Graph Pad Prism 5.04 (Graph Pad Software, Inc, La Jolla, CA, USA). The Shapiro-Wilk test was used to test for normal distribution. The Mann-Whitney non-parametric test and Kruskal-Wallis non-parametric test with Dunn's post hoc test were used to compare variables between groups as appropriate. Linear regression analysis was used to assess relationships between variables. Values are presented as mean \pm standard deviation and a p-value of <0.05 was considered statistically significant.

RESULTS

Subject characteristics

Subject characteristics are seen in Table 1. All athletes and 37 of 53 control subjects underwent maximal exercise testing and results are presented in Table 2. There were no significant differences in resting HR between groups.

Left and right atrial volumes

Absolute atrial volumes and volumes normalized for BSA and for THV are presented group wise in Table 2.

For men, absolute left and right atrial volumes were larger in athletes compared to controls (LA 116 ± 19 ml for athletes and 93 ± 19 ml for controls, RA 166 ± 32 ml for athletes and 133 ± 23 ml for controls, $p<0.0001$ for both). The differences remained when atrial volumes were normalized for body surface area (LA/BSA 56 ± 8 ml/m² for athletes, 47 ± 8 ml/m² for controls, $p<0.001$ and RA/BSA 81 ± 15 ml/m² for athletes and 67 ± 12 ml/m² for controls, $p<0.001$) (Figure 2A and B). However, when normalized for THV, neither LA/THV nor RA/THV differed between groups (LA/THV 0.11 ± 0.01 for both groups, $p=0.75$, RA/THV 0.15 ± 0.02 for both groups, $p=1.0$) (Figure 2C and D).

For women, LA volume was larger in athletes compared to controls (90 ± 15 ml versus 83 ± 17 ml, $p<0.05$) whereas RA volume did not differ (119 ± 24 ml and 108 ± 18 ml for athletes and controls respectively, $p=0.07$). When normalized for BSA, both LA/BSA and RA/BSA was larger in athletes (LA/BSA 51 ± 7 ml/m² for athletes and 46 ± 8 ml/m² for controls, $p<0.01$, RA/BSA 68 ± 13 ml/m² for athletes and 61 ± 9 ml/m² for controls, $p<0.05$) (Figure 2A and B). Conversely, when normalized for THV, both LA and RA were slightly, but significantly, larger in controls compared to athletes (LA/THV 0.11 ± 0.01 for athletes and

0.12±0.02 for controls, $p<0.05$, RA/THV 0.15±0.02 for athletes and 0.16±0.02 for controls, $p=0.08$) (Figure 2C and D).

Gender aspects

Atrial volumes for men and women are presented in Table 2. Left and right atrial volumes in the control group were larger in men compared to women ($p<0.05$ for LA and $p<0.001$ for RA). When normalized for BSA there were no differences between sexes (LA/BSA $p=0.56$, RA/BSA $p=0.07$). However, women had significantly larger LA/THV compared to men ($p<0.01$) whilst RA/THV did not differ ($p=0.16$). For the athletes, men had larger left and right atrial volumes ($p<0.001$ for both) and the difference remained when normalized for BSA (LA/BSA $p<0.01$, RA/BSA $p<0.0001$). When normalized for THV, there were no differences between men and women (LA/THV $p=0.06$, RA/THV $p=0.5$).

Atrial volumes in relation to heart rate, peak oxygen uptake, total heart volume and body size

There was a weak negative correlation between left and right atrial volumes and HR (LA $R^2=0.1$, $p<0.001$, RA $R^2=0.11$, $p<0.001$) and a positive correlation with VO_{2peak} ($ml\ min^{-1}$) (LA $R^2=0.38$, $p<0.0001$, RA $R^2=0.42$, $p<0.0001$) (Figure 3A and B). Left and right atrial volumes showed a strong positive correlation to THV (LA $R^2=0.67$, $p<0.0001$, RA $R^2=0.71$, $p<0.0001$) (Figure 4A and B) and correlations were also seen between atrial volumes and BSA (LA $R^2=0.42$, $p<0.0001$, RA $R^2=0.36$, $p<0.0001$) (Figure 4C and D).

DISCUSSION

This study presents normal left and right atrial volumes for male and female athletes active in a variety of sports as well as normal values for healthy controls. We also present the atrial

volumes normalized for total heart volume (THV). Using THV for normalization has previously been shown to be a powerful tool when discriminating between heart failure patients, athletes and healthy controls (1) and may also prove useful when assessing atrial volumes.

In line with previous studies, athletes have larger left atrial volumes compared to gender matched controls (6-8). Furthermore, this study shows that right atrial volumes increase with increasing fitness. When normalized for total heart volume, LA/THV and RA/THV in males did not differ between groups indicating a balanced enlargement of the atria. However, in females, LA/THV and RA/THV were higher in female controls which may suggest a gender difference in atrial adaptation to training.

Left and right atrial volumes have in previous studies been measured using either echocardiography (7, 9, 10, 15, 16) or CMR (8, 11, 12, 15, 17). Atrial volumes for the control subjects in the present study are comparable to the normal values for steady state free precession CMR presented by Hudsmith et al. (17) and Maceira et al. (11, 12). Furthermore, left atrial volumes in the male triathletes were comparable to the volumes shown by Scharf et al. (8) in a study of 26 male triathletes, supporting the accuracy of our measurements. The results of the present study contribute to the knowledge gained from previous studies by adding reference values for women as well as adding the effects of swimming, soccer and handball to the previously presented studies on male triathletes (8) and long-distance runners (7).

Scaling to body surface area vs total heart volume

Cardiovascular structures increase in size with increased body size (18) and thus total heart volume is increased with increased BSA. However, THV is further increased with increased

level of fitness (4). When scaling for BSA, atrial volumes remained higher in athletes compared to controls. In this athletic population, atrial volumes normalized for BSA in men were all higher than suggested cut off values for normal LA volume indices suggested by Scharf et al. ($>55\text{ml/m}^2$) (8) and a study of normal subjects by Maceira et al. (53ml/m^2) (11).

When normalizing for THV the atrial remodeling seen in athletes is shown to be part of a balanced physiological enlargement. We believe that scaling to THV is a better method for assessing physiological versus pathological enlargement of cardiac chambers than the commonly used BSA since it takes both body size and fitness into consideration. By scaling to THV the risk of interpreting the physiologically enlarged atria or ventricle as pathological is decreased. However, when assessing risk of atrial fibrillation, increased absolute LA volumes have been shown to be a risk factor and this risk likely remains although the atrial enlargement is balanced.

Gender differences

In line with previous studies (11, 12, 17) men had larger atrial volumes compared to women. Interestingly, female athletes did not increase their atrial volumes in the same order of magnitude as they increased their ventricular volumes, causing a decreased ratio for LA/THV and RA/THV compared to female controls. This difference in atrial size between men and women is in line with a large study by Pelliccia et al. (19) including 738 male athletes and 600 female athletes where women displayed left ventricular dimensions 11% smaller than in men, and left atrial dimensions 14% smaller. Increased LA size has been studied in both cross sectional (8-10) and longitudinal studies (16) and has been shown to correlate to an increased risk of atrial fibrillation. As the prevalence of atrial fibrillation has been shown to be higher in men compared to women (20), it is possible that the differences in atrial adjustment to

training hold a part of the explanation. The smaller absolute volumes in women may protect against atrial fibrillation by decreasing the risk of fibrosis formation in the atria.

Atrial volumes and age

The study population in the present study represented a wide range of ages where swimmers were amongst the youngest (mean age 18 years for women and 20 for men) and triathletes were approximately 13 years older (mean age 31 years for women and 33 for men). There were only small differences in LA and RA volumes between men whereas the differences between women were larger. However, this is likely explained by the higher training load in female triathletes. This is supported by the reference values for LA and RA volumes presented by Maceira et al. (11, 12) showing there are no differences in atrial dimensions between the age groups 20-29 and 30-39.

Limitations

The healthy controls included in the study were recruited by advertisement and it is possible that subjects responding to participate in cardiac examinations with exercise testing are more fit than the general population. Therefore, differences between athletes and controls may be even larger than shown in the present study. Furthermore, history of endurance training only covered the past six months and lifetime training hours for the athletes were not investigated in the study.

The study populations in this study were limited in number and the difference in atrial size between controls and athletes was very small. Future studies would gain from using larger and more homogenous study populations.

Conclusions

This study presents left and right atrial volumes for male and female elite athletes and control subjects. When normalized for total heart volume, LA/THV and RA/THV did not differ between athletes and controls indicating a balanced enlargement of the atria following long-term training. Interestingly, there was only a small difference between female controls and female athletes, suggesting that the atrial remodeling due to long term endurance training is more modest in females.

Acknowledgements

The authors wish to thank Cajsa Skarin for assistance in data analysis. This study was funded by World Village of Women Sports, Malmö, Sweden, the Swedish Research Council, the Swedish Heart and Lung Foundation, the Medical Faculty at Lund University, Sweden and the Region of Scania, Sweden. The authors have no conflicts of interest to disclose.

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Tables

Table 1. Subject characteristics (mean \pm SD)

	Group	N	Age (years)	Height (m)	Weight (kg)	BSA (m ²)	Resting HR (bpm)	Resting SBP (mmHg)	Resting DBP (mmHg)	VO ₂ peak (ml min ⁻¹ kg ⁻¹)
<i>Men</i>	Control	32	27 \pm 7	1.82 \pm 0.06	78 \pm 9	1.98 \pm 0.13	62 \pm 9	129 \pm 9	73 \pm 6	46 \pm 6
	Triathlon	11	33 \pm 9	1.85 \pm 0.05	82 \pm 6	2.05 \pm 0.10	56 \pm 8	135 \pm 8	74 \pm 7	58 \pm 5
	Swimming	12	20 \pm 3	1.89 \pm 0.09	83 \pm 11	2.08 \pm 0.18	54 \pm 9	126 \pm 13	68 \pm 7	53 \pm 11
	Soccer	12	25 \pm 4	1.84 \pm 0.06	79 \pm 6	2.01 \pm 0.10	58 \pm 5	133 \pm 5	75 \pm 9	52 \pm 5
	Handball	7	23 \pm 3	1.84 \pm 0.03	86 \pm 6	2.10 \pm 0.07	57 \pm 8	126 \pm 7	70 \pm 9	53 \pm 5
<i>Women</i>	Control	21	25 \pm 5	1.71 \pm 0.07	67 \pm 10	1.78 \pm 0.14	63 \pm 13	119 \pm 8	68 \pm 10	36 \pm 8
	Triathlon	6	31 \pm 5	1.70 \pm 0.05	62 \pm 5	1.71 \pm 0.09	51 \pm 7	121 \pm 9	71 \pm 9	58 \pm 5
	Swimming	11	18 \pm 2	1.69 \pm 0.06	63 \pm 5	1.73 \pm 0.10	62 \pm 9	120 \pm 12	70 \pm 7	46 \pm 6
	Soccer	9	24 \pm 4	1.71 \pm 0.06	65 \pm 7	1.76 \pm 0.12	58 \pm 9	119 \pm 7	72 \pm 7	47 \pm 5
	Handball	7	22 \pm 2	1.71 \pm 0.03	67 \pm 6	1.79 \pm 0.09	59 \pm 11	117 \pm 4	74 \pm 5	46 \pm 4

bpm=beats per minute, DBP = diastolic blood pressure, HR = heart rate, kg=kilogram, m=metre,
mmHg=millimetres of mercury, min = minute, ml = millilitres, SBP = systolic blood pressure

Table 2. Absolute left and right atrial volumes and atrial volumes normalized for body surface area and total heart volume presented as mean \pm SD (range).

	<i>Control</i>	<i>Triathlon</i>	<i>Swimming</i>	<i>Soccer</i>	<i>Handball</i>
<i>Males</i>	n=32	n=11	n=12	n=12	n=7
LA volume (ml)	94 \pm 19 (54-141)	121 \pm 20 (94-172)	115 \pm 24 (84-164)	111 \pm 17 (86-140)	120 \pm 14 (106-151)
LA/BSA (ml/m ²)	47 \pm 8 (30-66)	59 \pm 10 (52-88)	55 \pm 8 (45-75)	55 \pm 8 (44-68)	57 \pm 5 (50-68)
LA/THV	0.11 \pm 0.01 (0.08-0.14)	0.11 \pm 0.01 (0.10-0.13)	0.10 \pm 0.01 (0.09-0.13)	0.11 \pm 0.01 (0.08-0.12)	0.11 \pm 0.01 (0.10-0.12)
RA volume (ml)	133 \pm 23 (98-189)	174 \pm 46 (106-269)	169 \pm 31 (124-210)	161 \pm 22 (125-192)	159 \pm 27 (126-208)
RA/BSA (ml/m ²)	67 \pm 12 (51-90)	85 \pm 23 (51-137)	81 \pm 11 (67-95)	80 \pm 10 (63-95)	76 \pm 11 (60-93)
RA/THV	0.15 \pm 0.02 (0.12-0.19)	0.16 \pm 0.03 (0.12-0.19)	0.15 \pm 0.02 (0.12-0.18)	0.15 \pm 0.02 (0.12-0.17)	0.15 \pm 0.02 (0.12-0.17)
<i>Females</i>	n=21	n=6	n=11	n=9	n=7
LA volume (ml)	83 \pm 17 (60-126)	103 \pm 19 (78-131)	84 \pm 8 (70-93)	87 \pm 19 (55-119)	93 \pm 8 (82-106)
LA/BSA (ml/m ²)	46 \pm 8 (32-68)	60 \pm 8 (47-70)	49 \pm 4 (42-54)	49 \pm 8 (36-61)	52 \pm 3 (47-58)
LA/THV	0.12 \pm 0.02 (0.09-0.15)	0.12 \pm 0.01 (0.10-0.13)	0.11 \pm 0.01 (0.08-0.13)	0.11 \pm 0.01 (0.09-0.13)	0.12 \pm 0.01 (0.11-0.13)
RA volume (ml)	108 \pm 18 (72-137)	134 \pm 25 (96-162)	116 \pm 22 (72-151)	115 \pm 28 (71-146)	116 \pm 20 (89-151)
RA/BSA (ml/m ²)	61 \pm 9 (44-73)	79 \pm 15 (58-101)	67 \pm 12 (43-86)	65 \pm 15 (42-88)	65 \pm 9 (55-83)
RA/THV	0.16 \pm 0.02 (0.13-0.19)	0.16 \pm 0.02 (0.12-0.19)	0.15 \pm 0.02 (0.10-0.19)	0.14 \pm 0.02 (0.11-0.17)	0.15 \pm 0.02 (0.13-0.17)

BSA=body surface area, LA=left atrium, m=meter, ml=millilitre, RA=right atrium, THV=total heart volume

Figure legends

Figure 1. Example of manual delineation of atrial endocardial borders in the left atrium (Panel A) and the right atrium (Panel B). Basal parts of the atria are shown in the top left image in each panel and the level of the atrio-ventricular plane is shown at the bottom right. When parts of both the atrium and the ventricle were seen in the same slice, the atrial volume was defined as the volume without muscular myocardium. *Ao = aorta, LA = left atrium, Pulm = pulmonary artery, RA = right atrium*

Figure 2. Atrial volumes normalized for body surface area (BSA) and total heart volume (THV) in male and female controls and athletes. Atrial volumes normalized for BSA were significantly larger in athletes compared to gender matched controls. However, when normalized for THV, there were no differences between groups except for left atrial volumes in females where the control group had a higher LA/THV compared to controls. Error bars denotes standard error of the mean (SEM).

Figure 3. Correlation between atrial volumes and peak oxygen uptake (VO_{2peak}). The athletes with the largest atrial volumes also had the highest VO_{2peak} values.

Figure 4. Panel A and B shows the correlation between total heart volume and atrial volumes. Panel C and D shows the correlation between body surface area and atrial volumes. There was a close relationship between atrial volumes and total heart volume whereas the variation in atrial volumes for a given body surface area was larger. This was expected as both total heart volume and atrial volumes are affected by body size and physical fitness, whereas body surface area can be the same whether you are trained or untrained.

Figures

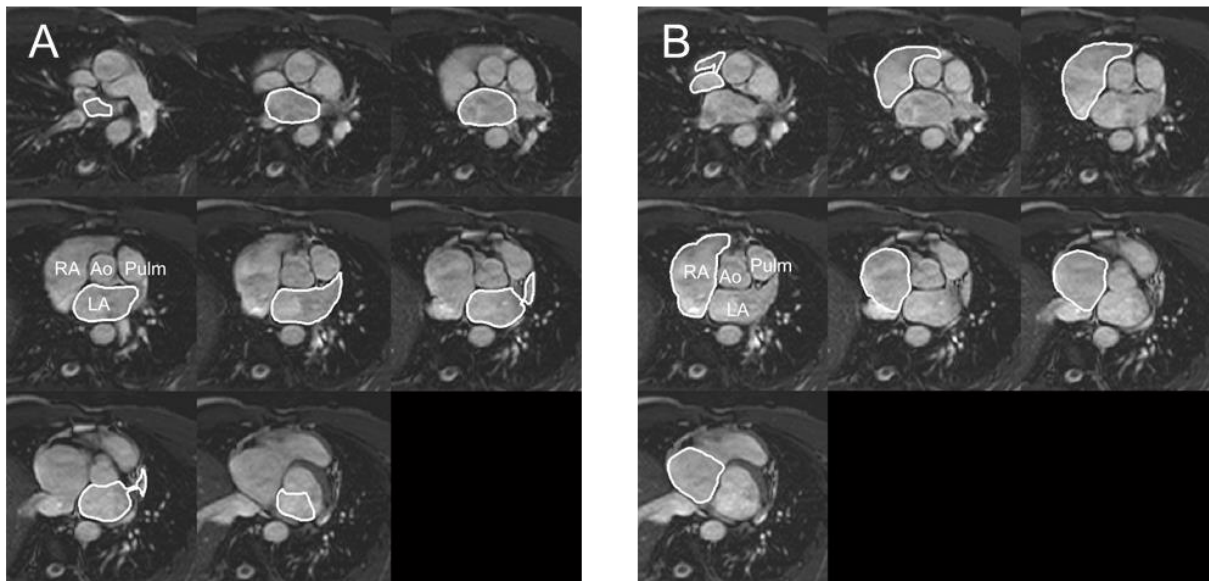


Figure 1.

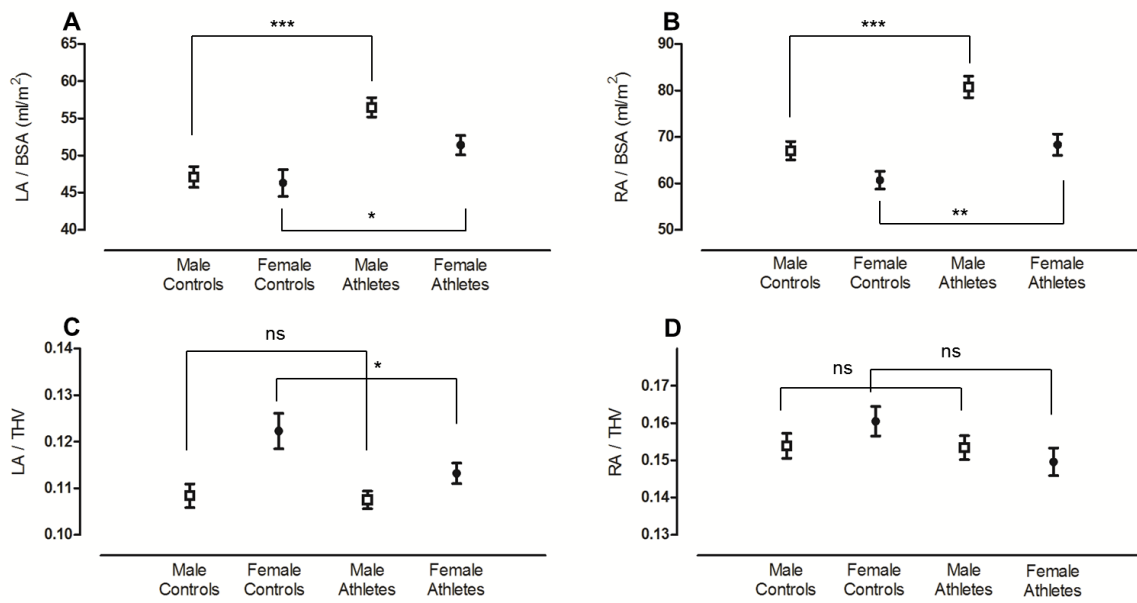


Figure 2.

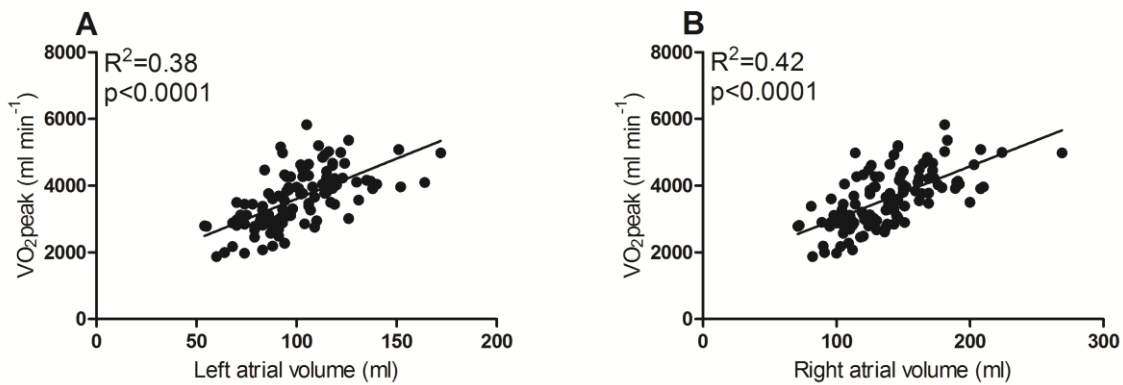


Figure 3.

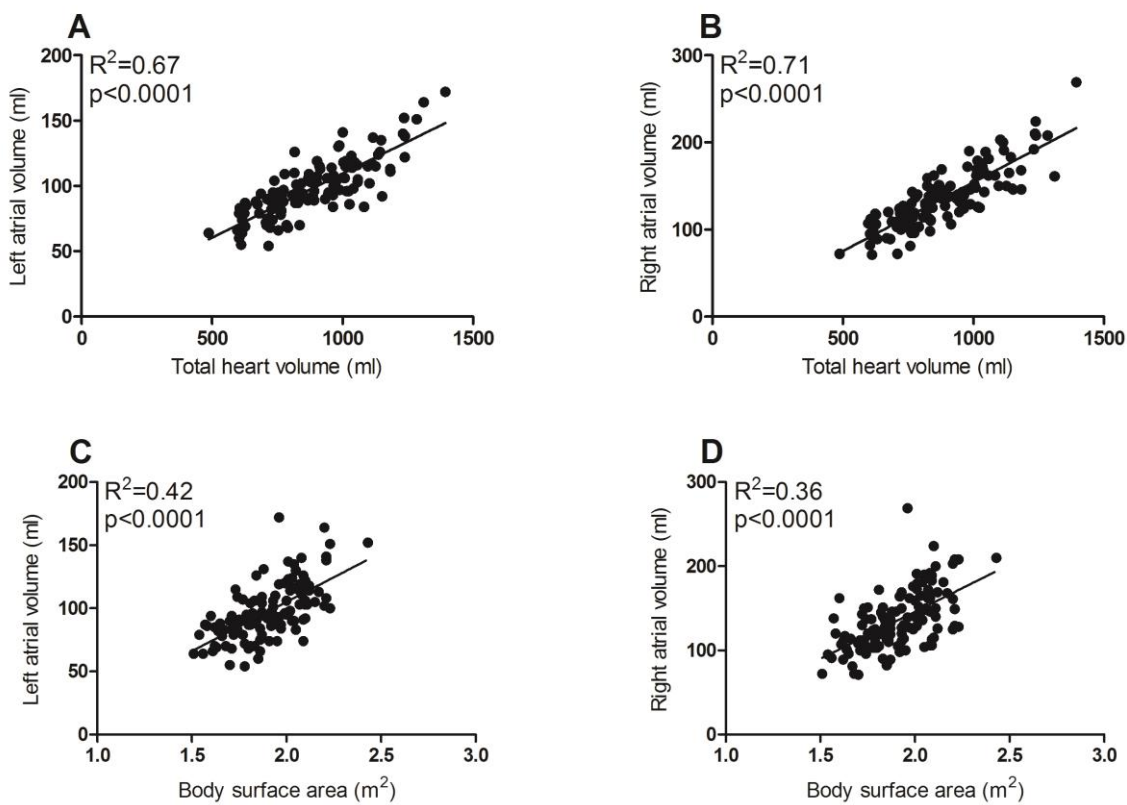


Figure 4.