Cardiac systolic regional function and synchrony in endurance trained and untrained females

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Cardiac systolic regional function and synchrony in endurance trained and untrained females

Kristofer Hedman,1 Éva Tamás,2 Niclas Bjarnegård,3 Lars Brudin,4 Eva Nylander1

ABSTRACT

Background: Most studies on cardiac function in athletes describe overall heart function in predominately male participants. We aimed to compare segmental, regional and overall myocardial function and synchrony in female endurance athletes (ATH) and in age-matched sedentary females (CON).

Methods: In 46 ATH and 48 CON, echocardiography was used to measure peak longitudinal systolic strain and myocardial velocities in 12 left ventricular (LV) and 2 right ventricular (RV) segments. Regional and overall systolic function were calculated together with four indices of dysynchrony.

Results: There were no differences in regional or overall LV systolic function between groups, or in any of the four dysynchrony indices. Peak systolic velocity (s') was higher in the RV of ATH than in CON (9.7±1.5 vs 8.7±1.5 cm/s, p=0.004), but not after indexing by cardiac length (p=0.331). Strain was similar in ATH and CON in 8 of 12 LV myocardial segments. In septum and anteroseptum, basal and mid-ventricular s' was 6–7% and 17–19% higher in ATH than in CON (p<0.05), respectively, while s' was 12% higher in CON in the basal LV lateral wall (p=0.013). After indexing by cardiac length, s' was only higher in ATH in the mid-ventricular septum (p=0.041).

Conclusions: We found differences between trained and untrained females in segmental systolic myocardial function, but not in global measures of systolic function, including cardiac synchrony. These findings give new insights into cardiac adaptation to endurance training and could also be of use for sports cardiologists evaluating female athletes.

INTRODUCTION

Numerous studies have provided support for cardiac dimensional adaptations in females engaging in endurance training.1 2 Typically, there is an increase in left ventricular (LV) cavity dimension together with a slightly increased LV wall thickness, in parallel with right ventricular (RV) and atrial enlargement.1 2,5

While meta-analyses have found traditional measures of LV global systolic function at rest to be similar in athletes and controls,2 4 5 evidence is not conclusive from studies utilising tissue Doppler imaging (TDI) or speckle tracking6 9 to measure global LV or RV systolic function.6 9 This could in part result from a variety of myocardial segments being used for calculating global measures. Hence, investigating and presenting segmental myocardial function could provide additional insight into cardiac adaptation to chronic exercise. To our knowledge, no previous study compares segmental myocardial function or global LV strain in trained and untrained females.

Moreover, the synchrony in contraction between myocardial segments is of importance for overall systolic function. Lack of synchrony, that is, dysynchrony, has been shown in patients with hypertrophic cardiomyopathy compared with power athletes.10 Studies of synchrony in endurance athletes are surprisingly few. While one study found increased dyssynchrony in less experienced male long-distance runners compared with experienced runners before a 30 km race,11 two studies report a similar degree of dysynchrony in healthy sedentary participants compared with different athletic samples.12 13 Interestingly, there are reports of higher dysynchrony indices in healthy females than in males,14 15 but it remains to be elucidated whether these indices are different between trained and untrained females.

We hypothesised that sedentary and endurance trained females would present a similar
degree of dyssynchrony, and that differences in segmental systolic function might exist. Thus, the purposes of the current study were (1) to compare the degree of cardiac dyssynchrony in female endurance athletes and in age-matched sedentary females, as well as (2) to evaluate and compare segmental myocardial longitudinal systolic function in the same groups.

METHODS

Subjects

Forty-six female athletes (ATH) under 26 years of age were recruited, all competing at a national level in orienteering (n=17), mid-distance or long-distance running (n=6), triathlon (n=5), canoeing (n=5), biathlon (n=4), cycling (n=3), swimming (n=3) or team handball (n=3). On average, the ATH had been competing for 6±2 years (mean±SD) and trained 13±5 h/week. Forty-eight female students of similar age, not engaged in regular endurance or resistance training in recent years, were recruited as controls (CON). Of these, 30 CON described themselves as ‘inactive’ and 18 as ‘normally active’. All participants were screened for cardiovascular disease, including a resting ECG, and underwent maximal bicycle ergometer testing. Details of inclusion procedure and exercise testing together with data on cardiac dimensions in these participants have previously been published. Informed consent was obtained from all participants. The study was approved by the regional ethical review board in Linköping, Sweden.

Echocardiography

Echocardiography was performed by experienced echocardiographers in accordance with current recommendations,16 our protocol for standard echocardiographic measurements has been previously described in detail.15 In the current study, colour TDI was used to measure peak systolic velocity off-line (s’, cm/s) from standard four-chamber, three-chamber and two-chamber apical views, with a frame rate of 89–184 frames/s. A 6×6 mm round sample volume was placed in six basal and six mid-ventricular segments in the LV (at septal, anteroseptal, anterior, lateral, posterolateral and posterior walls), and in the basal and mid-ventricular RV free wall. Measurements were averaged over two to three beats, with markers of aortic valve opening and closing superimposed on TDI-images to ensure measurements in ejection phase only. The time from onset of the QRS complex to s’ (Ts) was determined in all segments (see online supplementary file 1, where TDI and speckle tracking is visualised).

The 12 LV segments were further investigated with speckle tracking from two-dimensional (2D) images with a frame rate >40 frames/s in the same three apical views, and mid-wall peak systolic longitudinal strain (%) during ejection phase was determined. The myocardium was automatically outlined with a region of interest, which, if necessary, was corrected manually with regard to width and localisation to exclude the pericardium. The software automatically analysed the quality of speckle tracking in each segment; segments with poor tracking were excluded from further measurements.

Regional LV function was determined by calculating the arithmetic means of the six basal and six mid-ventricular LV segments, respectively, together with overall LV function for all 12 segments studied (LV-12). Only measurements from those individuals where all six basal or mid-ventricular segments were measurable were included in calculations of regional and overall function. As cardiac length previously has been found to influence measures of myocardial longitudinal function,3 9 peak systolic velocities were indexed by LV length.

Dyssynchrony indices

Four established systolic dyssynchrony indexes were calculated: (1) S-L-delay, the largest difference in Ts between basal septal-to-lateral and posterior-to-anterior LV walls,17 (2) Max-LV-delay, the largest difference in Ts between any 2 out of 12 LV segments,18 (3) Ts-SD, the SD of Ts in all 12 LV segments19 and (4) RV-LV-delay, the difference in Ts between basal RV free wall and LV lateral wall.19 In addition, Ts was indexed by one RR interval and was expressed as a percentage of total cardiac cycle length (Ts%). The dyssynchrony measurements were compared to cut-off values previously suggested for predicting outcomes following cardiac resynchronisation therapy.17–19

Statistical analysis

Normally distributed continuous variables were expressed as mean±SD, between-group differences were determined with Student t test and paired t tests were used for within-group analysis. Non-normally distributed variables were presented as median with 25th and 75th percentiles and between-group differences were determined with the Mann-Whitney test. The Fisher’s exact test or the χ² test was used for comparing categorical variables. A significance level of p≤0.05 was chosen since data are mainly descriptive and not inferential. IBM SPSS Statistics V.22 was used for all data analysis (IBM Software, 2013, Armonk, New York, USA).

In 16 randomly selected participants, the intratester and intertester variability of off-line analysis was explored for six strain, eight s’ and eight Ts measurements. Intratester variability was tested at least 2 weeks following the first measurements, and intertester variability was tested against a second experienced investigator. The coefficient of variation (CV) was calculated as (1/(∑di²/2n))/(overall means), where di is the difference between the ith paired measurement and n the number of differences.20 In addition, the single measure intraclass correlation coefficient was calculated for inter-observer and intraobserver variability in an absolute agreement two-way mixed model.
RESULTS

Data quality and reproducibility

In total, image quality permitted measurements of systolic peak velocities in 1283 (98%) myocardial segments and strain in 1048 (93%) segments. Reproducibility data are presented in table 1.

Subject characteristics and ECG data

Athletes and CON were of similar age (both 21±2 years, p=0.743) and had similar body mass index (22±2 and 21±2 kg/m², respectively, p=0.219). Athletes were heavier (61±6 vs 58±6 kg, p=0.009) and had larger body surface area (1.68±0.10 vs 1.63±0.09 m², p=0.008) than CON. Peak oxygen uptake was 52±5 mL/kg/min in ATH and 39±5 mL/kg/min in CON (p<0.001). Systolic and diastolic blood pressures at rest were similar and within normal limits for both groups. All measured cardiac dimensions were larger in ATH and have been described in detail previously. Median LV ejection fraction (LVEF) was 60% (57–62%) and 57% (54–61%) in ATH and CON, respectively.

ECG data at rest revealed a slightly longer mean QRS duration in ATH than in CON, with no other statistically significant difference between groups (table 2). No participant had a history of symptoms during exercise and all ECGs were categorised as normal by an experienced clinical physiologist.

Systolic timing and synchrony

While TS was longer in ATH than in CON in three mid-ventricular and one basal segment (figure 1), when adjusting for the lower heart rate in ATH than in CON (mean RR interval 1156±183 vs 878±130 ms, p<0.001), TS-% was longer in CON in all 14 myocardial segments (all p<0.05).

Absolute TS in the basal LV was 160±19 ms in ATH and 153±18 ms in CON (p=0.085), which corresponded to 14% and 18% of total cardiac cycle length in ATH and CON, respectively (p<0.001). Absolute (and relative) mid-ventricular TS was 158±18 (14%) and 150±17 ms (17%) in ATH and CON, with p=0.032 for absolute and p<0.001 for relative measures. The corresponding values for LV-12-TS were 159±17 and 150±17 ms (p=0.023), corresponding to 14% and 17% of cardiac cycle length, respectively (p<0.001).

In within-group comparison, there was no statistically significant difference between average basal and mid-ventricular TS in either ventricle.

No difference in any index of dyssynchrony was seen between groups (table 3). A majority of participants in both groups displayed dyssynchrony values clearly above previously suggested cut-off values for cardiac resynchronisation therapy (figure 2). For all participants, 95th percentiles (with maximum values) for the dyssynchrony indices were as follows: S-L-delay 120 ms (150 ms), Max-LV-delay 150 ms (160 ms), TS-SD 54 (59) and RV-LV-delay 140 ms (160 ms).

Table 1 Reproducibility data

<table>
<thead>
<tr>
<th></th>
<th>Intertester</th>
<th>Intratester</th>
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<tr>
<td></td>
<td>COV (%)</td>
<td>ICC</td>
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<tr>
<td>Velocity (s')</td>
<td>11.5</td>
<td>0.76</td>
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<tr>
<td>Strain</td>
<td>8.2</td>
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</tr>
<tr>
<td>TS</td>
<td>11.7</td>
<td>0.58</td>
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</table>

For details of calculations see Methods section. COV, covariance in per cent; ICC, intraclass correlation coefficient; TS, time to s’.

Table 2 ECG data at rest

<table>
<thead>
<tr>
<th></th>
<th>Athletes (ATH)</th>
<th>CON</th>
<th>p Value*</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Range</td>
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</tr>
<tr>
<td>PQ interval</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;120 ms</td>
<td>1</td>
<td>(108 ms)</td>
<td>1</td>
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<tr>
<td>120 to 220 ms</td>
<td>45</td>
<td>(120 to 210 ms)</td>
<td>46</td>
</tr>
<tr>
<td>Mean</td>
<td>154±22 ms</td>
<td>153±24 ms</td>
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<tr>
<td>QRS duration</td>
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<tr>
<td>&lt;100 ms</td>
<td>41</td>
<td>(76 to 100 ms)</td>
<td>43</td>
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<tr>
<td>&gt;100, &lt;120 ms</td>
<td>5</td>
<td>(104 to 112 ms)</td>
<td>4</td>
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<tr>
<td>Mean</td>
<td>92±8 ms</td>
<td>88±9 ms</td>
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<tr>
<td>QRS axis</td>
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<td></td>
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<tr>
<td>&lt;–30°</td>
<td>0</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>–30° to 90°</td>
<td>39</td>
<td>(–8° to 90°)</td>
<td>44</td>
</tr>
<tr>
<td>&gt;90°</td>
<td>7</td>
<td>(91° to 106°)</td>
<td>2</td>
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<tr>
<td>Mean</td>
<td>70°±24</td>
<td>66°±27</td>
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<tr>
<td>QTc interval</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;460 ms</td>
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<td>(376 to 457 ms)</td>
<td>47</td>
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<tr>
<td>≥460 ms</td>
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<td>(463 to 499 ms)</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>428±26 ms</td>
<td>428±18 ms</td>
<td></td>
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</tbody>
</table>

*Statistical significance tested with Student t test for means, Fisher’s exact test for two categorical variables and χ² for three categorical variables. Data presented as number of participants (n) with range of measurements, as well as group means with SDs.

Longitudinal systolic myocardial function

Peak systolic velocity and strain for separate myocardial segments are presented in figure 1. Mean strain in the basal LV was higher than at the mid-ventricular level in both ATH and CON (both p<0.001). Mean mid-ventricular strain was larger than mean basal strain in ATH (p<0.001) while similar in CON (p=0.511). LV-12-strain was lower than RV-strain in both ATH and CON (both p<0.001).

There were no between-group differences in LV regional (ie, basal or mid-ventricular) or in overall (LV-12) systolic function measured as strain (table 4). Mean peak systolic velocity in the RV free wall (RV-strain) was higher in ATH than in CON (9.7±1.5 vs 8.7±1.5 cm/s, p=0.004).

When accounting for the increased LV length in ATH (8.5±0.5 vs 7.9±0.5 cm, respectively, p<0.001), indexed strain' was only higher in ATH in the mid-ventricular septal wall (p=0.041, see online supplementary file 2).
Indexing RV-s’ by LV length eradicated statistical significance (p=0.331), while indexing LV-s’ revealed higher indexed s’ in CON than ATH in the basal LV (p=0.002) and in overall LV-12-s’ (p=0.019), but not at the mid-ventricular level (p=0.187).

**DISCUSSION**

The main finding of this study was a difference in segmental systolic myocardial function between trained and untrained females, despite similar overall and regional cardiac function, as well as a similar degree of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Dyssynchrony indexes in athletes and controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Athletics</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>S-L-delay (ms)</td>
<td>70</td>
</tr>
<tr>
<td>Max-LV-delay (ms)</td>
<td>105</td>
</tr>
<tr>
<td>T₅-S-D</td>
<td>39</td>
</tr>
<tr>
<td>RV-LV-delay (ms)</td>
<td>80</td>
</tr>
</tbody>
</table>

Data presented as median with 25th, 75th and 95th percentiles. S-L-delay, largest difference in Tₛ between basal septum and LV lateral wall and LV anterior and posterior wall; Max-LV-delay, largest difference in Tₛ between all 12 LV segments; Tₛ-S-D, SD of Tₛ in all 12 LV segments; RV-LV-delay, difference in Tₛ between basal RV free wall and LV lateral wall. LV, left ventricular; RV, right ventricular; Tₛ, time from onset of the QRS complex to s’.

**Figure 2** Histograms presenting distribution of dyssynchrony indices in athletes and controls. For details regarding calculations of dyssynchrony indices, see Methods section. Red lines and numbers represent suggested cut-off values in heart failure patients. (A) S-L-delay; (B) Max-LV-delay; (C) Tₛ-S-D and (D) RV-LV-delay. One athlete presenting a negative RV-LV-delay (~60 ms) was treated as an outlier and is not included in this histogram. S-L-delay, largest difference in Tₛ between basal septum and LV lateral wall, and LV anterior and posterior wall; Max-LV-delay, largest difference in Tₛ between all 12 LV segments; Tₛ-S-D, SD of Tₛ in all 12 LV segments; RV-LV-delay, difference in Tₛ between basal RV free wall and LV lateral wall; LV, left ventricular; RV, right ventricular; Tₛ, time from onset of the QRS complex to s’.
dysynchrony. However, indexing peak systolic velocities by the increased cardiac length of ATH eradicated statistical significance in all segments but one.

Systolic timing and synchrony
The normal heart is not perfectly synchronised, owing to a non-uniformity in ventricular geometry, architecture and fibre orientation, in combination with regional differences in electrical activation and activation-contraction coupling. Although increased dysynchrony has been found in patients with pathological hypertrophy (ie, hypertrophic cardiomyopathy), little is known regarding the synchrony in endurance trained athletes with physiological hypertrophy compared with sedentary participants. We found similar interventricular and intraventricular synchrony in trained and untrained females implicating that chronic endurance exercise in females, albeit associated with substantial cardiac remodelling, does not impose systolic mechanical dysynchrony compared with untrained females. Thus, dysynchrony above what is generally reported in females does not seem to be a physiological adaptation to endurance exercise and should merit further investigation if present in an athlete, bearing in mind, for example, previous findings of increased dysynchrony in hypertrophic cardiomyopathy. Furthermore, we showed that available cut-off values used in heart failure patients cannot be applied in determining an abnormal level of dysynchrony in endurance athletes, which is in line with previous studies on healthy participants.

Less than a handful of studies have compared cardiac synchrony in athletes and sedentary participants. Two studies have used 3D echocardiography to calculate a dysynchrony index normalised by cardiac cycle length (SDI %). No difference was observed between their cohorts of healthy participants versus male soccer players and Olympic athletes of different sports, respectively. In the latter study by Caselli et al., a tendency (p=0.058) towards a lower degree of SDI % in athletes was reported, which could be a result of indexing by longer cardiac cycles (ie, lower heart rate) in athletes. Finally, using similar dysynchrony indices as in the current study, Sahlen et al. reported larger S-L-delay in 20 male first-time runners (age 48±8 years) compared with 23 repeat runners (age 46±6 years) prior to a 30 km race. Interestingly, they found that after the race, dysynchrony increased significantly only in first-time runners and was correlated to an increase in biochemical markers of cardiac damage. Altogether, the few and diverse available studies call for further research.

Overall and regional LV and RV systolic function
Our results of a preserved overall LV systolic function together with enlarged cardiac dimensions in trained females depict the physiological hypertrophy seen with endurance training. There is a multitude of reports on normal LVEF at rest in trained participants. In males, average basal LV-s' is typically reported to be similar in endurance athletes and sedentary controls, while global peak systolic longitudinal LV strain is either reported as similar or lower in different samples of trained versus untrained participants.

However, mean RV-s' was found to be higher in ATH than in CON, which could imply an adaptation in resting RV longitudinal systolic function following endurance training in females. This may seem logical as the RV is more dependent on longitudinal shortening than the LV, and an augmentation in RV longitudinal function in athletes is supported by previous cross-sectional echocardiographic studies using M-mode and TDI. However, when accounting for increased cardiac length, these differences have been shown to diminish. Indeed, results are more conflicting from studies measuring RV strain which has been found unrelated to RV size. Our results indicate that previous results on increased cardiac longitudinal function must be interpreted with caution, and future studies should either account for cardiac length or apply relative measures of cardiac function.

Segmental LV and RV systolic function
Peak systolic velocity was higher in ATH than in CON in RV segments studied as well as in segments adjacent to the RV, while the opposite was seen in the basal LV lateral wall. This could imply that either the free RV wall and septum adapt to endurance training in a similar fashion, possibly augmenting RV longitudinal shortening, or that an adaptation in RV longitudinal function influences septal movement. The septum is an

Table 4

<table>
<thead>
<tr>
<th>Basal LV*</th>
<th>Mid-ventricular LV</th>
<th>LV-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>s' (cm/s)</td>
<td>Strain (%)</td>
<td>s' (cm/s)</td>
</tr>
<tr>
<td>ATH 6.7±0.7 (46)</td>
<td>−18.6±1.8 (45)</td>
<td>4.7±0.7 (45)</td>
</tr>
<tr>
<td>CON 6.8±0.7 (44)</td>
<td>−19.3±1.9 (37)</td>
<td>4.7±0.8 (36)</td>
</tr>
<tr>
<td>p Value 0.871</td>
<td>0.072</td>
<td>0.771</td>
</tr>
</tbody>
</table>

*Numbers in parenthesis represent number of participants included in analysis after exclusion of participants with missing segmental data as described in Methods section. Data presented as mean±SD.

ATH, athletes; CON, controls; LV, left ventricular.
important factor in ventricular interdependence, and both circumferential and longitudinal muscle fibres from the RV free wall traverse into the interventricular septum.\textsuperscript{31} Interestingly, training-induced changes in RV dimension and longitudinal systolic function have shown a negative correlation with changes in septal circumferential strain at the mid-ventricular level.\textsuperscript{32} Altogether, there could be a shift from circumferential towards longitudinal shortening in the mid-ventricular septum of endurance athletes. This needs to be confirmed in future studies, ideally in male as well as in female athletes, and the practical implications remain to be elucidated.

There are no available studies describing segmental systolic myocardial function in female athletes. However, there are some conflicting results from studies on predominately male participants examining individual LV segments, most often constrained to basal \textit{s} in LV septal and lateral walls. These two measures have been found either concomitantly higher in ATH than in CON,\textsuperscript{8, 33} or concomitantly similar between groups.\textsuperscript{28, 35, 37} In addition, a few studies report segmental strain in the same two segments to be either concomitantly similar,\textsuperscript{36} concomitantly higher\textsuperscript{37} in ATH than in CON or higher in CON in the basal septum but not in the basal lateral LV wall.\textsuperscript{38} Reports on RV segmental strain are equally conflicting.

So how does one explain these seemingly inconsistent results in endurance athletes? First, there is a large variation in the athletic populations studied, ranging from rowers\textsuperscript{8, 33, 34} and cyclists\textsuperscript{25, 24, 35} to soccer players\textsuperscript{6, 9, 36} and thus, training protocols will vary considerably. Cardiac function may also change with increasing age or duration of training. Our results apply to young females. Second, the characteristics of the included control group are of importance when searching for sometimes subtle differences between groups, and an objective measure of the physical conditioning of control participants is not always presented. Third, the methodology used for assessing myocardial function varies, especially for strain imaging, with different vendors and software platforms being used, and what measures and settings to apply is not fully determined. Considering the factors outlined above and with newer echocardiographic techniques continuously evolving, care must be taken in standardisation and validation of measurements, as well as in selection and description of participants in future studies.

There are some relevant limitations of the current study. First, although we report segmental tissue velocity data for both ventricles, our study protocol did not include RV strain measurements, which would be a measure independent of the increased cardiac length of athletes. Second, we chose to omit apical measurements on theoretical grounds—as it is doubtful that adequate longitudinal function measurements can be obtained in these segments—as well as on practical grounds, as these were not obtainable in some subjects. Third, the athletes included participated in a variety of endurance sports, all categorised as having a high-dynamic component according to the Mitchell classification.\textsuperscript{20} The amount of static component in the respective sports included, however, varied. As the study was not powered to allow for comparisons between different sports, the impact of the static component in high-dynamic sports on the female athlete’s heart was not addressed in this study. Possibly, this may to some extent explain previously conflicting results from studies investigating cardiac function in endurance athletes. Fourth, this study included exclusively young female endurance athletes, which has implication in generalising the results to older athletes and males. Finally, the inter-rater and intra-rater variability should always be considered. At least for strain measurements, this could in part be attributed to inherent limitations of the software algorithms, where small corrections of the width and placement of the region of interest may have large impact on strain data. This could contribute to the somewhat conflicting results from previous studies.

In conclusion, we found differences in segmental myocardial systolic function between trained and untrained females that imply there are adaptations in cardiac function at rest following endurance training not apparent with global measures of systolic function. As differences in segmental peak systolic velocities were clearly affected by cardiac length, a length-independent measure of systolic function, such as strain, may be preferable in athlete-control studies. Moreover, our finding of similar interventricular and intraventricular synchrony in trained and untrained participants could aid in sports cardiological evaluations.

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Contributors EN was responsible for study design and for performing echocardiography. NB was responsible for the exercise tests. KH performed data collection and measurements, under supervision by EN and ĖT. KH, ĖT, EN, and LB were engaged in primary data analysis, while all the authors took part in interpreting and discussing the results. KH drafted the first version of the manuscript, while ĖT, NB, LB and EN actively engaged in the critical revision for important intellectual content and final preparation of this manuscript. All the authors have approved the final manuscript and KH is the guarantor.

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Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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