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Impact of a 246 Km ultra-marathon running race on heart: Insights from advanced deformation analysis.

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ABSTRACT

Although previous studies suggest that prolonged intense exercise such as marathon running transitorily alters cardiac function, there is little information regarding ultramarathon races. Aim of this study was to investigate the acute impact of ultra-endurance exercise (UEE) on heart, applying advanced strain imaging. Echocardiographic assessment was performed the day before and at the finish line of "Spartathlon": A 246 Km ultra-marathon running race. 2D speckle-tracking echocardiography was performed in all 4 chambers, evaluating longitudinal strain (LS) for both ventricles and atria. Peak strain values and temporal parameters adjusted for heart rate were extracted from the derived curves. Out of 60 participants initially screened, 27 athletes (19 male, age 45±7 years) finished the race in 33:34:27(28:50:38-35:07:07) hours. Absolute values of right (RV) and left ventricular (LV) LS (RVLS -22.9±3.6 pre- to -21.2±3.0% post-, p=0.04 and LVLS -20.9±2.3 pre- to -18.8±2.0 post-, p=0.009) slightly decreased post-race, whereas atrial strain did not change. RV and LV LS decrease was caused mainly by strain impairment of basal regions with apical preservation. Inter-chamber relationships assessed through RV/LV, LV/LA, RV/RA and RA/LA peak values' ratios remained unchanged from pre to post-race. Finally, UEE caused an extension of the systolic phase of cardiac cycle with concomitant diastole reduction ($p<0.001$ for all strain curves). Conclusively, ventricular LS strain as well as effective diastolic period slightly decreased, whereas atrial strain and inter-chamber relationships remained unchanged after running a 246-km-ultra-marathon race. These changes may be attributed to

concomitant pre- and afterload alterations following UEE. **Key words:** Athlete's heart; ultra-endurance exercise; strain imaging; inter-chamber relationship.

INTRODUCTION

Endurance and ultra-endurance (UE) races have gained a growing popularity over the last years.[1] Although, mild to moderate systematic exercise is well known to play a protective role against the development of cardiovascular disease,[2] conflicting information has been published regarding the acute and chronic effects of UE exercise (UEE) on myocardium.[2-8] Recent reports have implicated that strenuous exercise and overtraining may have also detrimental effects on structure, function and electrical properties of the heart following a "U curve" paradox.[2-4] These UEE effects have been described by studies, the vast majority of which focused on single cardiac chambers [left ventricle (LV), right ventricle (RV) or atria], not presenting thus the potential impact of UEE on all cardiac chambers and on inter-chamber relationships.[2-8] This concept is of utmost significance, since heart may be considered as a "functioning consortium", where structural or functional alterations of one chamber may impose compensating or consequent changes to the others.[9,10] This interdependence reflects, without being limited to, the effect of septal thickening on RV systolic function, the impact of ventricular diastole on atrial contraction and vice versa, as well as, the right-to-left chambers' correlation under the spectrum of certain pathologic conditions. Especially after ultra-marathon running right heart chambers have been described to be more impaired compared to the left ones,[5,7,8] a condition that could potentially lead to a unique diversion of the above mentioned rule.

Based on the previous considerations, we could hypothesize that, ultra-marathon race may have a negative impact on heart function, leading to biventricular

systolic impairment post-race, as well as to a derangement of inter-chamber relationships. Thus, the aim of our study was to explore the acute impact of a unique UEE event on global and segmental longitudinal strain parameters of the heart and the inter-chamber relationships.

METHODS

Participating athletes

There was an open call for athletes to participate in the study published in the Spartathlon official web site, three months before the race, where the aim and the method of the study were clearly stated. Runners aged at least 18 years old, healthy and sufficiently trained were eligible participants. Twenty-seven ultramarathon runners who finished Spartathlon race in September 2017 volunteered to participate in the study. All participants gave a written informed consent. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Aristotle University of Thessaloniki (105680/2017). The trial is registered in ClinicalsTrials.gov (NCT03304483).

In brief, Spartathlon is a 246 km continuous running race of unique difficulty with 1053 m maximum elevation based on the historical run of Pheidippides, an Athenian messenger sent from Athens to Sparta in 490 BC to seek help against the Persians before the Battle of Marathon.[11] Athletes participating in the race were experienced and must have fulfilled strict performance criteria during specific official non-stop races within the previous two years (full list of races demonstrated in Spartathlon's official webpage https://www.spartathlon.gr/en/registration-en.html). All participants were examined twice, first within 24 h before the start of the race and

then, a second time, within 10 min after finishing their effort. Examinations included echocardiography as well as measurement of arterial blood pressure (BP) and body weight (BW) to assess hydration status.[12] Post-race echo exam lasted approximately 5 min. Ambient temperature during the race ranged from 13 to 22 °C. Hydration volume during the race was not evaluated since participating athletes were allowed to drink fluids and consume food freely. Body weight measurement at the finish line of the race was performed before participating athletes were allowed to hydrate.

Echocardiography

All echocardiographic images were acquired by three experienced cardiologists-ultrasonographers using commercially available ultrasound systems (Vivid S70; GE Medical; Horten, Norway) with M5S phased-array transducers applying the same echo settings and following the same acquisition protocols. Special care was taken to record apical views encompassing the entire LV and RV, as well as the respective left atrium (LA) and right atrium (RA), positioning focal point at the midlevel of the cavity of interest. Frame rate was maximized by decreasing the depth and the sector width to the extent possible.[13-18]

All studies were stored by each athlete's race bib number to avoid identification bias and to protect athlete’s personal data. Thereafter, they were transferred into a central work-station (Echopac, version 201) and were analyzed in a random order (to avoid bias) by two out of the three cardiologists who had performed the acquisition of the images. A comprehensive assessment of the structure and function (systolic and diastolic) of the right and left heart was undertaken in accordance with the European Association of Cardiovascular Imaging and American

Society of Echocardiography guidelines (appended in detail in **Supplementary Material**).[14-17]

Strain measurements were performed offline using EchoPAC BT201 software (GE Vingmed Ultrasound), as previously described (detailed description in **Supplementary Material**).[13-18] Peak LS values for each chamber were selected as well as time-to-peak (TTP) data, which were then corrected according to heart rate by dividing by the R-R interval (in ms) and multiplying by 100% to account for interpatient differences in heart rate.[13] Derived values were used to compare different subjects before and after the race and to quantify inter-chamber relationships (RV/LV, RV/RA, RA/LA and LV/LA peak LS ratios).[9]

Statistical analysis

All statistical analyses were performed using the software IBM SPSS Statistics 22.0. Shapiro–Wilk test was used to verify normality of the distributions of the parameters of interest. Parameters with normal distribution were expressed as mean±standard deviation and with skewed distribution as median (range). The comparisons between baseline and after exercise were performed with paired Student's t-test for normally distributed parameters and with Wilcoxon signed-rank test for non-normally distributed parameters. Mann–Whitney U test was performed for comparisons between two independent groups. The associations between the parameters of interest were assessed with Spearman's correlation analysis. Multiple linear regression analysis was used to identify the parameters with independent associations.

Intra- and inter-observer variability for the measured echocardiographic parameters were assessed in 12 randomly selected cases (before and after the race) using intra-class correlation coefficient (ICC). Based on the 95% confidence interval of the ICC estimate, values less than 0.50, between 0.50 and 0.75, between 0.75 and 0.90, and greater than 0.90 were indicative of poor, moderate, good, and excellent reliability respectively. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the participating athletes

Out of 60 athletes initially screened, 33 athletes dropped out during the race, with only 27 crossing the finish line [19 males (70.4%), 25 Caucasians and 2 Mongolians], being eligible for the study. The mean age was 45±7 years old and the median training age regarding long-distance running was 10(3-28) years. Their training regime included 110(50-200) Km of running per week. Median finishing time was 33:34:27(28:50:38-35:07:07) h.

After the race, BW decreased from 66.9±8.5 kg to 64.3±7.8 kg ($p<0.001$) resulting in 3.7±2.6% weight loss. Similarly, systolic blood pressure (SBP) marginally decreased from 124±17 mm Hg to 115±18 mm Hg ($p=0.045$) while diastolic and mean arterial pressure remained unchanged ($p=0.48$ and $p=0.11$ accordingly). Heart rate, as expected, significantly increased after the race (from 61±9 to 79±11 beats/min, $p<0.001$).

Change of basic echocardiographic parameters after the race.

Main traditional echocardiographic parameters' values after the race and their comparison to baseline are summarized in **Table 1**. Overall, there was a statistically significant increase of LV wall thickness and LV mass after the race, accompanied by a reduction of LV internal diameter and LV end diastolic volume. A significant decrease of transmitral E/A ratio was also observed. Concerning RV, an RV end-diastolic area enlargement was spotted, along with a slight but significant reduction of RV fractional area change and tricuspid annular plane systolic excursion (TAPSE) index. Both LV and RV filling pressures did not change after the race. Following a gender-based subgroup analysis, all echo parameters evaluated did not differ between males and females **(Supplementary Table 1).**

Global and segmental strain analysis of cardiac chambers.

Global and segmental longitudinal strain values of all cardiac chambers are presented in **Table 2**. There was a slight decrease of both LV and RV-GLS absolute values (-20.9±2.3% pre to -18.8±2.0% post race for LV, $p<0.009$ and -22.9±3.6% pre to -21.2±3.0 post-race for RV, $p=0.04$), even though both LV and RV strain values remained within normal range after the race for 85% of the participants. This longitudinal strain decrease was mainly originated by the basal segments of the ventricles, while both apical regions remained unaffected (**Table 2**). Similarly, both atrial longitudinal strain values remained unchanged after the race. An alteration of temporal characteristics of strain curves was also spotted. More specifically, the ultramarathon race caused an increase in both RV and LV mechanical dispersion. Additionally, there was a reduction of the "efficient" diastolic period after the race, as

evidenced by the heart rate-corrected longer time to peak strain and by strain curves' peaking after aortic valve closure (**Table 2**) for both ventricles.

With regard to LV and RV strain changes after the race (ΔLV-GLS and ΔRV-GLS), an improvement of absolute strain values of LV or RV after the race was shown in 33% of athletes, while an improvement of both LV and RV strain values was demonstrated in 16% of athletes. No significant differences in other echocardiographic or demographic characteristics were found when comparing those with preserved or improved LV-GLS and those with impaired LV strain after the race. On the other hand, athletes with improved RV strain finished the race later compared to the rest of the athletes (34:32:50±0:34:27 h vs 32:09:21±1:56:09 h, p=0.001). Finishing time and RV-GLS correlated negatively (**Figure 1)**. Additionally, heart rate-corrected time to peak strain values for both LV and RV correlated negatively with training age for long distance running (r=0.45, p=0.04 and r=0.54, p=0.02 accordingly), indicating that post-race LV and RV strain curves peaked later in athletes with less years of endurance exercise training.

Inter-chamber relationships and their alteration after the race.

RV and RA absolute strain values were constantly larger in magnitude than those of the LV and LA, while atrial strain values were significantly higher compared to the absolute values of ventricular longitudinal strains. RV/LV, LV/LA, RV/RA and RA/LA peak values' ratios remained unchanged from pre to post-race (p=0.64, p=0.66, p=0.52 and p=0.16 accordingly), as it is also shown in **Figure 2**. Similarly, there was also no change in the temporal inter-chamber relationships from pre- to post-race.

Intra- and Inter-Observer Variability analysis.

Concerning traditional echocardiographic parameters, analysis of the intra- and inter-observer variability yielded ICC values of 0.93 [95% confidence interval (CI) (0.92–0.95)] and 0.89 [% CI (0.82-0.94)] respectively, suggesting excellent intra-observer and good to excellent inter-observer reliability. Especially about 2D-LS, intra- and inter-observer variability showed very good correlations for ventricular LS [intra-ICC 0.98, 95%CI(0.98-0.99) and inter- 0.97, 95%CI (0.96-0.98), respectively] and slightly lower for atria [intra-ICC 0.95, 95%CI(0.91-0.97) and inter- 0.93, 95%CI(0.89-0.96), respectively].

DISCUSSION

In this study, we investigated for the first time the impact of a unique ultra-marathon running effort on myocardial strain characteristics and inter-chambers relationships, in a cohort of 27 ultra-endurance athletes who were able to complete a 246-km Spartathlon race.

The primary novelty for this study is derived from the unique population studied. The running distance of the race was the longest among studies evaluating cardiac changes after ultra-long duration exercise.[19] Additionally, our study assessed the athletes after completion of non-stop ultra-marathon running. Most studies in the field evaluated athletes participating in ultra-long duration races with interrupted exercise due to intermediate rests for some hours, including a few hours' sleep.[20] This

type of UEE represents a different kind of exercise stress possibly less challenging to the heart and with attenuated impact of dehydration as well as less preload and afterload alteration.[21]

One of our main findings is a subtle impairment of biventricular longitudinal strain following UEE. This finding is in accordance with previous studies in the field,[22-29] although a wide numeric discordance is observed mainly due to application of different softwares or versions for strain assessment between studies.[30,31] Despite these methodological differences, the main conclusion of the above mentioned studies appears to be the same: there is a subtle (although statistically significant) alteration of LV longitudinal strain following an UEE.[22-24,27,29] Similarly, UEE has caused a slight only decrease in absolute RV strain values,[24,25] with the vast majority of participating athletes (almost 85%) preserving their RV longitudinal strain within normal range after the race. These minimal alterations of strain values could be attributed to the significant alterations of pre- and after-load indices (merely reflected though body weight changes, heart rate and blood pressure alterations as well as LV and RV volume change) all of which significantly affect the numerical values of biventricular strain observed.[32] Based on this, it could be further supported that strain changes reflect mostly the consequences of race-related stress rather than irreversible myocardial damage predisposing to cardiomyopathy and heart failure.[22, 24, 25]

Following a segmental strain analysis it was evidenced that this subtle biventricular longitudinal strain decrease was mainly driven by a strain impairment of basal segments with a preservation of apical regions in both LV and RV. This finding is partially supported by a previous study, where LV and RV systolic impairment was mainly due to septal dysfunction triggered by RV volume and stress changes.[24] This strain gradient may have an explanation since inter-segmental wall stress, regional

wall thickness and previously observed curvature differences are greater in basal compared to apical regions as previously described in the literature (Laplace law), playing a crucial role in this phenomenon.[33]

Additionally, the negative correlation between finishing time and RV strain change coming out from this study, is a very interesting finding, suggesting that UE intensity (distance covered over time) rather than UEE 'burden' (distance covered) may have impact on potential RV systolic impairment. However, further evidence is needed to support this point and clarify its potential pathophysiologic implications.

Preload and afterload alterations connected to ultra-marathon running may also explain the significant impact UEE seems to have on temporal characteristics, reducing the effective diastolic period. This finding is interesting and consistent with other works in this area. Chan Dewar and colleagues as well as Oxborough D et al. demonstrated an increase in time to peak myocardial velocities from both the LV and RV after an 89-km ultramarathon,[24,34] whereas other work demonstrated increased time to peak LV twist and untwist after prolonged exercise.[27] The elongation of systolic phase over the diastolic one during the cardiac cycle, could be explained both by a significant preload decrease (connected to the severity of participating athletes' dehydration) and/or afterload increase (as evidenced through a reported elevation of central mean blood pressure).[11]

Finally, we observed that inter-chamber relationships, despite minor alterations in ventricular strain, remained stable and unaffected after UEE. These stable relationships, as assessed through longitudinal strain ratios, may lead to a basic conclusion: The stress factors connected to UEE affect similarly all chambers and heart remains a fully functioning consortium even after completing a very demanding

ultra-marathon race.[9,10] Additionally, the similarity of our findings with previous studies, despite differences in race length, could allow the generalization that the observed minimal alterations in strain should be attributed solely to preload-afterload alterations rather than to an exercise-related-cardiomyopathy procedure leading to irreversible myocardial damage.

Study Strengths and Limitations

Strengths of this study include: 1) The running distance of the race was the longest among the studies evaluating the cardiac changes after continuous ultra-long duration exercise.2) The ultra-long marathon selected was a non-stop challenge without intermediate rests or a few hours' sleep, representing one of the most demanding exercise bouts worldwide. 3) The current study had the largest study population and the greatest number of females of this kind of study. 4) Rather than focusing on a single chamber, we evaluated longitudinal strain of all chambers, assessing also inter-chamber relationships based on strain-ratios and temporal characteristics. The strain methodology applied may be considered one of the most complete strain assessments among similar studies in the field.

The results of our study should be interpreted in light of some limitations and in this respect, they can be considered only as hypothesis generating.

We did not assess radial and circumferential strains in this study. We focused on LS only, because this index has proven to be the most promising in the clinical arena, with the largest body of literature supporting its use.[13] Despite that, universal limitations about single plane 2D longitudinal strain imaging apply also in this study

including technical considerations and inter-vendor variability, which could affect numerical values presented, however not patterns and interactions described [30,31]

Another limitation of our study is that males predominated over females. However, as we have previously demonstrated exercise-induced cardiac alterations were similar between males and females.[11] We also did not perform serial post-exercise echocardiographic examinations to evaluate the reversibility of the exercise-induced cardiac changes.

The fact that each sonographer did not examine exactly the same participants before and after the race due to technical and time issues could also be considered a limitation of this study. To avoid potential variability in image acquisition, all three experienced sonographers were previously trained to follow the same protocol.

A final limitation of this (and other similar studies) in the potential for survivorship bias. That means that participants failing to finish the race and thus not examined at the end, might have presented significant decrements in cardiac function/strain as opposed to those, who were able to complete this ultra-long endurance activity not showing cardiac impairment.

Study conclusions, practical applications and future research implications

In a cohort of athletes who finished a 246 km ultra-marathon running, we showed that there was a slight, only, decrease of biventricular longitudinal strain following an UE event, a phenomenon mainly guided by an impairment of basal regions and preservation of apical strain. Additionally, we have observed that UEE causes an extension of the systolic phase of cardiac cycle with concomitant diastole reduction, while despite the subtle changes in strain, inter-chamber ratios/relationships remain unchanged after UEE, reflecting an unaffected inter-

chamber functionality. All these findings, point towards the direction that morphological and functional alterations imposed by UEE could be seen in the context of myocardial adaptations rather than that of myocardial necrosis or progression to cardiomyopathy. The above mentioned conclusions have an important practical application: When it comes to cardiovascular assessment of healthy athletes following UEE, no significant changes of either chamber longitudinal strain (compared both to baseline and normal range) should be expected. This practically means that slight changes should be attributed to pre- or afterload alterations, whereas major changes (exceeding normal range values) should raise suspicion of underlying pathology. On this context, it would be really useful to pursue dynamic rather than static (only during rest) evaluation of strain values during pre-participation screening of endurance athletes, a very interesting theme for future research. Additionally, the fact that few (and certainly not all) athletes present a significant impairment of cardiac function after years of ultra-endurance training potentially means that UEE is not the only factor to blame for this dysfunction. Genetic along with molecular-histologic pathways (for example desmosome connections' stability) may form a true susceptible substrate for UEE to act, a hypothesis needing clarification by future research.

Contributors

EDP, GAC, PGS, MAA, NAK, MPT, KAC, VPV, APD, EJK collected the data. EDP and GAC analyzed the data. EDP, GAC, APD and EJK drafted the manuscript. All authors contributed to study design, and the revision of the manuscript, and accepted the final version. The authors apologize for not being able to cite all the noteworthy work in this area because of constraints on space.

Disclosures

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Ethical approval

This study was conducted according to good clinical and scientific practice and the Declaration of Helsinki. The authors declare that the results of this study are presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation. All participants gave a written informed consent. The study protocol was approved by the Ethics Committee of Aristotle University of Thessaloniki (105680/2017). The trial is registered in ClinicalsTrials.gov (NCT03304483).

Data sharing

Researchers are encouraged to contact the authors and we will make every effort to accommodate additional analyses.

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Figure Legends

Figure 1: Correlation plot between change (pre- to post-race) in right ventricular (RV) longitudinal strain and ultra-marathon finishing time.

Figure 2: Bar plots representing inter-chamber longitudinal strain ratios (relationships) before (blue bars) and post-race (red bars). Numbers are mean ratio values. NS: Non Significant, LA: Left Atrium, LV: Left Ventricle, RA: Right Atrium, RV: Right Ventricle.

Table 1. Comparisons of echocardiographic parameters between baseline and after Spartathlon ultra-marathon.

Parameters		Baseline	After exercise	p value
LV INDICES	**LVIVSd (cm)**	0.9±0.2	1.0±0.1	**<0.001**
	LVPWTd (cm)	0.9±0.2	1.0±0.1	**0.001**
	LVIDd (cm)	4.8±0.5	4.7±0.5	**0.009**
	LVEDV (mL)	162 ± 38	151 ± 35	**0.024**
	LVmass (g)	149 ± 36	165 ± 43	**0.008**
	LAV (mL)	62(33-136)	57(19-100)	**0.011**
	LVEF (%)	56±7	54±5	0.160
	MVE (m/sec)	0.7±0.2	0.6±0.1	**0.007**
	MVA (m/sec)	0.5(0.4-0.9)	0.6(0.4-0.7)	0.063
	MVE/A	1.4±0.4	1.1±0.3	**0.001**
	MVEa (m/sec)	0.16(0.08-0.21)	0.14(0.09-0.21)	0.104
	MVAa (m/sec)	0.11±0.02	0.12±0.02	**0.030**
	MVSa (m/sec)	0.12±0.03	0.13±0.02	0.705
	MVE/Ea	5.1±1.2	4.6±0.9	0.085
RV INDICES	**RVbas (cm)**	4.1±0.7	4.3±0.9	0.299
	RVmid (cm)	3.2±0.6	3.4±0.5	0.152
	RVlon (cm)	8.4±0.8	8.6±0.7	0.116
	RVOTprox (cm)	3.8±0.5	3.7±0.5	0.290
	RVEDA (cm^2)	25.9±3.8	29.2±5.5	**0.005**
	RAA (cm^2)	18.1±4.2	19.5±4.3	0.068
	RVFAC (%)	50(26-55)	43(20-52)	**<0.001**
	TVE (m/sec)	0.58(0.41-0.87)	0.61(0.40-0.76)	0.889
	TVA (m/sec)	0.43(0.24-0.52)	0.43(0.24-0.83)	0.398
	TVE/A	1.5(0.9-2.2)	1.4(0.8-2.0)	0.484
	TVEa (m/sec)	0.15±0.05	0.15±0.03	0.759
	TVAa (m/sec)	0.15±0.03	0.15±0.04	1.000
	TVSa (m/sec)	0.17±0.03	0.16±0.02	0.410
	TVE/Ea	3.7(2.2-5.1)	3.6(2.2-6.6)	0.575
	TAPSE (cm)	2.9±0.5	2.6±0.3	**0.004**
	PASP (mm Hg)	28±9	25±10	0.076

Data are expressed as mean±standard deviation for normally distributed variables or median(range) for non-normal variables.

Abbreviations. LAV: left atrial end-systolic volume, **LVEDV:** left ventricular end-diastolic volume, **LVEF**: left ventricular ejection fraction, **LVIDd:** left ventricular end-diastolic internal diameter, **LVIVSd**: left ventricular interventricular septum thickness at end-diastole, LVmass: left ventricular mass, **LVPWTd:** left ventricular posterior wall thickness at end-diastole, **MVA:** late diastolic transmitral flow velocity, **MVAa:** average of septal and lateral late diastolic mitral annular velocity, **MVE:** early diastolic transmitral flow velocity, **MVE/A:** ratio of early to late diastolic transmitral flow velocity, **MVEa:** average of septal and lateral early diastolic mitral annular velocity, **MVE/Ea:** ratio of the early diastolic transmitral flow velocity to the average of septal and lateral early diastolic mitral annular velocity, **MVSa:** average of septal and lateral systolic mitral annular velocity, **PASP:** Pulmonary Artery Systolic Pressure, **RAA:** right atrial end-systolic area, **RVbas:** basal right ventricular diameter, **RVEDA:** right ventricular end-diastolic area, **RVFAC:** right ventricular fractional area change, **RVlon:** right ventricular longitudinal diameter, **RVmid:** right ventricular mid-cavity diameter, **RVOTprox:** proximal right ventricular outflow tract diameter, **TAPSE:** tricuspid annular plane systolic excursion, **TVA:** late diastolic transtricuspid flow velocity, **TVAa:** late diastolic tricuspid annular velocity, **TVE:** early diastolic transtricuspid flow velocity, **TVEa:** early diastolic tricuspid annular velocity, **TVE/A:** ratio of early to late diastolic transtricuspid flow velocity, **TVE/Ea** :ratio of early diastolic transtricuspid flow velocity to early diastolic tricuspid annular velocity, **TVSa:** systolic tricuspid annular velocity. Significant p values ($p<0.05$) are highlighted in bold.

Table 2. Global, segmental longitudinal strain values and temporal characteristics in all four cardiac chambers before and after Spartathlon race.

		PRE-RACE	POST-RACE	DIFF±SD	p values
LV-GLS (%)		-20.9±2.3	-18.8±2.0	2.1±3.3	**0.009**
	Bas. Segmen. (%)	-18.8±3.1	-15.5±3.5	3.4±4.4	**0.001**
	Mid. Segmen. (%)	-19.9±2.9	-17.6±2.7	2.4±4.1	0.06
	Ap. Segmen. (%)	-24.6±3.1	-23.4±4.8	1.1±5.2	0.49
RV-GLS (%)		-22.9±3.6	-21.2±3.0	1.7±3.1	**0.04**
RV-REG	Bas. Septal (%)	-17.7±2.3	-15.7±2.1	2.0±3.2	**0.01**
	Mid. Septal (%)	-19.9±2.3	-18±1.7	2.0±2.9	0.07
	Ap. Septal (%)	-24.5±3.4	-24.3±4.6	0.15±5.1	0.90
	Ap. Free RV (%)	-28.2±6.3	-26.9±5.8	1.4±7.6	0.46
	Mid. Free RV (%)	-28.3±3.8	-25.9±3.2	2.3±3.3	**0.008**
	Bas Free RV (%)	-23.4±5.9	-21.1±5.5	2.1±5.6	**0.02**
RV-FWS (%)		-26.6±5.3	-24.6±4.8	1.9±5.5	**0.04**
LA-GLS (%)		38.9±10.5	34±9.6	-4.6±12.2	0.12
RA-GLS (%)		44.6±15.5	44.3±14.4	-0.3±1.7	0.95
LV MECH. DISPERSION (msec)		28.7±12.2	47.3±24	18.6±24.5	**0.003**
RV MECH. DISPERSION (msec)		25.2±10	40.2±24.5	15±25	**0.02**
AVC corr. (msec)		360±46	436±48	75±57	**<0.0005**
TIME TO PEAK LV corr (msec)		358±44	444±47	86±6	**<0.0005**
TIME TO PEAK LA corr (msec)		395±60	491±61	95±69	**<0.0005**
TIME TO PEAK RV corr (msec)		353±46	438±50	85±56	**<0.0005**
TIME TO PEAK RA corr (msec)		361±83	440±54	79±71	**0.007**

Ap.: Apical**, AVC:** Aortic Valve Closure, **Bas.:** Basal, **Corr:** Corrected for heart frequency, **DIFF±SD:** Post-Race minus Pre-Race Value and standard deviation, **FWS:** Free Wall Strain, **GLS:** Global Longitudinal Strain, **LA:** Left Atrium, **LV:** Left Ventricle, **MECH. DISPERSION:** Mechanical Dispersion, **Mid.:** Middle, **RA:** Right Atrium, **REG:** Regional Strain, **RV:** Right Ventricle, **TIME TO PEAK:** Time to peak strain in each chamber as percentage of cardiac cycle, **Segmen:** Segments

SUPPLEMENTARY MATERIAL

Echocardiography Assessment

From 2D image obtained in the parasternal view, primary measurements were made as follows: left ventricular end-diastolic diameter (LVIDd), left ventricular end-systolic diameter (LVISd), interventricular septum thickness (LVIVSd) and posterior wall thickness (LVPWTd). Mean values of three cardiac cycles were analyzed. On the basis of the obtained measurements, the secondary dimension of left ventricular mass (LVM) was calculated. LV ejection fraction was calculated from LV volumes obtained using the Simpson's biplane method of disks. LV diastolic function was evaluated by Doppler echocardiography based on the ratio between the maximal flow velocities during the early diastolic rapid filling phase (mitral inflow E) and the late diastolic atrial contraction (A-wave velocities) (E/A), and the E/A ratio was calculated. The ratio of the early diastolic transmitral flow velocity (MVE) to the average of septal and lateral early diastolic mitral annular velocities (E') along with left atrial volume and peak tricuspid regurgitation velocity were used as an estimate of LV filling pressures. RV filling pressures were estimated through the ratio of early tricuspid inflow to annular diastolic velocity (E/E') (TVE/Ea).[14-17]

Assessment of basic right ventricular dimensions from parasternal short-axis and apical four-chamber views, along with evaluation of transtricuspid inflow parameters and tricuspid annular TDI velocities were performed according to the American Society of Echocardiography guidelines. Using a parasternal short-axis orientation at the level of the aortic valve, right ventricular outflow tract end-diastolic diameter (RVOTProx) was measured, while by visualizing a modified apical four-chamber orientation focusing on the right ventricle, basal right ventricular inflow diameter at the tips of the tricuspid valve (TV) leaflets (RVbas) and right ventricular

midventricular short axis (RVmid) and long axis from right ventricular apex to the level of the tricuspid annulus (RVlon) were calculated. Right ventricular end-diastolic area (RVEDA) and right ventricular end-systolic area (RVESA) were measured, allowing calculation of right ventricular FAC as (RVEDA -RVESA)/RVEDA. E and A waves and the deceleration time (DT) of transtricuspid inflow were also calculated, with RV filling pressures being estimated through the ratio of early tricuspid inflow to annular diastolic velocity (E/E') (TVE/Ea).[16,17]

Strain measurements were performed offline using EchoPAC BT201 software (GE Vingmed Ultrasound), as previously described. In 2D grey-scale images, a region of interest was created by manually outlining the endocardial and epicardial borders in each view of interest. Software permitted automatic tracking of tissue speckles frame by frame throughout the cardiac cycle, dividing also the myocardium into standard segments. Tracking was visually checked and, if necessary, adjusted. In LV, peak global longitudinal strain (LV-GLS) was calculated as an average of the three apical views, based on an 18-segment model.[13] Taking into consideration feasibility and reproducibility issues, RV peak global longitudinal strain (RVGLS) was derived from 2D speckle tracking of the entire RV contour in the apical four chamber view, making thus global RV strain calculations based on 6 segments. RV free wall strain (RVFW LS) was extracted as an average of the three free wall segments.[16,17] Accordingly, the interatrial septum was included in the LS measurements of both the LA and RA. In each atrium, conduit phase strain was selected as peak atrial strain, setting ECG based end-diastole as reference point.[13] Aortic valve closure (AVC), selected according to Doppler derived data, was the time point in which peak strain happened. Peak LS values for each chamber were selected as well as time-to-peak (TTP) data.[13]. To quantify LV mechanical dispersion, we used the standard deviation (SD) of the

different 18 segmental time intervals to maximum myocardial shortening in each participant athlete. Accordingly, in RV, mechanical dispersion was assessed through the SD of the different 6 segmental time intervals to maximum myocardial shortening of right ventricle.[18]

Supplemental Table 1. Comparisons of indicative echocardiographic parameters between baseline and after exercise in female athletes.

	Baseline	**After exercise**	**p value**
LVIVSd (cm)	0.94±0.20	0.98±0.22	0.041
LVPWTd (cm)	0.89±0.16	0.93±0.13	0.046
LVIDd (cm)	4.6±0.3	4.5±0.3	0.138
MVE/A	1.5±0.5	1.2±0.2	0.097
RVEDA (cm^2)	24.1±1.9	28.2±3.6	0.004
TAPSE (cm)	3.0±0.2	2.6±0.2	0.052

Abbreviations. LVIDd: left ventricular end-diastolic internal diameter, **LVIVSd:** left ventricular interventricular septum thickness at end-diastole, **LVPWTd:** left ventricular posterior wall thickness at end-diastole, **MVE/A:** ratio of early to late diastolic transmitral flow velocity, **RVEDA:** right ventricular end-diastolic area, **TAPSE:** tricuspid annular plane systolic excursion.