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Exploring the determinants of the cardiac changes after ultra-long duration exercise: The echocardiographic Spartathlon study

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Abstract

Aim: The investigation of the pathophysiological determinants of cardiac changes following ultra-long duration exercise.
Methods: Twenty-seven runners who finished a 246 km running race were examined both before and after the finish of the race. Examinations included echocardiography and measurement of body weight and blood biochemical parameters.
Results: Exercise increased left ventricular end-diastolic interventricular septum thickness (LVIVSd) ($p < 0.001$) and posterior wall thickness (LVPWTd) ($p = 0.001$) and right ventricular end-diastolic area ($p = 0.005$), while reduced tricuspid annular plane systolic excursion (TAPSE) ($p = 0.004$). A minor decrease in the peak absolute values of both left ventricular (from $-20.9 \pm 2.3\%$ to $-18.8 \pm 2.0\%$, $p = 0.009$) and right ventricular (from $-22.9 \pm 3.6\%$ to $-21.2 \pm 3.0\%$, $p = 0.040$) global longitudinal strains occurred. There was decrease in body weight ($p < 0.001$) and increase in both circulating high-sensitivity troponin I ($p = 0.028$) and amino-terminal pro-B type natriuretic peptide (NT-proBNP) ($p = 0.018$). The change in the sum of LVIVSd and LVPWTd correlated negatively with percentage change of body weight ($r = -0.416$, $p = 0.049$). The only independent determinant of post-exercise NT-proBNP was pulmonary artery systolic pressure ($r = 0.797$, $p = 0.002$). Post-exercise NT-proBNP correlated positively with percentage changes of basal (RVbas) ($r = 0.582$, $p = 0.037$) and mid-cavity (RVmid) ($r = 0.618$, $p = 0.043$) right ventricular diameters and negatively with percentage change of TAPSE ($r = -0.720$, $p = 0.008$). Similar correlations with RVbas, RVmid and TAPSE were found for pulmonary artery systolic pressure. Post-exercise high-sensitivity troponin I correlated negatively with percentage change of body weight ($r = -0.601$, $p = 0.039$), but was not associated with any cardiac parameter.
Conclusion: The main cardiac effects of ultra-long duration exercise were the decrease in left ventricular end-diastolic dimensions and increase in left ventricular wall thickness, as well as minimal dilatation and alteration in systolic function of right ventricle, possibly due to the altered exercise-related right ventricular afterload.

Keywords

Ultra-endurance exercise, myocardial injury, cardiac dysfunction

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Introduction

The growing popularity of endurance running races worldwide necessitates a clear understanding of the cardiac impact of such exercise. Ultra-endurance exercise has been demonstrated to induce alterations in cardiac structure and function, including enlargement of right ventricle (RV), decline in RV systolic function, as well as impairment of left ventricular (LV) diastolic

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function.[1–3] Furthermore, ultra-endurance exercise has been postulated to result in direct myocardial injury, as indicated by increased serum cardiac troponin levels after exercise in the majority of relevant studies.[2,4]

The acute impact of ultra-long duration exercise (i.e. >24 h) on the heart has not been thoroughly investigated, while the majority of the studies evaluating the acute cardiac effects of endurance exercise were based on data from races of shorter duration and especially marathons.[2,3] Ultra-long duration exercise that is performed continuously can be regarded as the ideal model for the investigation of the impact of utterly strenuous and extended duration exercise on the heart. The original version of uninterrupted ultra-long duration running events is the Spartathlon race. Spartathlon is a 246 km continuous running race of unique difficulty 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.

Studies to date have not performed analysis of all the possible factors influencing the cardiac responses after ultra-long duration exercise in an integrative manner. Uncovering the determinants of the cardiac changes following ultra-long duration exercise and their relative importance may prove invaluable for understanding the real nature of these changes, since it can be elucidated whether they represent intrinsic cardiac dysfunction or simply reflect other exercise-related modifiable factors, such as dehydration. Finally, the importance of such a study lies in the identification of possible modifiable predisposing factors that if changed could decrease the incidence and severity of adverse cardiac changes after ultra-endurance exercise. Thus, the aim of this study was to investigate, by means of basic and advanced echocardiography and blood biochemistry analysis, the acute changes in cardiac structure and function following a Spartathlon race, as well as the pathophysiological determinants of these changes.

Methods

Subjects

Twenty-seven ultramarathon runners who finished a Spartathlon race in September 2017 volunteered to participate in the study. The Spartathlon race is an ultra-endurance 246 km running race with 1053 m maximum elevation that takes place in Greece. Athletes participating in the race were experienced and must have fulfilled the eligibility criteria with qualified performance within the previous two years. All participants were examined twice, first within 24 h before the start of the race and then, a second time, within 10 min after the finish of the race. Examinations included echocardiography and measurement of arterial blood pressure (BP) and body weight. Hydration status after exercise was assessed by the percentage change of body weight.[5] Thirteen athletes complied with the request to be subjected to venous blood sampling both before and after exercise. Serum samples were stored at −80°C until analysis.

Ambient temperature during the race ranged from 13°C to 22°C. All athletes were allowed to drink fluids and consume food freely. 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).

Patient and public involvement

We did not involve patients or the public in our work.

Echocardiography

All echocardiographic images were acquired by three experienced cardiologists–ultrasonographers using commercially available ultrasound systems (Vivid I; GE Medical, Horten, Norway) with a 1.5- to 4-MHz phased-array transducer applying the same echo settings and following the same acquisition protocols. All studies were then transferred into a central workstation (Echopac, version 201) and were analysed 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 of the left and right heart was undertaken in accordance with the guidelines of European Association of Cardiovascular Imaging.[6–9] The sum (SWT) of LV end-diastolic interventricular wall thickness (LVIVSd) and posterior wall thickness (LVPWTd) was used as an estimate of LV wall thickness.[10] The ratio (MVE/Ea(s-l)) of the early diastolic transmitral flow velocity (MVE) to the average of septal and lateral early diastolic mitral annular velocity was used as an estimate of LV filling pressures. Pulmonary vascular resistance was estimated using the formula: $(TRV_{max}/RVOTTVI) \times 10 + 0.16$ (in Woods), where TRV_{max} is the peak velocity (in m/s) of the tricuspid valve regurgitant jet with continuous wave Doppler and RVOTTVI is the time–velocity integral in the RV outflow tract.

Strain measurements were performed offline using Echopac as previously described.[11] 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. Similarly, RV peak global longitudinal strain (RV-GLS) was derived from 2D speckle tracking of the entire RV contour in the apical four chamber view. Longitudinal strain was preferred to other deformation parameters due to ease of assessment, higher reproducibility and established pathophysiologic connection with other functional parameters evaluated in this study.

Measurement of central blood pressure

Peripheral BP was measured in the brachial artery with an automatic BP monitor (OMRON Healthcare Co. Ltd; M6 Comfort, Kyoto, Japan). Central BP was assessed using a Complior® device (ALAM Medical, Paris, France) with the athlete in supine position.

Biochemical measurements

Blood chemistry was performed using the Roche Cobas 6000 Chemistry Analyzer (Roche Diagnostics, Basel, Switzerland).

Serum levels of amino-terminal pro-B type natriuretic peptide (NT-proBNP; lower limit of detection: 35 pg/mL, upper limit of normal: 125 pg/mL) and high-sensitivity troponin I (TnI; lower limit of detection: <1.6 ng/L, upper limit of normal: 47.0 ng/L) were measured with Siemens ADVIA Centaur® immunoassay.

Statistical analysis

All statistical analyses were performed using the software IBM SPSS Statistics 23.0. Shapiro–Wilk test was used to verify the 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).[12] 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

Characteristics of the athletes

Participants included 19 males and eight females (25 Caucasians, 2 Mongolians). The mean age was 45 ± 7 years old. 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. Finishing time was 33:34:27 (28:50:38–35:07:07) h.

The 13 athletes subjected to blood sampling included nine males and four females (age: 45 ± 5 years).

Comparisons between baseline and after exercise

Body weight decreased from 66.9 ± 8.5 kg to 64.3 ± 7.8 kg ($p < 0.001$) resulting in $3.7 \pm 2.6\%$ weight loss.

Haemodynamic and echocardiographic parameters. Tables 1 and 2 show the comparisons of haemodynamic and echocardiographic parameters between baseline and after exercise. There was an increase in heart rate (HR), cardiac output, LVIVSd, LVPWTd and RV end-diastolic area (RVEDA). Exercise decreased central systolic blood pressure, stroke volume, LV end-diastolic internal diameter (LVIDd), LV end-diastolic volume (LVEDV), left atrial end-systolic volume, ratio of MVE to late diastolic transmitral flow velocity

Table 1. Comparisons of haemodynamic parameters between baseline and after exercise.

	Baseline	After exercise	*p* value
HR, beats/min	61 ± 9	79 ± 11	<0.001
SBPc, mmHg	124 ± 17	115 ± 18	0.045
DBPc, mmHg	74 ± 8	73 ± 8	0.483
MBPc, mmHg	91 ± 9	87 ± 11	0.109
SV, mL	89 ± 19	81 ± 15	0.001
CO, L/min	5.4 ± 1.5	6.4 ± 1.3	0.002
PVR, Wood	1.05 ± 0.26	1.07 ± 0.28	0.726
PASP, mmHg	28 ± 9	25 ± 10	0.076

Data are expressed as mean ± standard deviation.
CO: cardiac output; DBPc: central diastolic blood pressure; HR: heart rate; MBPc: central mean blood pressure; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; SBPc: central systolic blood pressure; SV: stroke volume

Table 2. Comparisons of echocardiographic parameters between baseline and after exercise.

	Baseline	After exercise	*p* value
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/s	0.7 ± 0.2	0.6 ± 0.1	0.007
MVA, m/s	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(s-l), m/s	0.16 (0.08–0.21)	0.14 (0.09–0.21)	0.104
MVAa(s-l), m/s	0.11 ± 0.02	0.12 ± 0.02	0.030
MVSa(s-l), m/s	0.12 ± 0.03	0.13 ± 0.02	0.705
MVE/Ea(s-l)	5.1 ± 1.2	4.6 ± 0.9	0.085
LV-GLS, %	−20.9 ± 2.3	−18.8 ± 2.0	0.009
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/s	0.58 (0.41–0.87)	0.61 (0.40–0.76)	0.889
TVA, m/s	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/s	0.15 ± 0.05	0.15 ± 0.03	0.759
TVAa, m/s	0.15 ± 0.03	0.15 ± 0.04	1.000
TVSa, m/s	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
RV-GLS, %	−22.9 ± 3.6	−21.2 ± 3.0	0.040

Data are expressed as mean ± standard deviation for normally distributed variables or median (range) for non-normal variables.
LAV: left atrial end-systolic volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LV-GLS: left ventricular global longitudinal strain; 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; MVA(s-l): 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(s-l): average of septal and lateral early diastolic mitral annular velocity; MVE/Ea(s-l): ratio of the early diastolic transmitral flow velocity to the average of septal and lateral early diastolic mitral annular velocity; MVSa(s-l): average of septal and lateral systolic mitral annular velocity; RAA: right atrial end-systolic area; RVbas: basal right ventricular diameter; RVEDA: right ventricular end-diastolic area; RVFAC: right ventricular fractional area change; RV-GLS: right ventricular global longitudinal strain; 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

(MVE/A), RV fractional area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE). The absolute values of both LV-GLS and RV-GLS decreased after the race. However, both ventricular strains remained within normal range after the race for the vast majority of athletes (85%). When MVE/A was indexed for RR interval, there was no change after exercise ($p = 0.358$). The percentage changes of all these parameters did not differ between males and females (Supplementary Material Table 1 online).

Table 3. Comparisons of biochemical parameters between baseline and after exercise.

	Baseline	After exercise	*p* value
AST, IU/L	23 ± 6	1134 ± 775	<0.001
ALT, IU/L	17 ± 7	220 ± 133	<0.001
γGT, IU/L	13 (10–34)	11 (6–29)	0.002
TBL, mg/dL	0.67 ± 0.59	1.55 ± 0.89	<0.001
DBL, mg/dL	0.26 ± 0.15	0.45 ± 0.17	<0.001
CK, IU/L	141 (65–273)	31,576 (6195–138,870)	0.001
Cre, mg/dL	0.84 ± 0.17	0.97 ± 0.16	0.001
CRP, mg/dL	2.5 ± 1.3	66.3 ± 33.1	<0.001

Data are expressed as mean±standard deviation for normally distributed variables or median (range) for non-normal variables.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; Cre: creatinine,; CRP: C-reactive protein; DBL: direct bilirubin; γGT: gamma glutamyl transpeptidase; TBL: total bilirubin

The same pattern of changes for the above-mentioned parameters was found for the subpopulation of athletes with blood measurements (Supplementary Table 2).

With regard to echocardiographic measurements, 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 (95% CI (0.82-0.94)) respectively, suggesting excellent intra-observer and good to excellent inter-observer reliability. Additionally, for LV wall thickness, the mean difference in measurements between the two investigators was 0.01 ± 0.05 cm, which was much smaller compared with the change in LV wall thickness between baseline and after the exercise.

Biochemical parameters. The race resulted in elevation of the serum levels of aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, creatine kinase, creatinine and C-reactive protein (CRP), while there was a decrease in gamma-glutamyl transpeptidase (Table 3).

Both serum TnI ($p = 0.028$) and NT-proBNP ($p = 0.018$) levels were elevated after the race compared with baseline. Post-exercise TnI was 115 ± 81 ng/L and eight of the 13 measured values were above the upper limit of normal. Post-exercise NT-proBNP was 1573 ± 985 pg/mL and all the measured values were above the upper limit of normal.

Correlation analysis for exercise-induced changes

Left heart. The percentage change of LVIDd correlated positively with percentage change of body weight ($r = 0.488$, $p = 0.018$) and negatively with percentage change of HR ($r = -0.453$, $p = 0.026$).

The change in SWT correlated negatively with training volume ($r = -0.583$, $p = 0.006$), pre-exercise SWT ($r = -0.475$, $p = 0.019$) and percentage change of body weight ($r = -0.416$, $p = 0.049$). The athletes with the most favourable post-exercise responses with regard to the change in SWT, defined as change in SWT ≤ 0.2 cm, corresponding to change in LV wall thickness ≤0.1 cm, were characterized by: 1) training volume >120 km/week (Figure 1(a)), 2) pre-exercise SWT ≥2.0 cm, corresponding to a pre-exercise LV wall thickness ≥1.0 cm (Figure 1(b)) and 3) percentage change of body weight ≥ −3.0% (Figure 1(c)).

Percentage change of MVE/A correlated positively with the percentage changes of body weight ($r = 0.427$, $p = 0.047$) and LVEDV ($r = 0.415$, $p = 0.039$) and negatively with percentage change of HR ($r = -0.513$, $p = 0.009$), but did not correlate with the percentage changes of MVE/Ea(s-l) or pulmonary artery systolic pressure (PASP).

Percentage change of PASP correlated positively with the percentage change of MVE/Ea(s-l) ($r = 0.612$, $p = 0.012$), which in turn correlated positively with the percentage change of central mean BP (MBPc) ($r = 0.527$, $p = 0.025$).

Right heart. Percentage change of RVEDA correlated positively with the percentage changes of basal RV diameter (RVbas) ($r = 0.773$, $p < 0.001$) and mid-cavity RV diameter (RVmid) ($r = 0.774$, $p < 0.001$), but not with the percentage change of longitudinal RV diameter (RVlon). Post-exercise PASP correlated positively with the percentage changes of RVbas ($r = 0.511$, $p = 0.018$) and RVmid ($r = 0.466$, $p = 0.025$), but not with the percentage changes of RVlon, proximal portion of RV outflow tract (RVOTprox) and right atrial end-systolic area (RAA). Post-exercise RVlon correlated positively with post-exercise body surface area ($r = 0.508$, $p = 0.013$).

Percentage change of RVFAC did not correlate with post-exercise PASP. Percentage change of TAPSE correlated positively with training volume ($r = 0.413$, $p = 0.040$), finishing time ($r = 0.575$, $p = 0.003$) and percentage change of body weight ($r = 0.497$, $p = 0.012$) and negatively with percentage change of ratio of early diastolic transtricuspid flow velocity to early diastolic tricuspid annular velocity (TVE/Ea; $r = -0.786$, $p = 0.036$) and post-exercise PASP ($r = -0.659$, $p = 0.001$). The athletes with the most favourable post-exercise responses with regard to the percentage change of TAPSE were characterized by percentage change of body weight ≥ −3.0% (Figure 1(d)). Percentage change of RV-GLS correlated negatively with finishing time ($r = -0.510$, $p = 0.010$) (i.e. deterioration of RV strain for faster runners). We performed backward linear regression analysis with percentage change of TAPSE as dependent variable and training volume, finishing time, post-exercise PASP and percentage change

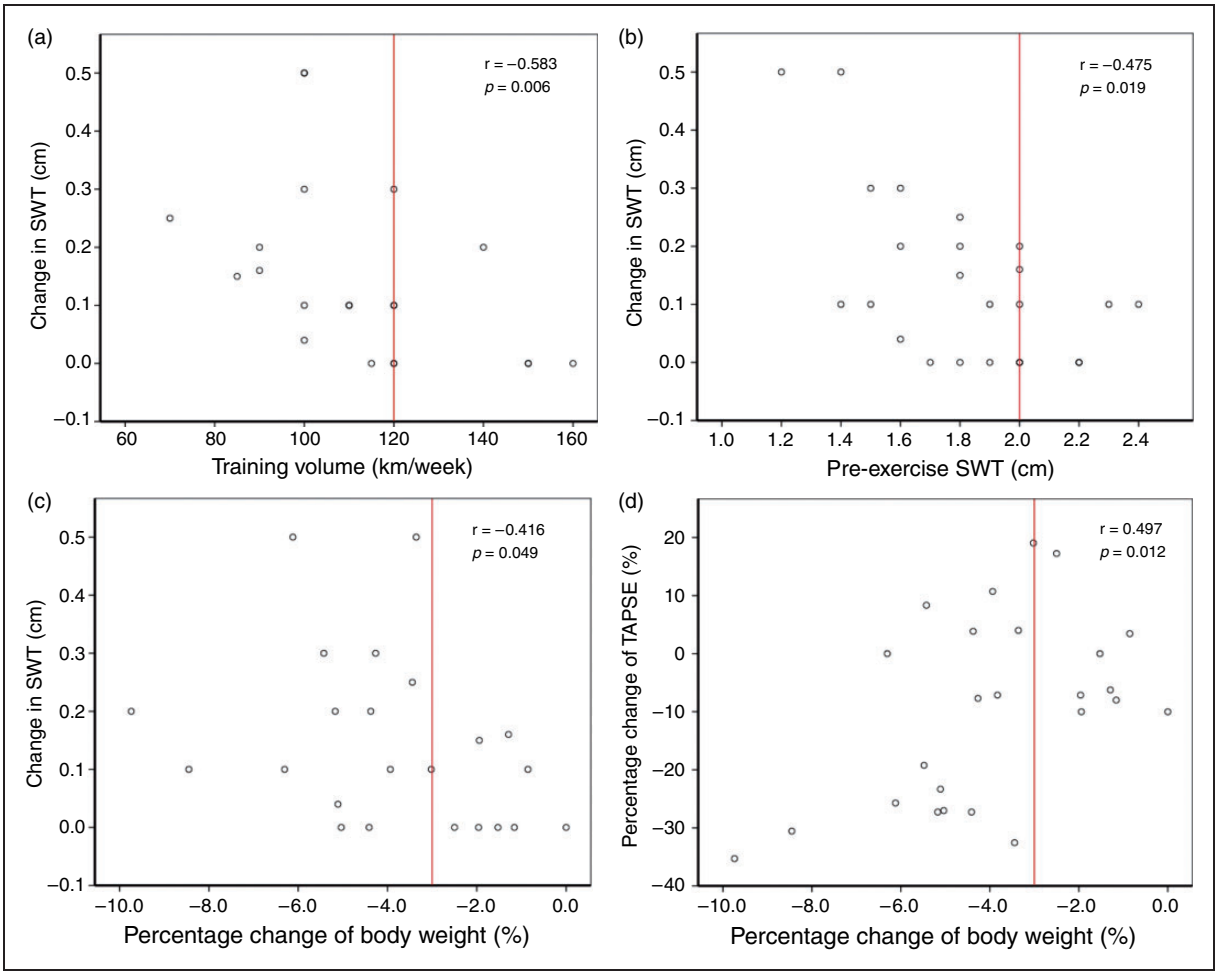

Figure 1. The relationships of the change in the sum of left ventricular end-diastolic interventricular septum thickness and posterior wall thickness (SWT) with training volume (a), pre-exercise SWT (b) and percentage change of body weight (c). The relationship of the percentage change of the tricuspid annular plane systolic excursion (TAPSE) with the percentage change of body weight (d).

of body weight as independent variables. The final model (adjusted $R^2 = 0.640$, $p < 0.001$) included only PASP ($\beta = -0.621$, $p < 0.001$) and percentage change of body weight ($\beta = 0.356$, $p = 0.024$).

Biochemical parameters. Post-exercise TnI correlated negatively with percentage change of body weight ($r = -0.601$, $p = 0.039$), but was not associated with percentage change of creatinine or any studied parameter of cardiac structure or function.

Post-exercise NT-proBNP correlated positively with post-exercise PASP ($r = 0.797$, $p = 0.002$), post-exercise CRP ($r = 0.725$, $p = 0.008$) and percentage change of direct bilirubin ($r = 0.720$, $p = 0.008$) and negatively with finishing time ($r = -0.874$, $p < 0.001$). There was no significant association between post-exercise NT-proBNP and percentage change of creatinine ($r = 0.423$, $p = 0.150$). We performed backward linear regression analysis with percentage change of NT-proBNP as dependent variable and post-exercise PASP, CRP, percentage change of direct bilirubin and finishing time as independent variables. The final model (adjusted $R^2 = 0.553$, $p = 0.003$) included only PASP ($\beta = 0.771$, $p = 0.003$). Post-exercise NT-proBNP correlated positively with percentage changes of RVbas ($r = 0.582$, $p = 0.037$) and RVmid ($r = 0.618$, $p = 0.043$) and negatively with percentage change of TAPSE ($r = -0.720$, $p = 0.008$), but did not correlate with percentage changes of RVlon, RVOTprox, RAA and RVFAC, as well as with pre-exercise RV end-diastolic diameters.

Percentage change of direct bilirubin was increased in the athletes with percentage change of weight loss below the median ($p = 0.022$) (i.e. marker of liver hypoperfusion), but did not correlate with post-exercise PASP, end-expiratory inferior vena cava or respiratory variation in inferior vena cava (i.e. markers of liver congestion).

Discussion

The key findings of the present study include: 1) there was an increase in LV wall thickness after the race that was less pronounced in athletes with increased pre-exercise LV wall thickness, higher training volume and less severe dehydration; 2) there were minimal dilatation and alteration in systolic function of RV; 3) the post-exercise increase in circulating NT-proBNP was associated with PASP (i.e. an index of RV afterload), as well as with dilatation and alteration in systolic function of the RV inflow segments; 4) the post-exercise elevation of serum TnI levels did not correlate with any cardiac parameter and was greater in the athletes with more severe dehydration.

LV changes

The current study demonstrated that LV end-diastolic dimensions decreased after the race and this reduction was correlated with the severity of dehydration and

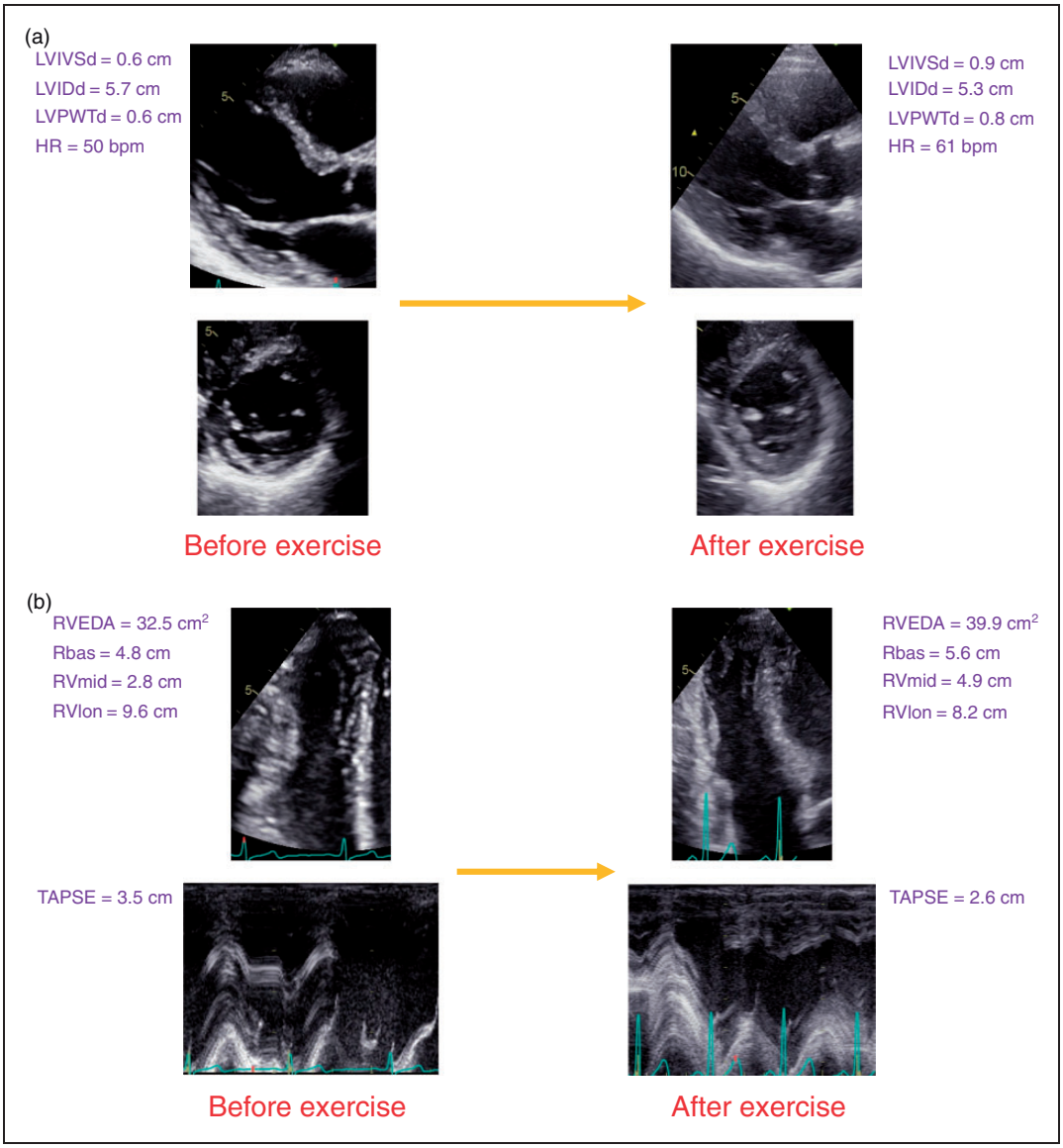

Figure 2. Characteristic example of an athlete with: (a) post-exercise increases of both left ventricular end-diastolic interventricular septum thickness (LVIVSd) and posterior wall thickness (LVPWTd) and decrease in left ventricular end-diastolic internal diameter (LVIDd) compared with baseline values; (b) increase in right ventricular dimensions and decrease in tricuspid annular plane systolic excursion (TAPSE) after exercise compared with baseline values.
HR: heart rate; RVbas: basal right ventricular diameter; RVEDA: right ventricular end-diastolic area; RVlon: right ventricular longitudinal diameter; RVmid: right ventricular mid-cavity diameter

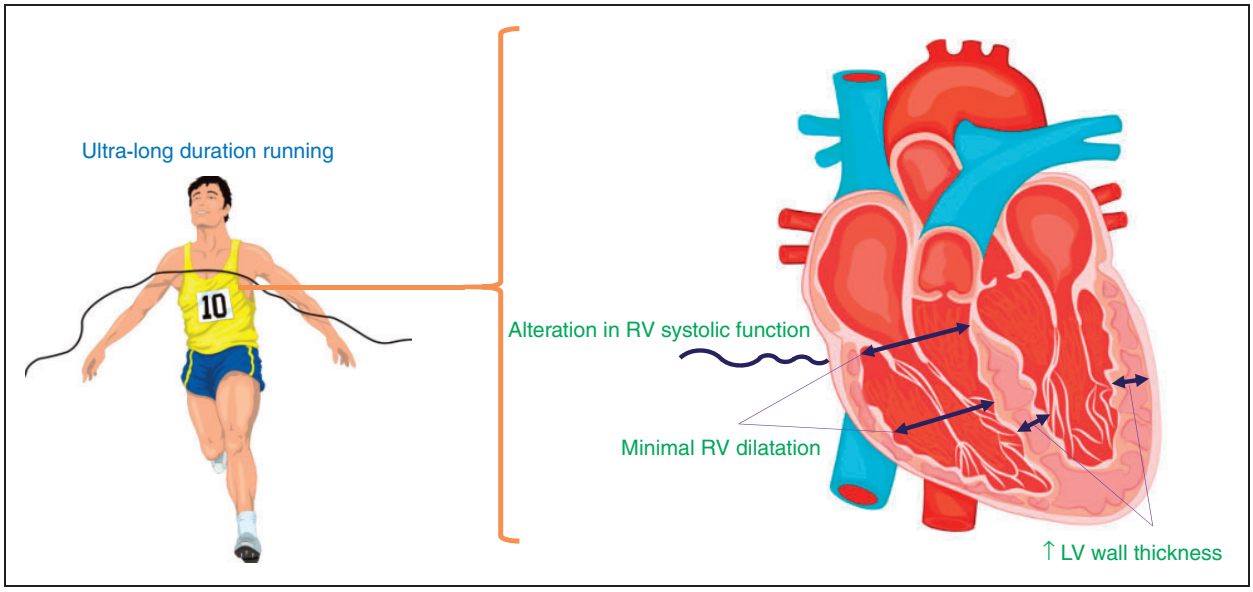

Figure 3. The main cardiac effects of ultra-long duration running. ↑: increase.
LV: left ventricle; RV: right ventricle

upregulation of post-exercise HR (Figure 2(a)). In this respect, post-exercise dehydration appears to result in underfilling of LV and post-exercise increase in HR possibly limits the diastolic period for adequate LV diastolic filling. Both of these mechanisms may lead to the post-exercise decrease in LV preload.

We found that LV wall thickness was increased immediately after the race compared with baseline values (Figure 2(a)). One potential explanation for this finding could be the development of myocardial oedema, as indicated by the study by Gaudreault et al., who reported the presence of myocardial oedema after marathon running with the aid of cardiac magnetic resonance (CMR) imaging performed within 48 h after finishing the race.[13] However, the study by Gaudreault et al. reported localized myocardial oedema accompanied by areas of segmental systolic LV dysfunction.[13] Whether these regional myocardial alterations occurred in the present study cannot be answered, since we did not perform cardiac MRI. Considering the previously reported effect of increased LV wall thickness to decrease longitudinal displacement of LV and thus LV-GLS, the post-exercise mild decrease in LV-GLS that was found in the current study may be explained at least in part by the accompanied increase in LV wall thickness based on geometrical considerations, though a mild impairment of intrinsic LV myocardial function cannot be totally excluded.[14,15] The present study is the first to demonstrate increased LV wall thickness immediately after the termination of ultra-long duration exercise. Echocardiographically measured LV wall thickness was reported not to change after finishing an Ironman triathlon.[16] The minimum duration of endurance exercise that induces an increase in LV wall thickness remains to be elucidated. Moreover, we found that the athletes that experienced the smallest increases in LV wall thickness were the more well-trained (especially >120 km/week) and with increased pre-exercise LV wall thickness (especially ≥ 1.0 cm), implying that these athletic characteristics may be protective for the occurrence of exercise-induced increase in LV wall thickness.

The present study showed that post-exercise reduction of MVE/A was mediated first by the decreased preload, due to dehydration, and second by the increased post-exercise HR, which limits the diastolic period for adequate LV diastolic filling. Consistently, the decreased MVE/A after finishing marathon running has been previously reported to increase during passive leg elevation, which results in preload augmentation.[3] Therefore, post-exercise decrease in MVE/A appears not to represent a sign of intrinsic LV myocardial dysfunction. In this respect, the increase in LV wall thickness in this study was not accompanied by any impairment of LV diastolic function.

We demonstrated that the percentage change of MBPc, as an estimate of LV afterload, was positively associated with the percentage change of LV filling pressures, suggesting the important role of LV afterload to determine the exercise-induced cardiac responses. Consistently, Warner et al. reported that functional capacity of well-controlled hypertensive patients increased after losartan treatment, attributed to the blunted hypertensive response to exercise.[17]

Further studies are needed to confirm the effects of MBPc on cardiac function in various exercise settings. To our knowledge, the impact of altered LV afterload on cardiac function after ultra-endurance exercise has not been investigated before.

RV changes

The current study showed for the first time that the post-exercise increase in RV dimensions and reduction of RV systolic function affected mainly the basal and mid portions of the RV and were determined by the altered exercise-related RV afterload, as estimated by PASP (Figure 2(b) and 2(c)). This regional pattern of acute minor dilatation and alteration in systolic function of the RV may be analogous with the relevant RV changes after acute pulmonary embolism, the so-called McConnell's sign.[18] Indeed, the dominant role of altered RV strain to mediate these changes was suggested by the strong relationship of post-exercise NT-proBNP levels with PASP (i.e. the cause of altered RV strain), as well as with percentage changes of RVbas, RVmid and TAPSE (i.e. the results of altered RV strain).[19] Consistently, La Gerche et al. found that the increase in NT-proBNP correlated with the decrease in RV ejection fraction after ultra-endurance exercise.[20] However, there was no association between post-exercise NT-proBNP levels and RV end-diastolic diameters, suggesting that RV preload may not have an important role in determining post-exercise NT-proBNP levels. Moreover, we found that the exercise-related elevation of circulating NT-proBNP may have been caused mainly by the altered RV afterload, secondly by the nature of NT-proBNP to be an acute phase reactant, as suggested by its relationship with CRP, and thirdly by the exercise-related liver hypoperfusion accompanied with decreased hepatic clearance of NT-proBNP, as implied by its association with direct bilirubin.[19–25] Nevertheless, the absence of association of post-exercise circulating NT-proBNP with percentage change of creatinine suggests that the post-exercise decline in renal function may not have a significant role in the post-exercise elevation of serum NT-proBNP levels.

With regard to the exercise-related acute alteration in basal RV systolic function, as estimated by TAPSE, the present study demonstrated that the main causes were not only the altered RV afterload, but also hypovolaemia, possibly due to the inadequate filling of the dilated RV. Taking into account first that RV myocardial strain is influenced by RV afterload and second that RV-GLS refers to the systolic function of not only RV free wall but also interventricular septum, the mild decrease of RV-GLS in the current study may not represent intrinsic RV myocardial dysfunction.[6,26] Further well-designed studies are needed to elucidate whether there is some degree of intrinsic RV myocardial dysfunction after ultra-long duration exercise to contribute to the alteration in RV systolic function, apart from the mechanisms of altered RV afterload and RV underfilling. The more favourable acute responses of RV systolic function after ultra-long duration exercise were noticed in the athletes with higher training volume. This finding is in line with the results from Neilan et al. regarding marathon running.[2] Interestingly, the relationship of post-exercise RVlon with body surface area, as an estimate of the total tissue mass perfused during the race, implies that the enlargement of the RV in the longitudinal direction may have been caused by the volume overload during exercise.[27] The reversibility, as well as the potential long-term consequences of the enlargement and alteration in systolic function of RV after ultra-long duration exercise, remain to be investigated.

Biomarkers

The present study demonstrated that ultra-long duration exercise resulted in elevation of serum TnI levels, which were not correlated with any cardiac parameter. Hence, this increase in circulating TnI may represent release of troponin from the myocardial cytosolic pool, rather than true myocardial necrosis.[28] This process was possibly caused, at least in part, by the dehydration-induced increase in cell membrane permeability, as indicated by the higher elevation of circulating TnI in the athletes with greater weight loss.[29] The absence of significant association between post-exercise TnI and percentage change of creatinine in our study implies that the reduced renal clearance of TnI due to the post-exercise deterioration of renal function may not substantially contribute to the post-exercise elevation of serum TnI levels. No previous study has addressed these issues.

Study strengths and limitations

Strengths of this study include first the fact that the running distance of the race was the longest among the studies evaluating the cardiac changes after continuous ultra-long duration exercise.[30] Furthermore, the present study assessed the athletes after the completion of continuous exercise. However, studies that evaluated athletes participating in ultra-long duration races with interrupted exercise due to intermediate rests for some hours, including a few hours' sleep, represent a different kind of exercise stress possibly less challenging to the heart and with attenuated impact of dehydration.[31] Third, the current study had the largest study population and the greatest number of females of this kind of

study. Fourth, we assessed myocardial injury for the first time through the use of high sensitivity cardiac TnI assay, as recommended by the relevant guidelines of the European Society of Cardiology.[28] Specifically, highly sensitive cardiac troponin assays can detect even small increases in serum troponin levels, as opposed to the conventional troponin assays that were used in previous studies of ultra-endurance exercise, with which all the pre-exercise values and the majority of post-exercise values were below the lower limit of detection.[2,28] Regarding the type of measured troponin, increases in cardiac TnI values have not been reported to occur following injury of non-cardiac tissues, while exercise-induced injured skeletal muscle expresses proteins that can be detected by cardiac troponin T assays.[28] Finally, we performed for the first time evaluation of the cardiac effects of post-exercise LV afterload, through the combined application of echocardiography and measurement of central arterial BP.

The results of our study should be interpreted in light of some limitations. First, males predominated over females. However, we demonstrated that the exercise-induced cardiac alterations were similar between males and females. Second, it was not feasible to obtain blood samples from all of the studied participants due to non-compliance. Despite that, the changes of the echocardiographic parameters in the subpopulation of athletes with blood measurements followed the same pattern with the whole study population. Third, we did not perform serial post-exercise echocardiographic examinations to evaluate the reversibility of the exercise-induced cardiac changes. Finally, we did not use CMR imaging to evaluate whether exercise-induced myocardial oedema developed, as the use of CMR soon after the termination of exercise was not practically feasible. In this respect, the results of the present study can be considered only as hypothesis generating and further well-designed studies are needed to investigate the exact pathophysiological mechanism underlying the ultra-long duration exercise-induced increase in LV wall thickness.

Conclusions

The present study demonstrated that the main cardiac changes after ultra-long duration exercise were the decrease in LV end-diastolic dimensions and increase in LV wall thickness, as well as the minimal dilatation and alteration in systolic function of the RV, possibly due to the altered exercise-related RV afterload (Figure 3). Although the acute cardiac changes after ultra-long duration exercise did not correlate with serum TnI levels, indicating the absence of true myocardial necrosis, further studies are needed to clarify whether they predispose to any long-term cardiac sequelae.

Author contribution

All authors contributed to the conception and design of the work. All authors contributed to the acquisition, analysis and interpretation of data for the work. All authors drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Supplemental material

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References

1. Knechtle B and Nikolaidis PT. Physiology and pathophysiology in ultra-marathon running. *Front Physiol* 2018; 9: 634.
2. Neilan TG, Januzzi JL, Lee-Lewandrowski E, et al. Myocardial injury and ventricular dysfunction related to training levels among nonelite participants in the Boston marathon. *Circulation* 2006; 114: 2325–2333.
3. Hart E, Shave R, Middleton N, et al. Effect of preload augmentation on pulsed wave and tissue Doppler echocardiographic indices of diastolic function after a marathon. *J Am Soc Echocardiogr* 2007; 20: 1393–1399.
4. Kim YJ, Shin YO, Lee JB, et al. The effects of running a 308 km ultra-marathon on cardiac markers. *Eur J Sport Sci* 2014; 14(Suppl. 1): S92–S97.
5. McDermott BP, Anderson SA, Armstrong LE, et al. National Athletic Trainers' Association Position Statement: Fluid replacement for the physically active. *J Athl Train* 2017; 52: 877–895.
6. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39.e14.
7. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; 29: 277–314.
8. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the

Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713.
9. Cavarretta E, Maffessanti F, Sperandii F, et al. Reference values of left heart echocardiographic dimensions and mass in male peri-pubertal athletes. *Eur J Prev Cardiol* 2018; 25: 1204–1215.
10. Paolisso G, Galderisi M, Tagliamonte MR, et al. Myocardial wall thickness and left ventricular geometry in hypertensives. Relationship with insulin. *Am J Hypertens* 1997; 10: 1250–1256.
11. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: Consensus document of the EACVI/ASE/ Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16: 1–11.
12. Bjerring AW, Landgraff HE, Leirstein S, et al. Morphological changes and myocardial function assessed by traditional and novel echocardiographic methods in preadolescent athlete's heart. *Eur J Prev Cardiol* 2018; 25: 1000–1007.
13. Gaudreault V, Tizon-Marcos H, Poirier P, et al. Transient myocardial tissue and function changes during a marathon in less fit marathon runners. *Can J Cardiol* 2013; 29: 1269–1276.
14. López-Candales A. Automated functional imaging for assessment of left ventricular mechanics in the presence of left ventricular hypertrophy. *Echocardiography* 2014; 31: 605–614.
15. Soufi Taleb Bendiab N, Meziane-Tani A, Ouabdesselam S, et al. Factors associated with global longitudinal strain decline in hypertensive patients with normal left ventricular ejection fraction. *Eur J Prev Cardiol* 2017; 24: 1463–1472.
16. Whyte GP, George K, Sharma S, et al. Cardiac fatigue following prolonged endurance exercise of differing distances. *Med Sci Sports Exerc* 2000; 32: 1067–1072.
17. Warner JG Jr, Metzger DC, Kitzman DW, et al. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol* 1999; 33: 1567–1572.
18. Patra S, Math RS, Shankarappa RK, et al. McConnell's sign: An early and specific indicator of acute pulmonary embolism. *BMJ Case Rep* 2014; 2014: bcr2013200799.
19. Hori Y, Tsubaki M, Katou A, et al. Evaluation of NT-pro BNP and CT-ANP as markers of concentric hypertrophy in dogs with a model of compensated aortic stenosis. *J Vet Intern Med* 2008; 22: 1118–1123.
20. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J* 2012; 33: 998–1006.
21. Mrakic-Sposta S, Gussoni M, Moretti S, et al. Effects of mountain ultra-marathon running on ROS production and oxidative damage by micro-invasive analytic techniques. *PLoS One* 2015; 10: e0141780.
22. Jensen J, Ma LP, Fu ML, et al. Inflammation increases NT-proBNP and the NT-proBNP/BNP ratio. *Clin Res Cardiol* 2010; 99: 445–452.
23. Palmer SC, Yandle TG, Nicholls MG, et al. Regional clearance of amino-terminal pro-brain natriuretic peptide from human plasma. *Eur J Heart Fail* 2009; 11: 832–839.
24. Henrion J, Schapira M, Luwaert R, et al. Hypoxic hepatitis: Clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore)* 2003; 82: 392–406.
25. Bartzeliotou AI, Margeli AP, Tsironi M, et al. Circulating levels of adhesion molecules and markers of endothelial activation in acute inflammation induced by prolonged brisk exercise. *Clin Biochem* 2007; 40: 765–770.
26. Wright L, Negishi K, Dwyer N, et al. Afterload dependence of right ventricular myocardial strain. *J Am Soc Echocardiogr* 2017; 30: 676–684.e1.
27. Jegier W, Sekelj P, Auld PA, et al. The relation between cardiac output and body size. *Br Heart J* 1963; 25: 425–430.
28. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019; 40: 237–269.
29. Rapoport AI, Khrustaleva GM, Chamanis Gia, et al. Yeast anhydrobiosis: Permeability of the cytoplasmic membrane. *Mikrobiologiia* 1995; 64: 275–278.
30. Scott JM, Esch BT, Shave R, et al. Cardiovascular consequences of completing a 160-km ultramarathon. *Med Sci Sports Exerc* 2009; 41: 26–34.
31. Maufrais C, Millet GP, Schuster I, et al. Progressive and biphasic cardiac responses during extreme mountain ultramarathon. *Am J Physiol Heart Circ Physiol* 2016; 310: H1340–H1348.