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Cardiac troponin elevations in marathon runners. Role of coronary atherosclerosis and skeletal muscle injury. The MaraCat Study

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ABSTRACT

Background: Marathon running is associated with transient risk of sudden cardiac death and high cardiac troponin levels are common after race. There is limited data whether coronary atherosclerosis or skeletal muscle injury are related to troponin release caused by strenuous exercise. We aimed to assess whether coronary artery calcification (CAC), plaque vulnerability or skeletal muscle injury relate to cardiac troponin T (cTnT) elevations after marathon race.

Methods: In this observational study, 40 male runners participating in Paavo Nurmi 2018 Marathon were recruited with an open email invitation to evaluate the prevalence of post-race cTnT elevations and their predictors. In addition to baseline and post-race laboratory investigations, 28 runners aged >44 years underwent CAC measurement with computed tomography. Coronary plaque vulnerability was evaluated by free pregnancy-associated plasma protein A (fPAPP-A) concentration and skeletal muscle injury by skeletal troponin I (skTnI) measurement.

Results: The post-marathon cTnT concentrations rose above the normal reference limit in 38 (95%) participants. A 10-fold increase in skTnI concentrations was observed and elevated post-race values were seen in all participants. The correlation between the post-race cTnT and post-race skTnI ($r_s = -0.26$, $p = 0.11$) was non-significant. CAC was detected (Agatston score > 0) in 15 (53.6%) participants, with a median score of 2.0 (interquartile range [IQR] 80). There was no correlation between cTnT with CAC score or post-race fPAPP-A levels.

Conclusions: Asymptomatic cardiac troponin elevations are common after prolonged strenuous exercise, but are not related to markers of coronary atherosclerosis, plaque vulnerability or skeletal muscle injury.

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1. Introduction

Cardiac troponins are highly sensitive and specific biomarkers for cardiac injury and are a key element in the diagnosis of acute coronary syndromes [1]. Numerous studies have demonstrated marked increase in troponins after prolonged endurance exercise in the absence of clinical symptoms of a myocardial infarction [2–5]. Strenuous physical exercise like marathon running is also associated with transient risk of sudden cardiac death and myocardial infarction [6] and active endurance training seems to be associated with coronary atherosclerosis [7]. There is, however, limited data whether coronary atherosclerosis or markers of plaque vulnerability are related to cardiac troponin release after strenuous exercise. Secondly, cardiac troponins may be present in the skeletal muscle of patients with skeletal myopathy, and cross-reaction of the immunoassays with skeletal muscle troponin is possible [8,9]. Whether these observations are relevant to current high-sensitive cardiac troponin measurements after strenuous endurance exercise is presently not known. Skeletal troponin I (skTnI) is a unique protein of skeletal muscle and a specific marker of muscle damage released after tissue injury [10,11].

Therefore, the aim of this study was to identify independent predictors for high-sensitivity cardiac troponin T (cTnT) elevations after a marathon in male runners. The novel approach of our study is that we examined the potential roles of coronary atherosclerosis, plaque vulnerability and muscle injury assessed by skTnI in the exercise-induced cTnT release.

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2. Methods

A total of 43 runners (age < 35 [$n = 12$] years or > 44 years [$n = 31$]) participating in the 2018 Paavo Nurmi Marathon in Turku were initially recruited to the MaraCat Study (ClinicalTrials.gov Identifier: NCT03738631) with an open email invitation. Three runners did not, however, participate in the race because of acute illness or could not complete the race and give blood samples. All participants completed an online questionnaire on subject characteristics, including daily physical activity, marathon experience (e.g. training history, completed marathons and the average weekly running distances in the preceding 3 months), medical history and medication use.

The study protocol included two visits. The post-race visit (within 30 min after finishing the marathon) included laboratory tests, a questionnaire about perceived exertion after the run (using the Borg scale), analgesic use, physical complaints and race-induced muscle soreness (scale 1–10) [12]. Data on maximum heart rate during the run was recorded from 29 runners wearing their own heart rate monitors (commercially available models by Polar and Garmin). Finish time (exercise duration) was provided by the official competition organizers.

A control visit was performed either on the day before the marathon or 2–4 weeks after the race with at least two weeks pause in long-distance running. Laboratory tests, echocardiography and an electrocardiogram were obtained after physical examination. Computed tomography was performed at Turku PET Centre, Turku University Hospital with a GE Discovery 690 MI PET/CT 128-slice CT/positron emission tomography device (GE Healthcare, Milwaukee, Wisconsin). Coronary artery calcium (CAC) scores were calculated using the Agatston method for each coronary artery [13]. Absence of CAC was defined as an Agatston score of 0 and presence of CAC as a score of 1 or greater [14].

Certified laboratory services by Turku University Hospital (TYKSLAB) took care of blood samples both after the race near the start/finish area and at control visit in the hospital. After centrifugation, serum was aliquoted, frozen and stored at −70 °C for later analysis. Analysis was performed on a single day using the same calibration and set-up to minimize variation.

cTnT was analyzed using a commercial high-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany). Determined by the manufacturer, the 99th percentile upper reference limit was 14 ng/l for the assay. Additionally, samples were analyzed with investigational in-house sandwich-type immunoassays at the Biotechnology unit at the University of Turku: skeletal muscle injury was assessed with skTnI assay (Limit of Detection, LoD, 1.2 ng/ml) (unpublished assay), cardiac troponin I (cTnI) with 3 + 1-type assay free from autoantibody induced interference and plaque vulnerability with free pregnancy-associated plasma protein A (fPAPP-A) assay (LoD 0.4 mIU/l) [15,16]. N-terminal pro-brain natriuretic peptide (NT-proBNP) was analyzed using electrochemiluminescence method (ECLIA). In the laboratory analysis, concentrations below the detection limit are set to concentration of zero.

All participants provided written informed consent. The study complies with Declaration of Helsinki as revised in 2002 and the study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland.

2.1. Statistical analysis

Continuous variables were reported as mean ± standard deviation when normally distributed, and as median [inter-quartile range (IQR)] if they were skewed unless stated otherwise. The normality of the data distribution was examined by the Shapiro-Wilk test. Statistical significance was assumed at a p value < 0.05. Categorical variables were described with absolute and relative (percentage) frequencies. Chi-squared test and Fisher's exact test were used for categorical variables as appropriate. For all variables with >0.5% missing data, the exact number of patients with missing data is marked in the table. Independent samples t-test and Mann–Whitney U test were used for univariate analysis. Control and post-race tests were compared with paired Student's t-test and Wilcoxon signed rank-test as appropriate. Correlation between continuous variables was estimated using the Spearman test. Linear regression analysis with backward selection was used to identify factors significantly relating to post-race cTnT levels. All predictors with a P value < 0.1 in univariate analysis were included in the final regression model. Statistical analysis was computed using SPSS version 25 statistical software (IBM SPSS Inc.).

3. Results

The baseline cTnT values were below the reference limit (<14 ng/l) in 39 (97.5%) participants. The post-marathon cTnT concentration rose above the reference limit in 38 (95%) participants. The median post-race cTnT was 41 ng/l [IQR 40] and the 95th percentile concentration 90 ng/l. None of the participants reported cardiac symptoms after the race.

The baseline concentrations of skTnI were almost 1000-fold higher than those of cTnT and a 10-fold rise in concentrations was observed during the race (Table 1). Post-race fPAPP-A was higher than baseline in 82.5% (n = 33) of participants and the post-race fPAPP-A concentration was above the detection level in all runners. Similarly, marathon caused a significant increase in all other measured laboratory parameters, except for hemoglobin. Among these, numerically largest was the increase in NT-proBNP with the maximum post-race value of 1250 ng/l (Table 1). Furthermore, post-race D-dimer concentrations rose above the normal reference range (<0.5 mg/l) in 42.5% (n = 17) participants.

CAC was detected in 15 (53.6%) of the 28 middle-aged participants with a median score of 2.0 (range 0–608; [IQR] 80). There was no correlation between CAC score and post-race cTnT ($r_s = -0.013$, $p = 0.95$). No association was found between post-race fPAPP-A levels and post-race cTnT ($r_s = -0.26$, $p = 0.11$) or CAC score ($r_s = -0.23$, $p = 0.24$), and the correlations between post-race cTnT concentration and post-race skTnI ($r_s = 0.25$, $p = 0.12$) was not significant.

Age correlated significantly with cTnT ($r_s = -0.54$, $p < 0.001$) concentrations after the run and remained the only significant predictor of elevated cTnT in the multivariate linear regression analysis (Table 2). Subjective exertion or self-reported muscle symptoms did not correlate with post-race cTnT or skTnI levels (Supplementary Table 1). Laboratory parameters suggestive of dehydration after the run (elevated creatinine, sodium and change in hemoglobin) showed no correlation with cTnT or skTnI concentrations (Table 2, Supplementary Table 1). The baseline characteristics, electrocardiographic and echocardiographic parameters and post-race laboratory data according to the median post-race cTnT level are presented in Table 3. Post-race cTnT was not related to post-race NT-proBNP level or any echocardiographic parameters.

Table 1
Baseline and post-marathon laboratory data in 40 participants.

Variable	Baseline	Post-race	p value
Hemoglobin, g/l	142 ± 0.95	146 ± 1.14	0.065
Potassium, mmol/l	3.87 ± 0.24	4.06 ± 0.42	0.008
Sodium, mmol/l	141 ± 1.88	144 ± 3.25	<0.001
Creatinine, μmol/l	91.6 ± 9.57	130 ± 29.8	<0.001
Creatine kinase total, U/l	158 [103−203]	376 [274–601]	<0.001
Creatine kinase subunit MB mass, μg/l	3.05 [2.00–4.65]	5.75 [4.95–8.50]	<0.001
cTnT, ng/l	7.00 [5.25–8.75]	41.0 [26.0–65.5]	<0.001
cTnI, ng/l	<2.9*	12.0 [4.30–21.9]	<0.001
skTnI, ng/ml	1.80 [0.00–4.05]	19.3 [10.3–31.5]	<0.001
D-Dimer, mg/l	0.00 [0.00–0.30]	0.3 [0.20–0.68]	<0.001
fPAPP-A, mIU/l	1.14 [0.86–1.44]	1.63 [1.31–1.92]	<0.001
NT-proBNP, ng/l	<50*	82.0 [<50–162]	<0.001

Values are mean ± standard deviation, median [inter-quartile range 25th–75th percentiles].
cTnI = cardiac troponin I; cTnT = high sensitivity cardiac troponin T; skTnI = skeletal troponin I; fPAPP-A = free pregnancy-associated plasma protein A; NT-proBNP = N-terminal pro b-type natriuretic peptide.
* Values under lower limit of detection.

Table 2
Correlations of clinical parameters with high-sensitivity cardiac troponin T (cTnT).

Univariate correlation of post-race cTnT with:	Spearman's r	*p* value
Age	−0.542	<0.001
Body mass index	−0.286	0.073
Years of active training	0.111	0.494
Completed marathons	−0.274	0.087
Running kilometers/week in the last 3 months	0.022	0.894
Maximum heart rate during race	0.541	0.003
Echocardiography		
LV end diastolic diameter	0.097	0.550
LV ejection fraction	−0.160	0.324
LV mass	0.009	0.961
Laboratory parameters		
ΔHemoglobin	−0.389	0.017
ΔCreatinine	0.070	0.668
ΔCreatine kinase subunit MB mass	0.312	0.050
ΔCreatine kinase, total	0.341	0.031
ΔSkeletal troponin I	0.292	0.068
ΔN-terminal proBNP	0.068	0.678
ΔfPAPP-A	0.078	0.633
ΔD-Dimer	0.042	0.795
Multivariate regression analysis	β	*p* value
Age	−4.049	<0.001

LV = left ventricular; proBNP = pro brain natriuretic peptide; fPAPP-A = free pregnancy-associated plasma protein A. Δ = change between baseline sample and post-race sample.

4. Discussion

Our study showed that the majority of marathon runners have post-race cTnT levels above the rule-in criteria for the diagnosis of acute myocardial injury and even myocardial infarction. Importantly, however, troponin release was not related to coronary atherosclerosis or release of fPAPP-A, a marker of plaque vulnerability. We observed a 10-fold increase in skTnI concentrations measured post-race, but the cTnT levels showed no relation to simultaneous rise in skTnI concentrations. Our comprehensive search for potential novel contributors to the exercise-induced cTnT release demonstrated that younger age was the only independent predictor of higher post-race cTnT levels.

Physical activity is known to protect from cardiovascular disease [17,18], but on the other hand strenuous physical activity like marathon running is associated with transient risk of sudden cardiac death and myocardial infarction [6]. Furthermore, recent studies have suggested that higher levels of physical activity are associated with higher prevalence of CAC [7]. Importantly, our present observations strongly support the view that exercise-induced cTnT elevations in middle-aged marathon runners are unlikely to be related to coronary atherosclerosis, since nearly half of them had no coronary calcium but still elevated post-marathon cTnT concentrations.

Pregnancy- associated plasma protein A (PAPP-A) is high-molecular weight zinc-binding metalloproteinase produced in high quantities in eroded and ruptured plaques, but only in small amounts in stable plaques [19] (see supplementary file for further reading on fPAPP-A). In patients with stable coronary artery disease it is associated with more widespread disease and in acute coronary syndromes with poor prognoses [15,20–22]. There also seems to be a link between CAC and increased levels of PAPP-A [23]. Although rigorous exercise may cause plaque rupture, our present findings show that exercise induced troponin release does not seem to reflect coronary plaque vulnerability assessed by fPAPP-A. In line with these findings, exercise induced fibrin turnover, i.e. increased thrombotic activity (assessed with D-dimer) does not seem to be connected with cardiac troponin elevations.

Several studies have described an elevation of cTnT in patients with skeletal myopathies [9]. It has been suggested that the cross-reactivity with skeletal TnT or cardiac TnT expression in skeletal muscle may contribute to elevated cTnT concentrations in patients with skeletal myopathies. These observations have given rise to hypothesis that skeletal muscle injury might contribute to the cTnT elevations after rigorous exercise. The other main focus of our study was to evaluate potential association between race-induced skeletal muscle injury assessed by novel skTnI measurements and cTnT release. We observed a significant increase in both of these laboratory markers, but the changes showed no significant concordance supporting the view that skeletal muscle strain or injury is not a major cause of exercise-induced cTnT rise.

Earlier studies have shown widely varying results on predictors of post-race cardiac troponin elevations; exercise duration, age, training status, exercise intensity, hydration status have been associated with

Table 3
Clinical characteristics, echocardiographic and post-race laboratory data according to median (40 ng/l) post-race cardiac troponin T (cTnT).

	cTnT < 40	cTnT ≥ 40	*p* value
	n = 18	n = 22	
Age, years	53.3 ± 12.2	44.0 ± 11.9	0.020
Body mass index, kg/m^2	24.0 [23.0–26.0]	23.0 [21.0–25.0]	0.251
Years of active training	12.0 [7.00–20.0]	17.0 [9.50–25.3]	0.190
Completed marathons	14 [3–45]	10 [3−30]	0.286
Weekly training kilometers, preceding 3 months	46.0 ± 19.6	48.4 ± 25.6	0.747
Race finish time, min	258 ± 37.7	240 ± 37.4	0.164
Muscle symptoms	7 (38.9)	11 (52.4)	0.523
Echocardiography			
LV end diastolic diameter, mm	50.0 [49.0–55.0]	52 [49.8–55.3]	0.321
LV ejection fraction	70.0 [67.0–71.0]	68 [65.0–72.5]	0.757
LV mass, g[#]	199 [179–241]	196 [164–250]	0.883
Laboratory results, post-race			
Hemoglobin, g/l	146 ± 12.3	145 ± 10.9	0.673
Creatinine, μmol/l	128 ± 27.7	131 ± 32.0	0.763
Sodium, mmol/l	144 ± 2.31	144 ± 3.89	0.661
Potassium, mmol/l	4.13 ± 0.48	4.01 ± 0.37	0.401
Creatine kinase total, U/l	336 [236–485]	399 [328–647]	0.163
Creatine kinase MB mass, μg/l	5.75 [4.43–7.43]	6.15 [5.05–9.60]	0.638
fPAPP-A, mIU/l	2.00 ± 0.92	1.46 ± 0.45	0.030
NT-proBNP, ng/l	91.0 [44.3–170]	76.5 [<50–134]	0.717
D-Dimer, mg/l	0.3 [0.275–0.50]	0.5 [0.15–0.80]	0.563
Skeletal troponin I, ng/ml	16.4 [7.60–30.3]	20.1 [16.7–34.9]	0.229
Cardiac troponin I, ng/l	4.40 [<2.9–9.80]	21.1 [11.5–29.7]	< 0.001

Values are n (%), mean ± standard deviation, median [inter-quartile range, 25th–75th percentiles].
LV = left ventricular; fPAPP-A = free pregnancy-associated plasma protein A; NT-proBNP = N-terminal pro brain natriuretic peptide.
[#] Data missing on 5 participants.

cardiac troponin rise in some of the reports, yet research on causes of troponin rise remain equivocal [3,5,24–29]. In line with some earlier studies, young age was the only significant predictor of post-race cTnT elevation. Our observations cannot provide explanation for this finding, although higher exercise intensity and exhaustion in younger athletes as reflected in higher maximum heart rate during the race may be contributing. On the other hand, dehydration status evaluated by laboratory parameters showed no association with troponin release.

The pathophysiology of exercise-induced cTnT elevations remains unclear. Proposed mechanisms for the rise include increased membrane permeability or cellular release of proteolytic troponin degradation products during exercise. Other potential candidates suggested include enhanced myocyte turnover, necrosis or apoptosis [2,3]. In this respect it was noteworthy that cardiac stress reflected in levels of natriuretic peptides was not associated with exercise-induced cTnT release. Similarly, the amount of stressed myocardial cells estimated by left ventricular mass had no relation to post-race cTnT.

4.1. Limitations

The small number runners and the heterogeneous nature of the group can be considered to be a limitation of this study. Secondly, we cannot be certain that the recruited cohort of runners is representative of the spectrum of all marathon runners. Thus as only male runners were recruited, the conclusions are not applicable to female runners. Coronary CT-scans were performed without contrast media in order to reduce the radiation dosage of study participants.

5. Conclusions

We found that cTnT levels increase in majority of runners after completing a marathon. There is a wide interindividual variation in the rise which cannot be reliably predicted by any individual or exercise characteristic and shows no association with markers of coronary atherosclerosis or skeletal muscle injury. Measuring high sensitivity cTnT is a cornerstone in the diagnostic workup of myocardial infarction and acute myocarditis. In view of the present and earlier findings, clinicians should be cautious when interpreting post-exercise cTnT levels without clinical symptoms and signs of myocardial ischemia or myocarditis.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.08.019.

Declaration of Competing Interest

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