Predictors of cardiac troponin release after a marathon

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Abstract

Objective: Exercise leads to an increase in cardiac troponin I (cTnI) in healthy, asymptomatic athletes after a marathon. Previous studies revealed single factors to relate to post-race cTnI levels. Integrating these factors into our study, we aimed to identify independent predictors for the exercise-induced cTnI release.

Design: Observational study.

Methods: Ninety-two participants participated in a marathon at a self-selected speed. Demographic data, health status, physical activity levels and marathon experience were obtained. Before and immediately after the marathon fluid intake was recorded, body mass changes were measured to determine fluid balance and venous blood was drawn for analysis of high-sensitive cTnI. Exercise intensity was examined by recording heart rate. We included age, participation in previous marathons, exercise duration, exercise intensity and hydration status (relative weight change) in our model as potential determinants to predict post-exercise cTnI level.

Results: cTnI increased significantly from 14±12 ng/L at baseline to 94±102 ng/L post-race, with 69% of the participants demonstrating cTnI levels above the clinical cut-off value (40 ng/L) for an acute myocardial infarction. Linear backward regression analysis identified younger age (β=-0.27) and longer exercise duration (β=0.23) as significant predictors of higher post-race cTnI levels (total r=0.31, $p<0.05$), but not participation in previous marathons, relative weight change and exercise intensity.

Conclusion: We found that cTnI levels significantly increased in a large heterogeneous group of athletes after completing a marathon. The magnitude of this response could only be partially explained, with a lower age and longer exercise duration being related to higher post-race cTnI levels.

Keywords: endurance exercise, cTnI, cTnT, cardiac biomarkers, athletes, cardiology

1. Introduction

The presence of the cardiac troponin I (cTnI) in blood is a highly sensitive and specific biomarker for cardiac injury and serves as a central marker in the diagnosis of acute coronary syndromes [1-3]. Many studies have demonstrated an increase in cTnI after prolonged endurance exercise, in the absence of clinical symptoms of a myocardial infarction **[4-6]**. Relatively little is known, however, about factors that may be associated with, and thus potentially predict, the degree of elevation in cTnI after strenuous running exercise. This important information may help clinicians and laboratories with the challenging interpretation of elevated cTnI levels in athletes.

Studies examining factors that relate to the exercise-induced increase in cTnI have predominantly included small and homogeneous groups of athletes. These studies demonstrated that subject characteristics (i.e. age and running experience) [7], exercise characteristics (i.e. exercise duration and intensity) [5, 8, 9], and hydration status [10] may relate to the exercise-induced increase in cTnI. These studies typically focused on a single factor only, thereby being unable to assess multiple parameters which may relate to post-race cTnI levels. As an exception to this rule, Fortescue *et al.* studied cardiac troponin responses in >400 Boston marathon runners [6]. Although age and running inexperience were identified as factors contributing to post-exercise increases in cTnT, they did not correct for important confounders, such as exercise intensity [11, 12]. Therefore, current studies provide only a limited insight into factors that could independently, or in combination, predict the magnitude of the exercise-induced increase in cTnI.

Therefore, the aim of this study was to identify parameters that predict the elevation in cTnI after a marathon in a large and heterogeneous group of athletes, and to explore the interaction of the identified parameters using regression analysis.The novel aspect of our study is that we examined the potential independent predictive capacity of parameters that have previously been related to the exercise-induced cTnI release. We hypothesized that exercise intensity, exercise duration, age, loss of body mass and running experience independently predict post-race cTnI levels.

2. Methods

A total of 92 moderately to highly trained runners (26 to 71 years of age) of the Eindhoven Marathon 2010 (The Netherlands) were recruited to the study. An advertisement was placed on the Eindhoven Marathons website to recruit participants. Before participation all participants provided written informed consent. The medical ethical committee of the Radboud University Nijmegen Medical Centre approved the study which was conducted in line with the Declaration of Helsinki.

All participants completed an online questionnaire about subject characteristics, including daily physical activity, marathon experience (e.g. previous completed marathons, personal record) and health (e.g. medical history and medication use). On the day of the marathon, participants underwent a series of measurements in our laboratory near the start/finish area. After demographic data were obtained a venous blood sample was taken. Heart rate was monitored continuously during the race using a chest band. Immediately after the marathon (<5 minutes), all measurements were repeated in the same order. Additionally, participants reported their fluid intake, use of analgesics, physical complaints and rate of perceived exertion.

Ten ml of blood was drawn from an antecubital vein before and immediately after the race. Whole venous blood was collected in serum-gel vacutainer tubes and allowed to clot for ~45 minutes. After centrifugation, serum was aliquoted, frozen, and stored at -80°C for later analysis. Analysis was performed on a single day using the same calibration and set-up to minimize variation. cTnI was analysed using a high-sensitive cTnI assay (Centaur TnI-Ultra, Siemens Healthcare Diagnostics, Breda, the Netherlands). The assay imprecision was 5.3% at 80 ng/L and 3.0% at 27200 ng/L, with a detection limit of 6 ng/L. A cTnI value of 40 ng/L was used as the clinical cut-off value for an acute myocardial infarction [13].

Heart rate during the marathon was measured in 70 athletes by using a 2-channel ECG chest band system (Polar Electro Oy, Kempele, Finland). Mean heart rate (HRmean) was determined as the average heart rate between the start and finish of the marathon. Maximal predicted heart rate

(HRmax=208–0.7*age) and exercise intensity (Exercise intensity=100*HRmean/HRmax) were calculated subsequently [14].

Finish time (exercise duration) was obtained using the ChampionChip time registration (ChampionChip®, MYLAPS, The Netherlands), out of which mean running speed was calculated (Speed=42.195/exercise duration).

After the marathon, participants completed a questionnaire indicating analgesic use and physical complaints. A visual analogue scale (0 - no effort; 10 - maximal effort) was used to measure rate of perceived exertion.

Participants were allowed to drink *ad libitum* during the race, whereas they registered the time and amount (standard sized cups, bottles, etc.) of their individual fluid intake after the finish.

Baseline and post-exercise body mass were assessed (Seca 888 Scale, Seca, Hamburg, Germany) to detect changes in hydration status. The relative change in body mass (in %) between the measurements was calculated, while dehydration was defined as a body mass loss of 2% or more [15, 16].

An additional 2 ml of blood was drawn at baseline and directly after finishing to determine plasma levels of sodium, hematocrit and haemoglobin (RapidLab® 1265, Siemens Healthcare Diagnostics Inc., Tarrytown, New York, U.S.A.). Hyponatraemia was defined as a sodium concentration ≤135mmol/L, whereas hypernatraemia was defined as a sodium concentration ≥145 mmol/L [17, 18].

All data were reported as mean±SD [range] unless stated otherwise and statistical significance was assumed at a p-value<0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The normality of the data distribution was examined by the Kolmogorov-Smirnov test. When data demonstrated a non-Gaussian distribution, natural logarithmic transformation was applied. Differences between pre- and post-race levels for continuously distributed data were tested for significance with a Paired Student's t-test. A backward stepwise linear regression analysis was used to identify factors that significantly relate to post-exercise cTnI-levels. Based on our hypothesis, we have included age, participation in previous marathons, exercise duration, exercise intensity and hydration status in our

model as potential determinants to predict post-exercise cTnI level. All predictors with a p-value<0.1 were retained in our final regression model.

3. Results

During the race mean wet bulb globe temperature (WBGT) was 18.8 °C, with a relative humidity of 52%. Of the 92 participants who started the race, 9 participants did not finish the race, because of exhaustion (n=2), acute knee problems (n=1), heat (n=1), dyspnoea (n=1), hip problems (n=1), headache (n=1) or another sport-related injury (n=2) and were therefore not included in the analysis. One participant was excluded afterwards because of missing multiple data-points. Therefore, 82 participants were included in the data analysis (17 females and 65 males). Demographic characteristics and the medical history of participants are presented in Table 1. On average, participants exercised 8.4±3.4 [3-18] hours per week and had completed 8±16 [0-102] marathons in the past, with a mean personal record (marathon PR) of 210±22 [166-256] minutes.

Post-race blood withdrawal failed in 2 participants. Ln-transformation was applied to the cTnI data set, as a non-Gaussian distribution was found. A significant exercise-induced increase in cTnI was observed, from 14±12 [0-49] ng/L at baseline to 94±102 [3–530] ng/L immediately after the finish (Figure 1, $p<0.001$). In total, 96 % of the participants demonstrated an increase in cTnI levels, with 55 participants (69%) exceeding the clinical cut-off value of 40 ng/L after completing the marathon (Table 2).

The average finish time of the marathon was 227±28 [169-307] minutes with a mean speed of 11.3±1.4 [8.2-15.0] km/hr. Participants demonstrated an mean heart rate of 161±9 [136-178] beats per minute, which is comparable to an exercise intensity of 91±5 [76-100] % of the maximal predicted heart rate. Participants scored the post-race rate of perceived exertion with 7±2 [1-10] (Table 2).

Between 12.00 PM and the start of the marathon (i.e. 11.00 AM), participants consumed 1311±848 [125-5330] ml fluid. During the race a total of 2406±1597 [300-6750] ml was consumed (Table 2), which is equal to 644±430 [70-1852] ml/h. As a measure of hydration status, changes in body mass were determined. Our population demonstrated a significant decrease in body mass after finishing the marathon ($p<0.001$). The average change in body mass was -1.8±0.9 kg [-4.3–+0.5 kg], with 52 participants (63%) meeting the criteria for being dehydrated (≥2% body mass loss). This was accompanied by a significant increase in plasma sodium concentration ($p<0.005$), whilst 18 athletes (22%) finished with a sodium level above 145 mmol/l (Table 2). No significant changes in haemoglobin concentration ($p=0.81$) and hematocrit levels ($p=0.88$) were observed between baseline and finish.

Backward linear regression analysis was performed in a dataset of 67 athletes in whom all parameters were successfully measured. We identified lower age (standardized $\beta=-0.265$, $p<0.05$) and longer exercise duration (standardized $\beta=0.230$, $p=0.066$) as independent predictors of higher post-race cTnI levels. Participation in previous marathons, exercise intensity and hydration status (relative body mass change) did not reach statistical significance and were therefore excluded by the regression analysis as contributors of post-race cTnI levels. Our prediction model had an overall $r=0.305$ ($p<0.05$), with an explained variance of 9.3%.

4. Discussion

This study confirmed the presence of exercise-induced release of cTnI in asymptomatic, healthy athletes competing in a marathon. In accordance with previous studies, cTnI levels increased significantly in our post-race blood sample, with 69% of the participants showing cTnI levels above the clinical cut-off point used for the diagnosis of an acute myocardial infarction [6, 7, 19]. The novel aspect of our study is that we examined the potential independent predictive capacity of parameters that have previously been related to the exercise-induced cTnI release. We determined that only younger age and longer exercise duration were significantly related to higher post-race cTnI levels.

Despite including a range of personal and exercise related factors that have previously been linked to post-exercise cTnI levels, we could only predict a small portion of the total variance in post-race cTnI levels.

Age and post-race cTnI levels demonstrated an inverse relationship. This observation is in line with other studies [6, 7, 11], but in contrast with a meta-analysis [20]. A potential relation may be explained by the exercise mode. Whilst the meta-analysis included data from running, cycling and triathlon studies [20], we focussed on marathon athletes only and included a heterogeneous group of participants in respect to age (n=82, 26-71 years). Indeed, another review that included marathon studies only, revealed a trend for a lower post-race troponin in older athletes [21]. A potential explanation for the age-dependent cTnI release might relate to the higher exercise intensity, and therefore the higher work of the heart muscle, in younger athletes [12]. Previous studies in small and homogenous cohorts reported that a higher exercise intensity is related to a larger exercise-induced cTnI increase [20, 22]. The variation in exercise intensity in our participants was, however, too small to support these findings (91 ± 5% of HRmax). However, additional analysis revealed a significant correlation between age and absolute heart rate ($r=-0.41$, $p<0.001$). Accordingly, the higher post-race cTnI levels in the younger athletes may be related to their higher absolute heart rate, which apparently results in a larger cardiac stress.

We also observed a positive relationship between exercise duration and post-race cTnI levels. Although this finding is in line with some of the recent field and laboratory studies [8, 9], others have reported an opposite relationship between post-race cTnI levels and exercise duration [20, 23]. These latter studies suggest that longer exercise duration is usually related to lower exercise intensity, and consequently to a lower increase in exercise induced cTnI levels [20, 24]. In our study, participants did not demonstrate a relation between finish time and exercise intensity ($r=0.11$, $p=0.36$). Given the homogeneous exercise intensity in our population, participants with longer exercise duration were exposed to a higher cardiac stress. The release of exercise-induced cTnI levels in participants with longer exercise duration may therefore relate to the higher cardiac work. However, it must be

emphasised that future studies should further examine whether troponin-release after exercise relates to absolute cardiac work, independent of exercise type.

Previous studies have identified various factors that may contribute to exercise-induced release of cTnI. Nonetheless, when including these factors in our statistical model, only exercise intensity and age were independently related to the exercise induced cTnI levels during this field-based study. In contrast with a previous study [10], we found no evidence for a relation between hydration status and post-race cTnI levels. Also, running experience (previous marathon participation) was not related to the magnitude of post-race cTnI release in our data set [6, 7, 12]. Whilst previous studies typically focused on a single factor, our statistical model corrected for the potential underlying interaction between predictors for post-race cTnI levels. For example, higher age is strongly related to running experience and exercise intensity. As a result, our study indicates that neither marathon (in)experience nor hydration status are related to the exercise-induced troponin elevations.

The aetiology of exercise-induced elevations in cardiac troponins remains a topic of debate. Six pathobiological mechanisms that explain the elevated cTnI levels have been proposed. First, elevated troponin levels could be related to an increased membrane permeability during exercise [25, 26], allowing unbound cardiac troponins in the cystolic pool (<10%) to enter the circulation [27]. Second, cellular release of proteolytic troponin degradation products may contribute to elevated cTnI levels [28], while membrane integrity is maintained [29]. Third, formation and active release of membranous blebs during temporary ischemia of cardiac cells may cause elevation of troponin concentrations [30]. Fourth, exercise may stimulate myocyte turnover, which subsequently could cause an elevation in cTnI levels [31]. Finally, myocyte necrosis and/or an elevated rate of apoptosis may contribute to the exercise-induced increase of cTnI. Whilst our study provides novel insight into factors that relate to the exercise-induced increase in cTnI, studies are warranted to directly examine the underlying mechanisms of elevated post-race troponin levels. Such information will reveal important information regarding the physiological *versus* pathological nature of troponin release in athletes after exercise.

We found that 96% of our marathon athletes demonstrated an increase in cTnI, while 69% of our population exceeded the clinical cut-off value. Since cTnI is recommended as a sensitive and specific marker for cardiac damage in the diagnosis of acute myocardial infarction [3, 32], caution should be taken when interpreting post-race cTnI levels. As our participants did not report any symptoms, it is likely that the elevated cTnI levels represent a physiological rather than a pathological response [33]. Clinicians should therefore take caution when examining troponin levels *without* clinical signs indicative of myocardial ischemia [34]. Our study provides some additional clinical insight as we found that lower age and longer exercise duration, albeit weakly, independent predict post-race cTnI levels. Such information is relevant for clinicians as it could improve medical decision making.

The predictive value of our statistical model is low (r^2=9.3%) and indicates that a large portion of the post-race cTnI levels cannot be explained. Therefore, one may suggest that responses are apparently irrespective of subject and exercise characteristics, and post-race cTnI levels may reflect a physiological response during exercise. Another limitation may be our single post-exercise assessment of cTnI, as previous observations reported a time-dependent change in cTnI after a marathon [35]. While we focused on post-race cTnI levels only, the relative contribution of predictors might differ during the time-course of exercise-induced cTnI-release.

5. Conclusion

In conclusion, we found that cTnI levels increased in a large heterogeneous group of athletes after completing a marathon. Including previously identified factors that relate to the exercise-induced release of cTnI into a statistical model, we found that the presence of this response was inversely correlated to the age of participants, whilst longer exercise duration also resulted in higher exercise induced troponin levels. Other factors that have previously been demonstrated to relate to post-exercise cTnI (i.e. exercise intensity, fluid status and marathon experience), were not related to post-marathon cTnI levels when correcting for potential interactions. Given the low explained variance of

9.3%, exercise-induced cTnI levels seem to be largely irrespective of individual and exercise characteristics.

Practical implications

- Cardiac troponin levels elevate in all athletes after running a marathon
- 69% of marathon athletes exceed the clinical threshold of cardiac troponin levels directly post-race.
- Age and exercise duration can partially predict the post-race cardiac troponin levels
- Exercise-induced cardiac troponin elevations are more likely to reflect a physiological rather than a pathological response.

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Figure legends

Figure 1: Frequency distribution of cardiac troponin I levels (cTnI) in 82 athletes directly after the finish of the Eindhoven marathon. The average cTnI level increased from **14±12 ng/L** at baseline to **94±102 ng/L** directly post-exercise. In addition 55 (69%) of our participants exceeded the clinical cut-off value for an acute myocardial infarction (represented by the dashed line).

Figure 1.

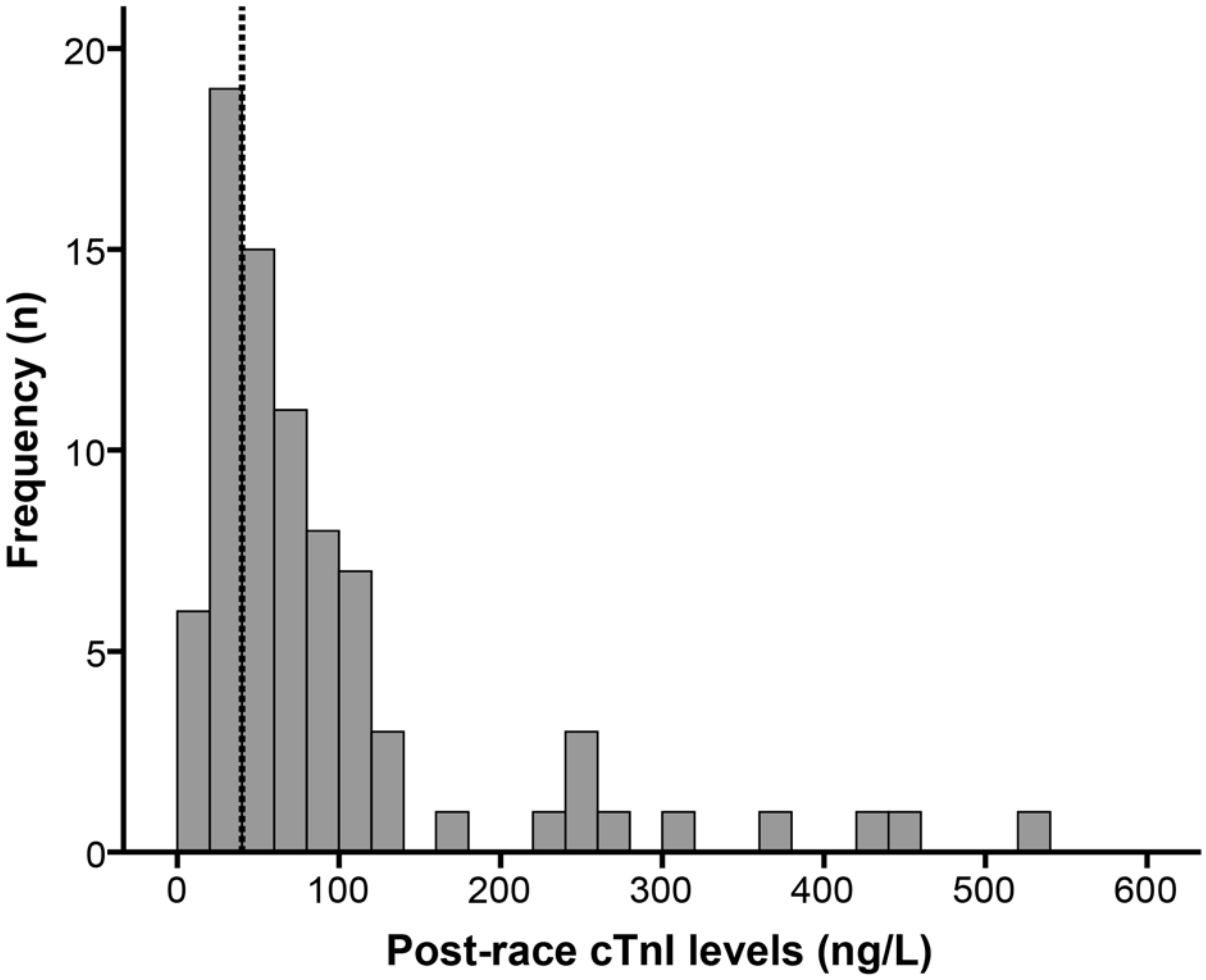
Frequency (n)
20
15
10
5
0
0
100
200
300
400
500
600
Post-race cTnI levels (ng/L)

Table 1. Subject characteristics and details about the health status of 82 athletes that finished the Eindhoven marathon.

	N	Mean±SD	Range
Demographic characteristics			
Age (yr)	82	45±8	26-71
Height (m)	82	1.79±0.10	1.58-2.00
Body-mass index (kg/m^2)	82	22.9±2.2	16.2-29.0
Previous marathons	82	8.2±15.7	0-103
Completed marathons	82	8±16	0-102
Sport (hrs/week)	82	8.4±3.4	3-18
Marathon PR (min)	58	210±22	166-256
Medical history	**N**	**Percentage**	
Hypercholesterolemia	10	12%	
on medication	3	4%	
Asthma	8	10%	
on medication	1	1%	
Hypertension	4	5%	
on medication	3	4%	
Anaemia	4	5%	
Rheumatic complaints	3	4%	
on medication	1	1%	
Cancer (history)	2	2%	

Table 2. Baseline and finish values of cardiac troponin, exercise characteristics and hydration status.

	Baseline	Finish	P-value
Cardiac troponin			
cTnI (ng/L)	**14±12**	**94±102**	<0.001
	[0-49]	***[3–530]***	
cTnI > 40 ng/L (n (%))	5 (6%)	55 (69%)	<0.001
Exercise characteristics			
Heart rate (bpm)		161±9	
		[136-178]	
Exercise intensity (% HRmax)		91±5	
		[76-100]	
Exercise duration (min)		227±28	
		[169-307]	
Speed (km/hr)		11.3±1.4	
		[8.2-15.0]	
Rate of perceived exertion		7±2	
		[1-10]	
Hydration status			
Fluid intake during race (L)		2.4±1.6	
		[0.3-6.8]	
% water		59%	
% sports drink		39%	
% other		2%	
Body mass (kg)	73.3±10.5	71.5±10.1	<0.001
	[52.5–93.9]	*[51.6–92.2]*	
Absolute body mass changes (kg)		-1.8±0.9	
		[-4.3–+0.5]	

Relative body mass changes (%)		-2.4±1.2	
		[-5.6–0.6]	
Dehydration (n (%))		52 (63%)	
Plasma sodium concentration (mmol/L)	141.3±1.9	142.4±3.0	0.003
	[137.2-145.8]	*[132.6-148.5]*	
Hypernatreamia, ≥ 145 mmol/L (n (%))	4 (5%)	14 (17%)	0.012
Hyponatreamia, ≤ 135 mmol/L (n (%))	0 (0%)	3 (4%)	0.075
Hemoglobin concentration (mmol/L)	9.5±0.6	9.5±0.7	0.811
	[8.1-10.8]	*[7.5-11.8]*	
Hematocrit levels (%)	45±3	45±3	0.883
	[39-51]	*[36-56]*	

P-value refers to a Paired Student's t-test between baseline and finish values