ORIGINAL RESEARCH

Duration of Elevated Heart Rate Is an Important Predictor of Exercise-Induced Troponin Elevation

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***Background*—**The precise mechanisms causing cardiac troponin (cTn) increase after exercise remain to be determined. The aim of this study was to investigate the impact of heart rate (HR) on exercise-induced cTn increase by using sports watch data from a large bicycle competition.

***Methods and Results*—**Participants were recruited from NEEDED (North Sea Race Endurance Exercise Study). All completed a 91-km recreational mountain bike race (North Sea Race). Clinical status, ECG, blood pressure, and blood samples were obtained 24 hours before and 3 and 24 hours after the race. Participants (n=177) were, on average, 44 years old; 31 (18%) were women. Both cTnI and cTnT increased in all individuals, reaching the highest level (of the 3 time points assessed) at 3 hours after the race ($P<0.001$). In multiple regression models, the duration of exercise with an HR >150 beats per minute was a significant predictor of both cTnI and cTnT, at both 3 and 24 hours after exercise. Neither mean HR nor mean HR in percentage of maximum HR was a significant predictor of the cTn response at 3 and 24 hours after exercise.

***Conclusions*—**The duration of elevated HR is an important predictor of physiological exercise-induced cTn elevation.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02166216. **(*J Am Heart Assoc*. 2020;9: e014408. DOI: 10.1161/JAHA.119.014408.)**

Key Words: cardiac troponins • cardiac work • heart rate • physical exercise

Prolonged strenuous physical exercise leads to elevation in circulating cardiac troponin (cTn) levels in healthy subjects.[1] Although increased cTn levels are considered to reflect myocardial damage, the exercise-induced cTn elevation in healthy subjects is considered to be a physiological response.[2] The cause and implications of the activity-mediated cTn response remain to be determined.[3,4]

We recently demonstrated an inverse correlation between race duration and exercise-induced cTn elevation, suggesting that the duration of high-intensity exercise is a significant determinant of the cTn response.[5] Heart rate (HR) is a major marker of exercise intensity.[6] A relationship between HR during exercise and the exercise-induced cTn elevation may therefore be anticipated. However, studies reporting on the relationship between HR and cTn levels have been conflicting: Some studies have found a relationship between HR and cTn levels,[7–10] whereas others have not.[11,12] The relationship between HR and the exercise-induced cTn response therefore remains obscure. Previous studies have been subject to several potential limitations: no study included >100 subjects, and most studies only reported on the relationship between cTn and mean and maximum HR.[9]

The aim of the present study was 3-fold: (1) to describe the relationship between HR and the exercise-induced cTn elevation in a larger population of healthy recreational athletes, (2) to explore the additional value of a comprehensive HR feature analysis for the prediction of the exercise-induced cTn response, and (3) to determine the presence of a potential HR threshold associated with the exercise-induced cTn response.

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Accompanying Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014408

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Received August 28, 2019; accepted January 7, 2020.

Clinical Perspective

What Is New?

- The duration of elevated heart rate >150 beats per minute is an independent and important predictor of exercise-induced troponin elevation.
- There may be a heart rate threshold associated with an exercise-induced troponin elevation.

What Are the Clinical Implications?

- Sport watches may be used to monitor exercise intensity and duration in relation to troponin release.
- The clinical role of heart rate threshold values associated with exercise-induced troponin elevation needs to be determined.
- Heart rate threshold of exercise-induced troponin release may potentially represent both training targets and safety margins of training.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Study subjects were recruited among healthy recreational cyclists participating in NEEDED (North Sea Race Endurance Exercise Study) 2014 (NCT 02166216). All study subjects completed the 91-km recreational mountain-bike race, the North Sea Race (Figure 1), in 2014. Participants in whom coronary artery disease was revealed by examinations after the race were excluded from the present analysis. Recruitment, inclusion and exclusion criteria, and data sampling in the main NEEDED 2014 have been described previously.[5] HR data were extracted from personal sport watches used by study subjects during the race (Figure 2). Digital HR data were harmonized, and HR features were calculated. The various HR features were compared with cTn levels acquired before and 3 and 24 hours after the race. All participants signed informed consent before enrollment into the study. The study was conducted according to the Declaration of Helsinki and approved by the Regional Ethics Committee (Regional Etisk komité No. 2013/550).

Sport Watch Data Processing

The sport watch files containing HR and geopositioning data were downloaded after the race, on site, sent by e-mail, or uploaded via a web-based solution delivered by Trainingpeaks (Trainingpeaks.com, CO). Sport watch data files were processed and analyzed at the Department of Electrical Engineering and Computer Science, University of Stavanger, Stavanger, Norway. The HR files did not contain information on the specific sport watch type. We were therefore not able to adjust for the different types of sport watch used.

To minimize the potential differences between different sport watches, we applied stringent measures to harmonize data and to ensure as high-data quality as possible. We excluded all files (n=114; Figure 2) with incomplete data sets, insufficient data sampling frequency, longer periods of missing data, or HR=0 (as described below).

The following file types were excluded because of missing combination of HR and/or geopositioning data: GPX, WKO,

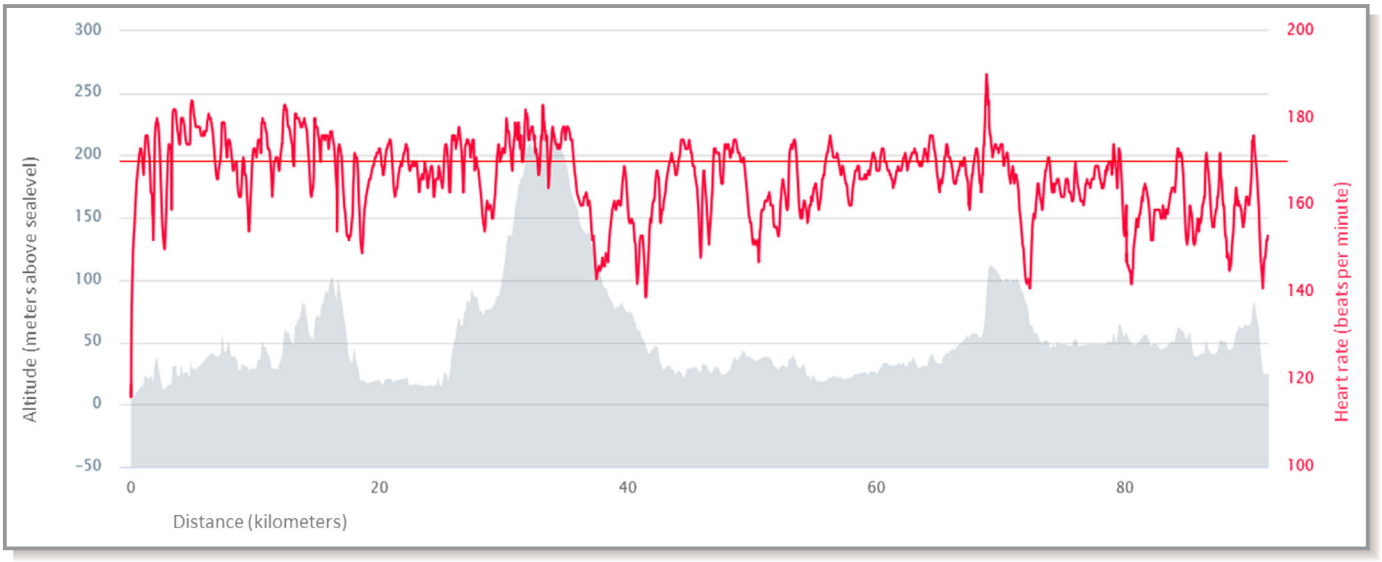

Figure 1. Diagram of heart rate (HR), altitude, and distance at the 91-km North Sea Race. HR is outlined in red, and altitude is in gray. The diagram is a representative presentation of HR from a single study participant, and the horizontal line is the subject's mean HR during the race (168 bpm). Distance (in kilometers) is along the *x* axis. The diagram is exported from the Garmin Connect website (copyright Garmin International, KS, US).

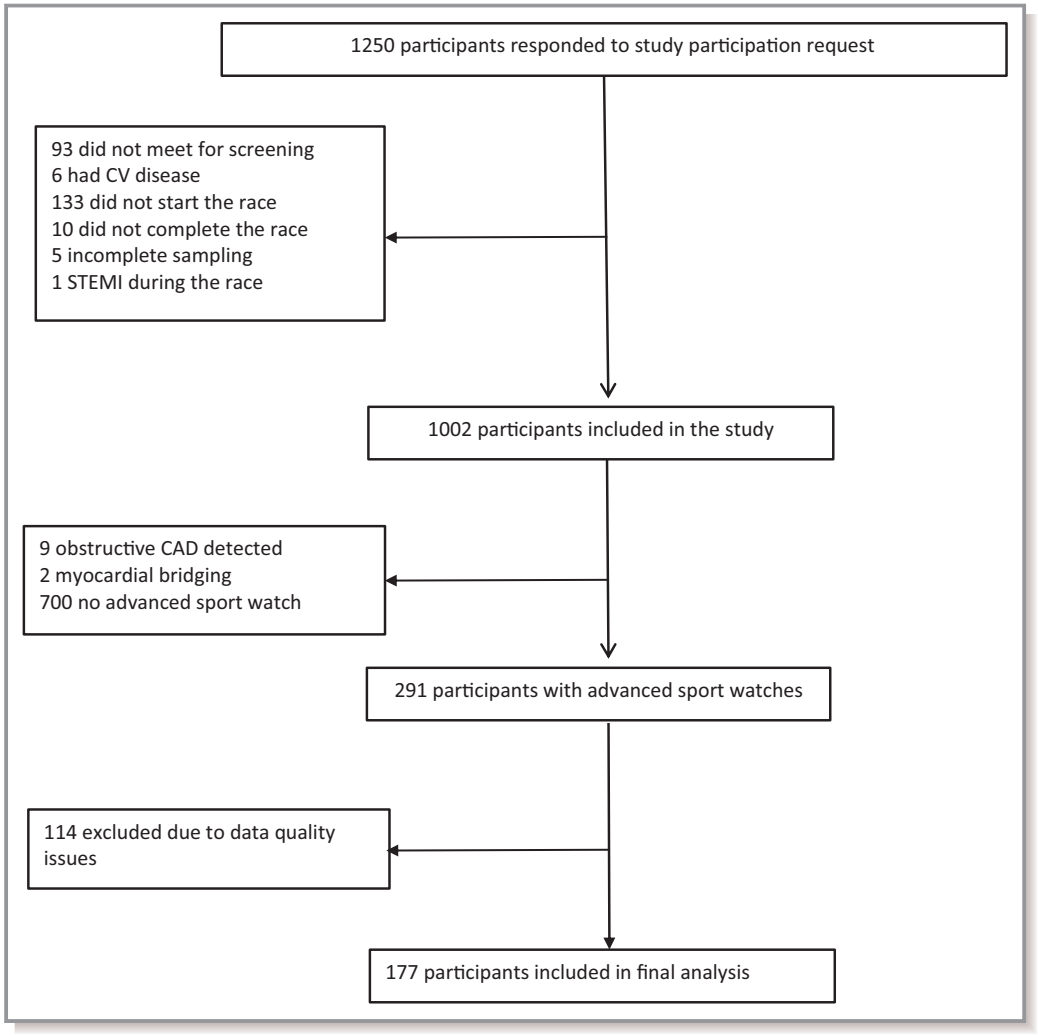

Figure 2. Flowchart depicting the recruitment of the study participants. CAD indicates coronary artery disease; CV, cardiovascular; STEMI, ST-segment–elevation myocardial infarction.

HRM, LSX, and OPL (n=14). The files included in the initial evaluation were CSV files (n=212), FIT (n=38), TCX (n=15), PWX (n=21), and XML (n=4).

These files were given a unique identifier and imported into MATLAB (Mathworks Inc, MA) for further processing. The files were harmonized by accurately defining start/stop of activity. All data were adjusted to a frequency of 1 HR value (beats per minute [bpm]) per 1 second. To correct for missing data, HR per second was interpolated from neighboring HR data. Files that did not allow harmonization of starting/stopping points or contained insufficient data to allow HR interpolation every second were excluded. A total of 177 files were included in the final analysis.

HR Features

HR data were downloaded and analyzed for the whole race, and mean and maximal HR values were calculated. The theoretical age-adjusted HR was estimated using the formula of Tanaka et al.[13] The intensity/time domain was analyzed by calculating the duration of time spent above HR thresholds of 140, 150, and 160 bpm for the complete race. Mean HRs and the time/HR integrals (above each of these HR thresholds) were calculated. The purpose of the variable time-HR integral, HR >×bpm, was to allow an interpretation of the troponin response to the combined effects of the duration and the magnitude of HR elevation above the specified HR limit. The time-HR integral corresponds to the area under the HR curve for all HR values exceeding the given HR threshold. The chosen HR thresholds were based on prior studies that suggest a stepwise increase in cTn between mean HR of 140 and 160 bpm.[14] In addition, the time spent with an HR >85%, >90%, and >95% of the maximal achieved HR during the race was calculated to allow a global assessment of HR distribution close to maximal effort.

Blood Samples

Blood samples were acquired 24 hours before and at 3 and 24 hours after exercise. The decision to sample blood at 3 hours

rather than immediately after exercise was based on the findings from the NEEDED 2013 pilot study that demonstrated better hydration and cTn levels more close to the expected physiological postexercise peak when cTn was sampled at 3 hours after exercise.[15] Venous blood samples were drawn from the antecubital vein. Cardiac TnI (serum) was analyzed within 24 hours at Stavanger University Hospital on an Architect i2000SR using the high-sensitive cTnI STAT assay from Abbott Diagnostics (IL). Frozen samples were transported on dry ice to Haukeland University Hospital, Bergen, Norway; and cTnT was analyzed using a high-sensitivity cTnT assay on Cobas e601 (Roche Diagnostics, Switzerland) on first-time thawed serum. The cTnI assay has a lower limit of detection of 1.6 ng/L, and the 99th percentile of the assay was set at 26 ng/L. The cTnT assay had a limit of blank of 3 ng/L and a 99th percentile of 14 ng/L.[16]

Statistical Analysis

Continuous and fairly symmetrically distributed variables are reported as mean±SD, whereas continuous variables with markedly skewed distributions are reported as median and interquartile range, reporting the 25th and 75th percentiles. The Shapiro-Wilk test was used to test for normality. Mann-Whitney *U* test and Student *t* test were used to test for difference between groups. For changes over all 3 time points, a Friedman test was used for markedly skewed distributions and a repeated-measures ANOVA was used for normally distributed variables. For comparison between 2 time points, Wilcoxon signed rank test was used for variables with markedly skewed distribution and paired Student *t* test was used for normally distributed variables. For bivariate correlations, Spearman's rank-order correlation was used. Because of the considerable number of statistical tests performed and the corresponding increased false-positive rate, a $P<0.01$ was regarded as significant. Multiple linear regression was used to study possible associations between HR variables and cTn levels. Because of markedly skewed distributions, cTn values were ln transformed. In the multiple regression models, we prespecified a fixed set of parameters for a basic model based on our findings from our main study.[5] The following variables were included in this model: age, sex, body mass index, race duration, systolic blood pressure (SBP), estimated glomerular filtration rate, low-density lipoprotein, Framingham Risk Score, resting HR, and baseline ln cTn. Different HR features were then added to the model one by one to see the changes in coefficient of determination (R^2). The following variables were added by this method: mean HR, maximum HR, mean HR in percentage of estimated maximum HR, time spent with an HR >140, >150, and >160 bpm, integral of time and HR with an HR >140, >150, and >160 bpm, integral of time with an HR >85%, >90%, and >95% of maximum achieved HR, mean HR >140, >150, and >160 bpm, and percentage of race time with an HR >140, >150, and >160 bpm. Recent data suggest that training history influences the exercise-induced cTn response.[17] Therefore, in addition to the basic model described in the Introduction, we constructed a new extended basic model that also contained training history expressed as years of endurance training. The following variables were included in the "extended basic model": age, sex, body mass index, race duration, SBP, estimated glomerular filtration rate, low-density lipoprotein, Framingham Risk Score, resting HR, baseline ln-cTn, and years of endurance training. Linear regression models using backward selection and forward inclusion showed similar effects on both the level of prediction and the level of significance. For all statistical analyses, the statistical software programs SPSS, version 24, and R[18] were used.

Results

A total of 177 subjects, 44±8 years of age, 31 (18%) women, were included in this analysis (Figure 2). Baseline values for the included subjects are outlined in Table 1. There was no former history of diabetes mellitus, hypertension, or heart disease among study participants. Mean race duration was 3:23 hours for men and 4:00 hours for women ($P<0.001$). Maximal and mean HR, as well as total time spent above the HR thresholds, are shown in Table 2.

cTn and Clinical Variables

Median cTnI at baseline was 1.9 (1.6–3.3) ng/L, increased to 60.0 (36.0–99.3) ng/L at 3 hours ($P<0.001$) and declined at 24 hours to 10.9 (6.1–22.4) ng/L ($P<0.001$). A similar profile was found for cTnT: baseline, <3.0 (<3.0–3.8) ng/L; 3 hours, 38.3 (25.6–55.2) ng/L ($P<0.001$); and 24 hours, 11.0 (7.2–17.4) ng/L ($P<0.001$) (Figure 3). HR at baseline was 59±10 bpm. At 3 hours after the race, mean resting HR increased to 78±10 bpm ($P<0.001$). Both SBP and diastolic blood pressure were significantly ($P<0.001$) decreased 3 hours after the race, compared with baseline: SBP, 138 (126–148) mm Hg (baseline) versus 129 (120–172) mm Hg (3 hours); and diastolic blood pressure, 80 (74–86) mm Hg (baseline) versus 74 (69–79) mm Hg (3 hours). Blood pressure was lower at 24 hours compared with baseline: SBP, 130 (120–138) mm Hg; and diastolic blood pressure, 73 (68–79) mm Hg ($P<0.001$). There was no change in HR at 24 hours compared with baseline. SBP at baseline was correlated with cTnI and cTnT levels at 24 hours after the race, but not with the peak cTn levels 3 hours after the race. There was no major change in body weight from baseline to 3 and 24 hours after exercise (Table 1).

Table 1. Baseline Variables

Variables	Values (n=177)
Age, y	43.9±8.0
Men, n (%)	142 (82)
Weight, kg	82.2±11.5
BMI, kg/m^2	25.6±2.7
Resting HR at baseline, bpm	59±10
SBP at baseline, mm Hg	138 (126 to 148)
DBP at baseline, mm Hg	80 (74 to 86)
Framingham Risk Score	1 (0 to 2)
Training status and competitive experience	
Endurance training, y	11.8±10.6
METs, minimum, min/wk	3948±2976
No. of endurance competitions in past 5 y	10 (5 to 20)
Biomarkers at baseline	
cTnI, ng/L	1.9 (1.6 to 3.3)
cTnT, ng/L	<3.0 (<3.0 to 3.8)
Total cholesterol, mmol/L	5.1 (4.5 to 5.7)
LDL, mmol/L	3.1±0.83
HDL, mmol/L	1.5 (1.3–1.7)
eGFR, mL/min per 1.73 m^2	93±13
Race data	
Race duration (h:min)	3:33 (3:09–3:54)
Change in body weight from baseline to 3 h, %	0.5 (−0.6 to 1.4)
Change in body weight from baseline to 24 h, %	0.0 (−1.0 to 0.81)

Baseline characteristics and race performance in study subjects (n=177). Values are given as mean±SD or median (25th–75th percentile) if markedly skewed distributions. BMI indicates body mass index; bpm, beats per minute; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; MET, metabolic equivalent; SBP, systolic blood pressure.

Table 2. HR Variables During the Race

HR Variables	Values
Mean HR, bpm	158±11
Maximum HR, bpm	179±11
Mean HR of estimated maximum HR, %	89±6
Maximum HR of estimated maximum HR, %	100 (97–105)
No. of episodes with HR >150 bpm	32 (11–64)
Mean HR >140 bpm, bpm	160 (153–166)
Mean HR >150 bpm, bpm	162 (157–167)
Mean HR >160 bpm, bpm	167 (163–170)
Time-intensity (HR) domain	
Race time with HR >140 bpm, min	200 (175–215)
Race time with HR >150 bpm, min	175 (133–203)
Race time with HR >160 bpm, min	97 (36–166)
% Race time with HR >140 bpm, %	98 (91–100)
% Race time with HR >150 bpm, %	88 (63–97)
% Race time with HR >160 bpm, %	52 (16–80)
Time-HR integral HR >140 bpm, HR h	62.5 (43.8–90.1)
Time-HR integral HR >150 bpm, HR h	30.7 (15.5–55.5)
Time-HR integral HR >160 bpm, HR h	8.9 (2.1–25.0)
Race time >85% of maximum achieved HR, min	183 (159–211)
Race time >90% of maximum achieved HR, min	159 (88–189)
Race time >95% of maximum achieved HR, min	69 (16–138)
Time-HR integral >85% of achieved maximum HR, HR h	43.9 (36.8–52.3)
Time-HR integral >90% of achieved maximum HR, HR h	19.3 (14.6–23.7)
Time-HR integral >95% of achieved maximum HR, HR h	3.7 (2.5–5.4)

HR variables during the race in 177 study subjects. Values are given as mean±SD or median (25th–75th percentile) if markedly skewed distributions. Mean HR >140, >150, and >160 bpm relates to the mean of HR values exceeding the HR threshold in each individual. Table 2 reports the distribution of these individual mean HR values between all study subjects. The distribution of the mean individual HR values was skewed, and these data are therefore presented as medians (25th–75th percentiles). Bpm indicates beats per minute; HR, heart rate.

Exercise-Induced Troponin Response and HR Variables During the Race

Bivariate correlations with cTn and HR variables are outlined in Table 3. At 3 hours after the race, only time spent with HR >150 bpm correlated significantly to both the cTnI (r=0.18; P=0.017) and cTnT (r=0.16; P=0.034) responses. The same relationship could be found with the integral of race-time with HR >150 bpm and the percentage of race-time with an HR >150 bpm. No significant association was found to time spent in HR zones defined as the percentage of maximum HR. The number of episodes with HR >150 bpm did not correlate with cTn levels at any time point.

Multiple Regression Models

The basic model reached approximately the same R^2 in this subgroup analysis as in the main study[5] (3-hour cTnI R^2=0.15 and cTnT R^2=0.16; 24-hour cTnI R^2=0.36 and cTnT R^2=0.28). By adding HR features, the R^2 increased by a maximum of 5 percentage points. Duration of time with an HR of ≥150 bpm was the only explanatory variable showing significant association with both cTnI and cTnT at both 3 and 24 hours. At the same time, between all the candidate variables, this variable produced the relatively largest increase in explained variance in

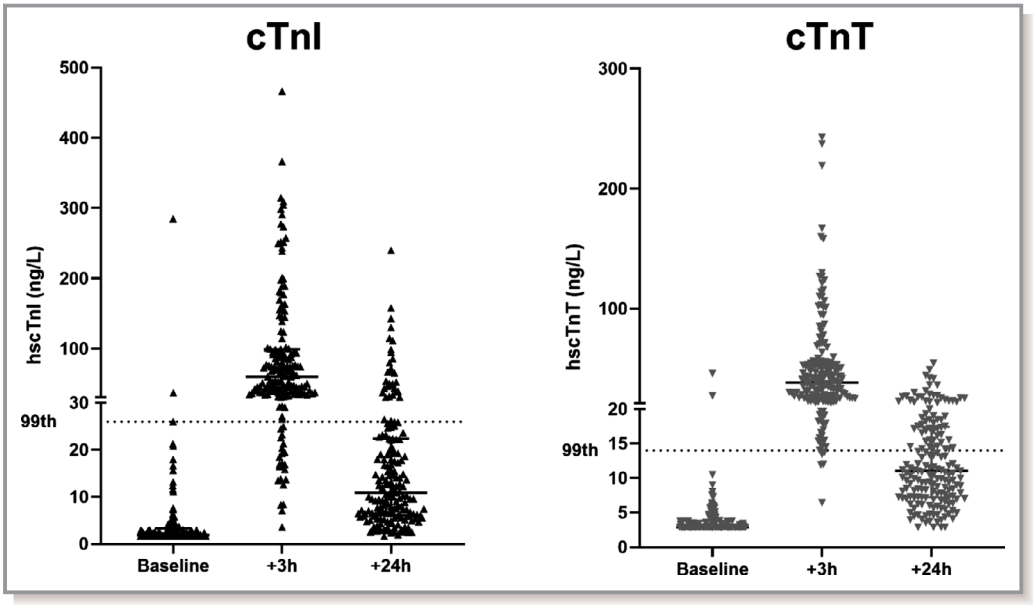

Figure 3. Scatter plot of cardiac troponin (cTn) values at all postrace time points. The *y* axis has been modified to allow a representative display of both high and low numbers in the same figure. The timing of blood sampling is represented by the *x* axis: baseline blood samples were acquired between 24 and 12 hours before the race, whereas blood samples +3 h and +24 h were acquired 3 and 24 hours after the race, respectively. The dotted lines represent the 99th percentile (high-sensitivity cTnT [hscTnT], 14 ng/L; and high-sensitivity cTnI [hscTnI], 26 ng/L). The horizontal black lines represent the median value.

the regression models of cTn elevation (Table 4). The same results could be found when using time >150 bpm in percentage of total race-duration. The extended basic model (including years of endurance training as an additional explanatory variable) increased the R^2 in all subgroups compared with the original basic model derived from the main study. The model increased the R^2 value at 3 hours (cTnI R^2=0.25 and cTnT R^2=0.23) and at 24 hours (cTnI R^2=0.44 and cTnT R^2=0.32). Also in the extended model, the duration of HR of ≥150 bpm was the variable with the highest increase in R^2 that also remained significant for both cTnI and cTnT at both time points: the R^2 increased between 3 and 5 percentage points in the models (Table 5). Full models containing all variables could be found in the supplemental tables: basic model (Table S1), basic model with time >150 bpm (Table S2), basic model with percentage of race duration >150 bpm (Table S3), and extended basic model with time >150 bpm (Table S4).

Discussion

The present study is the largest study to date to investigate the relationship between HR and the exercise-induced cTn response in recreational athletes. The study indicates that the duration of elevated HR is an important determinant of the physiological cTn response. Our findings suggest that there may be a HR threshold defining the lowest exercise intensity needed to generate an exercise-induced troponin response. Pure chronotropic measures, such as mean HR and mean HR in percentage of maximum HR, did not increase the level of prediction of the cTn response. In contrast, features that combined HR with duration of exercise improved the prediction models up to 5 percentage points.

During prolonged high-intensity exercise, there is a cTn elevation in healthy individuals without evidence of myocardial injury.[19] Several mechanisms have been proposed to explain this response, including increased wall tension and ventricular strain caused by volume overload, neurohormonal stimulation, and/or reversible ischemia attributable to increased myocardial energy demands.[1,20] In the main NEEDED 2014, we demonstrated that SBP and race duration were major determinants of the physiological cTn response after exercise.[5] The present study confirms and extends these findings by demonstrating independent effects of the time-intensity domain on the prediction models of the exercise-induced cTn response.

A relationship between HR and cTn elevation is expected. Myocardial perfusion occurs predominantly during diastole. Increased HR shortens diastole with subsequent decrease in subendocardial perfusion, potentially inducing ischemia during exercise. In patients with normal coronary arteries admitted for supraventricular tachycardia, subjects with elevated troponin T had significantly higher HR compared to those with normal levels (191 versus 170 bpm; P=0.008). Furthermore, there was a significant correlation between maximum HR and the level of troponin elevation (r=0.64; P=0.001).[21] A recent meta-analysis by Donaldson et al may indicate a potential link between diastolic function and exercise-induced cTn elevation: In the

Table 3. Bivariate Correlations

	cTnI + 3 h		cTnT + 3 h		cTnI + 24 h		cTnT +24 h	
Variables	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value
Basic variables and race duration								
Age	−0.10	0.20	0.04	0.62	0.08	0.29	0.04	0.59
Resting HR	−0.04	0.57	−0.05	0.54	−0.09	0.22	−0.11	0.14
SBP baseline	0.11	0.14	0.07	0.37	0.22	0.004†	0.17	0.02*
DBP baseline	0.04	0.58	−0.04	0.57	0.18	0.02*	0.07	0.37
Resting HR 3 h after the race	−0.05	0.49	−0.04	0.62	−0.09	0.22	−0.10	0.21
SBP 3 h after the race	0.15	0.04*	0.09	0.26	0.18	0.02*	0.19	0.01*
DBP 3 h after the race	0.09	0.26	0.02	0.84	0.14	0.07	0.03	0.69
BMI	−0.05	0.50	−0.05	0.53	0.06	0.44	0.09	0.26
Weight	−0.02	0.78	0.02	0.84	0.06	0.46	0.18	0.02*
Waist circumference	−0.10	0.18	−0.05	0.52	0.02	0.77	0.15	0.04*
METs, min/wk	0.04	0.64	0.05	0.50	0.05	0.53	0.07	0.36
Years of endurance training	−0.09	0.24	−0.10	0.22	0.05	0.95	−0.03	0.67
Race duration	−0.13	0.10	−0.19	0.01*	−0.09	0.22	−0.22	0.004†
HR variables during the race								
Maximum HR	0.04	0.65	−0.01	0.94	−0.05	0.52	−0.01	0.89
Mean HR	0.13	0.08	0.11	0.14	−0.01	0.91	0.03	0.67
Maximum HR in % of estimated maximum	0.04	0.59	0.01	0.87	0.04	0.63	0.03	0.69
Mean HR in % of estimated maximum HR	0.10	0.21	0.07	0.34	0.09	0.24	0.06	0.38
No. of HR periods >150 bpm	−0.13	0.09	−0.11	0.15	−0.04	0.61	−0.06	0.40
Mean HR >140 bpm	0.16	0.03*	0.13	0.08	0.03	0.75	0.05	0.51
Mean HR >150 bpm	0.13	0.10	0.09	0.23	0.0	1.0	0.02	0.75
Mean HR >160 bpm	0.09	0.22	0.05	0.50	−0.03	0.72	0.01	0.94
Time-intensity (HR) domain								
Race time with HR >140 bpm	0.12	0.12	0.08	0.28	0.04	0.63	−0.03	0.66
Race time with HR >150 bpm	0.18	0.02*	0.16	0.03*	0.06	0.45	0.04	0.59
Race time with HR >160 bpm	0.15	0.05	0.11	0.16	0.00	0.99	0.01	0.90
% Race time with HR >140 bpm	0.18	0.02*	0.18	0.02*	0.06	0.43	0.13	0.10
% Race time with HR >150 bpm	0.19	0.01*	0.18	0.02*	0.06	0.44	0.11	0.15
% Race time with HR >160 bpm	0.18	0.02*	0.14	0.06	0.04	0.60	0.06	0.43
Time-HR integral >140 bpm	0.17	0.03*	0.13	0.08	0.02	0.75	0.04	0.65
Time-HR integral >150 bpm	0.16	0.04*	0.13	0.10	0.01	0.86	0.04	0.64
Time-HR integral >160 bpm	0.13	0.08	0.10	0.20	0.0	0.99	0.03	0.73
Race time >85% of achieved maximum HR	0.07	0.33	0.08	0.29	0.05	0.50	0.05	0.51
Race time >90% of achieved maximum HR	0.02	0.81	0.06	0.44	0.00	1.00	−0.02	0.76
Race time >95% of achieved maximum HR	−0.01	0.94	−0.02	0.78	−0.06	0.45	−0.02	0.79

Continued

Table 3. Continued

Variables	cTnI + 3 h		cTnT + 3 h		cTnI + 24 h		cTnT +24 h	
	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value	Rho	*P* Value
Time-HR integral >85% of achieved maximum HR	0.18	0.02*	0.14	0.06	0.08	0.30	0.03	0.71
Time-HR integral >90% of achieved maximum HR	0.22	0.004†	0.19	0.01*	0.11	0.13	0.07	0.35
Time-HR integral >95% of achieved maximum HR	0.19	0.01*	0.16	0.03*	0.11	0.13	0.07	0.36

Bivariate correlations (*P* values based on Spearman's rank test) between troponin (cTnI and cTnT) response and baseline and HR variables in blood samples acquired 3 and 24 hours after the race. BMI indicates body mass index; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DBP, diastolic blood pressure; HR, heart rate; MET, metabolic equivalent; SBP, systolic blood pressure.
*$P<0.05$, †$P<0.01$.

meta-analysis, exercise HR was the strongest predictor of increased cTn levels (R^2=0.31).[22] More important, the analysis found diastolic function to be influenced by exercise HR and cTn release, implying that high-intensity exercise elicits cTn release and reduces left ventricular diastolic function. One may therefore anticipate the exercise-induced cTn elevation to be related to increased HR.[23] However, as demonstrated by the present study, it is the combination of duration and HR, and not solely HR, that relates to the exercise-induced cTn elevation. Hence, to generate a cTn release, HR elevation must persist for a certain period. These findings are in line with the study by Lara et al demonstrating increasing cTnT levels in running competitions of increasing duration.[24] Our findings suggest that there may be an HR threshold required to generate an exercise-

Table 4. Changes After Adding HR Variables to the Basic Multiple Regression Model

Dependent Variables	Ln cTnI 3 h			Ln cTnT 3 h			Ln cTnI 24 h			Ln cTnT 24 h		
	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value
Basic model	0.19	. . .	. . .	0.17	. . .	. . .	0.37	. . .	. . .	0.26	. . .	. . .
Mean HR	0.20	0.01	0.18	0.17	0.01	0.29	0.38	0.01	0.48	0.26	0.01	0.22
Mean HR % of estimated maximum HR	0.20	1.88	0.18	0.17	1.08	0.29	0.38	0.93	0.49	0.26	1.08	0.24
Mean HR >140 bpm	0.20	0.02	0.09	0.18	0.01	0.13	0.38	0.01	0.20	0.28	0.01	0.09
Mean HR >150 bpm	0.19	0.01	0.34	0.17	0.01	0.35	0.38	0.01	0.46	0.27	0.01	0.19
Mean HR >160 bpm	0.19	0.00	0.78	0.17	0.01	0.64	0.37	0.01	0.77	0.27	0.01	0.26
Race time with HR >140 bpm	0.23	0.36	0.003	0.21	0.26	0.003	0.39	0.26	0.03	0.29	0.20	0.01
Race time with HR >150 bpm	**0.24**	**0.25**	**0.001**	**0.21**	**0.16**	**0.002**	**0.40**	**0.19**	**0.009**	**0.29**	**0.13**	**0.01**
Race time with HR >160 bpm	0.21	0.12	0.06	0.18	0.07	0.12	0.38	0.07	0.25	0.27	0.06	0.14
% Race time >140 bpm	0.23	1.41	0.004	0.21	1.03	0.003	0.39	1.05	0.02	0.29	0.83	0.009
% Race time >150 bpm	**0.24**	**0.97**	**0.001**	**0.21**	**0.63**	**0.003**	**0.40**	**0.77**	**0.006**	**0.30**	**0.52**	**0.007**
% Race time >160 bpm	0.20	0.43	0.07	0.18	0.26	0.13	0.38	0.29	0.20	0.27	0.25	0.11
Integral of time and HR >140 bpm	0.21	0.005	0.03	0.19	0.00	0.05	0.38	0.00	0.14	0.28	0.00	0.05
Integral of time and HR >150 bpm	0.20	0.01	0.11	0.18	0.00	0.15	0.38	0.00	0.33	0.27	0.00	0.13
Integral of time and HR >160 bpm	0.19	0.00	0.49	0.17	0.00	0.51	0.37	0.00	0.81	0.27	0.00	0.34
Time-HR integral >85% of achieved maximum HR	0.24	0.02	0.001	0.20	0.01	0.02	0.40	0.02	0.006	0.28	0.006	0.10
Time-HR integral >90% of achieved maximum HR	0.24	0.03	0.001	0.20	0.02	0.02	0.41	0.03	0.003	0.28	0.01	0.08
Time-HR integral >95% of achieved maximum HR	0.22	0.09	0.008	0.19	0.05	0.06	0.41	0.09	0.004	0.27	0.04	0.10

This table shows the effects of adding a single extra HR variable to the basic multiple model derived from the main NEEDED (North Sea Race Endurance Exercise Study) 2014. Variables included in the basic multiple linear regression model were as follows: baseline ln cTnI/cTnT, body mass index, age, sex, race duration, resting HR at baseline, systolic blood pressure at baseline, low-density lipoprotein cholesterol, estimated glomerular filtration rate, and Framingham Risk Score. Individual HR variables were added to the basic model to assess the impact of these variables on the R^2 and the association with cardiac troponin. The strongest models that were significant at all time points for both cTnT and cTnI were race time with HR >150 bpm and percentage of race time with an HR >150 bpm (outlined in bold letters). The full basic model is presented in Table S1. cTnI indicates cardiac troponin I; cTnT, cardiac troponin T; HR, heart rate; R^2, coefficient of determination.

Table 5. Changes After Adding HR Variables to the Extended Basic Model

	Ln cTnI 3 h			Ln cTnT 3 h			Ln cTnI 24 h			Ln cTnT 24 h		
Dependent Variables	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value	R^2	B	*P* Value
Extended basic model	0.25	. . .	. . .	0.23	. . .	. . .	0.44	. . .	. . .	0.32	. . .	. . .
Mean HR	0.26	0.01	0.28	0.23	0.01	0.43	0.44	0.01	0.55	0.33	0.01	0.37
Mean HR % of estimated maximum HR	0.26	1.61	0.28	0.23	0.86	0.42	0.44	0.81	0.56	0.33	0.81	0.39
Mean HR >140 bpm	0.26	0.02	0.13	0.24	0.01	0.19	0.45	0.01	0.17	0.34	0.01	0.13
Mean HR >150 bpm	0.25	0.01	0.40	0.23	0.01	0.40	0.44	0.01	0.39	0.33	0.01	0.21
Mean HR >160 bpm	0.25	0.004	0.78	0.23	0.01	0.60	0.44	0.01	0.63	0.33	0.01	0.22
Race time with HR >140 bpm	0.28	0.35	0.01	0.25	0.23	0.03	0.46	0.27	0.04	0.34	0.18	0.05
Race time with HR >150 bpm	**0.30**	**0.25**	**0.003**	**0.26**	**0.15**	**0.01**	**0.47**	**0.20**	**0.01**	**0.35**	**0.11**	**0.04**
Race time with HR >160 bpm	0.26	0.10	0.15	0.23	0.05	0.27	0.45	0.07	0.28	0.33	0.05	0.30
% Race time with HR >140 bpm	0.28	1.23	0.02	0.25	0.83	0.03	0.45	0.97	0.06	0.34	0.66	0.06
% Race time with HR >150 bpm	0.29	0.90	0.004	0.26	0.55	0.02	0.47	0.75	0.01	0.34	0.42	0.04
% Race time with HR >160 bpm	0.26	0.35	0.17	0.23	0.18	0.31	0.45	0.27	0.25	0.33	0.17	0.28
Integral of time and HR >140 bpm	0.27	0.005	0.06	0.24	0.003	0.11	0.45	0.004	0.11	0.34	0.003	0.09
Integral of time and HR >150 bpm	0.26	0.004	0.18	0.23	0.003	0.25	0.45	0.003	0.26	0.33	0.003	0.18
Integral of time and HR >160 bpm	0.26	0.003	0.57	0.23	0.002	0.59	0.44	0.002	0.63	0.33	0.003	0.32
Time-HR integral >85% of achieved maximum HR	0.29	0.02	0.008	0.24	0.01	0.11	0.46	0.01	0.02	0.33	0.003	0.44
Time-HR integral >90% of achieved maximum HR	0.29	0.03	0.008	0.24	0.01	0.09	0.47	0.02	0.01	0.33	0.01	0.34
Time-HR integral >95% of achieved maximum HR	0.28	0.08	0.02	0.24	0.04	0.11	0.46	0.08	0.02	0.33	0.02	0.28

This table shows the effects of adding a single extra HR variable to the extended basic model. Variables included in the "extended basic model" are as follows: age, sex, body mass index, race duration, systolic blood pressure, low-density lipoprotein cholesterol, estimated glomerular filtration rate, Framingham Risk Score, resting HR, baseline ln cTnI/cTnT, and years of endurance training. The model reaching the highest R^2 and keeping significance was race time with an HR >150 bpm (outlined in bold letters). cTnI indicates cardiac troponin I; cTnT, cardiac troponin T; HR, heart rate; R^2, coefficient of determination.

induced cTn response. This is in line with the small (n=10) mechanistic study by Stewart et al[14] that found a difference in mean HR between subjects with a high (HR, 160±3 bpm) compared with a low (HR, 145±2 bpm) cTnI response. In the study by Stewart et al,[14] the exercise protocols were repeated in the same subjects comparing the same total amount of work, but with increased intensity (and shortened duration). There was a highly significant increase in cTnI levels after the high-intensity compared with the medium-intensity protocol, suggesting that there may be an exercise intensity threshold for inducing an accentuated cTnI response. Only 10 study subjects were examined; the possibility to assess interindividual variations in HR thresholds was therefore limited. The present study was not able to precisely define the HR threshold associated with an exacerbated exercise-induced cTn response. Our data suggest that it may be between 140 and 150 bpm. Future studies need to address these issues further.

The development of myocardial stress and myocardial injury is reflected by several factors influencing myocardial work and myocardial energetics. Weil et al[20] used infusion of phenylepinephrine in pigs to induce an increased HR and SBP with a subsequent increase in cTnI. The cTn elevation occurred without evidence of myocardial injury.[20] These findings suggest that neurohormonal activation during strenuous exercise may be an important determinant of the physiological cTn release. In this context, HR may be a consequence rather than a determinant of factors causing a cTn release. Fourth, in line with the main study, the present analysis found an association between the exercise-induced cTn elevation and SBP. From other studies, we know that resting SBP is significantly correlated to SBP in exercise[25] (Knut Gjesdal, personal communication [Date of communication: May 27, 2019]). Although we were unable to measure SBP during the race, these findings may suggest that the exercise-induced cTn response is exacerbated in subjects likely to have increased cardiac work during exercise.

Limitations

Our study is a prespecified subgroup analysis of the NEEDED 2014 cohort of presumably healthy recreational athletes with

self-owned advanced sport watches. Our analyses are based on recordings from several different sport watch producers that used different data acquisition and storage algorithms. We had to remove data from 114 subjects because of insufficient data quality. The present analysis used conventional methods to harmonize data between the different sport watches, and extrapolated missing data only in files with sufficiently high data density. However, despite challenges related to data acquisition and analysis, our findings are consistent, suggesting that simple chronotropic parameters (mean and maximum HR) are not related to the exercise-induced cTn elevation if they are not linked with the duration of exercise. Our findings underscore that the duration of intensity is more important than short episodes of high HR. Sampling time of 1 HR value (bpm) per 1 second should therefore be sufficient. Beat-to-beat data were not available in the current analysis, and a more comprehensive assessment of HR variability was not possible. We therefore cannot exclude a relationship between HR variability and the exercise-induced cTn response. Because there is a link between HR variability and neurohormonal activation, exploration of beat-to-beat measurements and the exercise-induced cTn response is warranted in future studies.

The present study did not assess individual maximal oxygen uptake or anaerobic threshold. It is therefore not possible to determine the relationship between cTn levels and HR at these biological hallmarks.

Conclusions

The present study shows that the duration of elevated HR is an independent predictor of exercise-induced cTn elevation. The present study does not allow the determination of the minimum duration of exercise required to cause an exacerbated exercise-induced cTn release, and it does not allow the determination of a potential threshold of HR. Future studies should aim to identify both the duration and the HR level associated with an exercise-induced cTn elevation.

Both the present and earlier studies have used HR as a surrogate marker of intensity.[26] No direct measurement of cardiac or total work was performed. Development of new activity trackers and power meters allows more comprehensive measurements of both total work and cardiac work. Future studies should combine these methods to further increase our understanding of the underlying mechanisms of the exercise-induced cTn response.

Acknowledgments

This study could not have been conducted without close collaboration with the North Sea Race organization. We highly appreciate their support, both financial and during planning and data collection.

Sources of Funding

This work was supported by an operating grant from Abbott Diagnostics (Abbott Diagnostics, IL), the Laerdal Foundation (Stavanger, Norway), Stavanger University Hospital, and a research grant from the Western Norway Health Authorities.

Disclosures

The following modest conflicts of interest have been reported by Drs Skadberg and Aakre. Dr Skadberg has received lecture fees from Abbott Diagnostics. Dr Aakre has served on one advisory board for Roche Diagnostics. The remaining authors have no disclosures to report.

References

1. Gresslien T, Agewall S. Troponin and exercise. *Int J Cardiol*. 2016;221:609–621.
2. Shave R, Baggish A, George K, Wood M, Scharhag J, Whyte G, Gaze D, Thompson PD. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol*. 2010;56:169–176.
3. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res*. 2017;113:1708–1718.
4. Samaha E, Avila A, Helwani MA, Ben Abdallah A, Jaffe AS, Scott MG, Nagele P. High-sensitivity cardiac troponin after cardiac stress test: a systematic review and meta-analysis. *J Am Heart Assoc*. 2019;8:e008626. DOI: 10.1161/JAHA.118.008626..
5. Kleiven O, Omland T, Skadberg O, Melberg TH, Bjorkavoll-Bergseth MF, Auestad B, Bergseth R, Greve OJ, Aakre KM, Orn S. Race duration and blood pressure are major predictors of exercise-induced cardiac troponin elevation. *Int J Cardiol*. 2019;283:1–8.
6. Karvonen J, Vuorimaa T. Heart rate and exercise intensity during sports activities: *practical application. Sports Med*. 1988;5:303–311.
7. Fu F, Nie J, Tong TK. Serum cardiac troponin t in adolescent runners: effects of exercise intensity and duration. *Int J Sports Med*. 2009;30:168–172.
8. Serrano-Ostariz E, Terreros-Blanco JL, Legaz-Arrese A, George K, Shave R, Bocos-Terraz P, Izquierdo-Alvarez S, Bancalero JL, Echavarri JM, Quilez J, Aragones MT, Carranza-Garcia LE. The impact of exercise duration and intensity on the release of cardiac biomarkers. *Scand J Med Sci Sports*. 2011;21:244–249.
9. Eijsvogels TM, Hoogerwerf MD, Oudegeest-Sander MH, Hopman MT, Thijssen DH. The impact of exercise intensity on cardiac troponin I release. *Int J Cardiol*. 2014;171:e3–e4.
10. Li F, Yi L, Yan H, Wang X, Nie J, Zhang H, Fu FHK, Zang Y, Yang S, Lu Y. High-sensitivity cardiac troponin T release after a single bout of high-intensity interval exercise in experienced marathon runners. *J Exerc Sci Fit*. 2017;15:49–54.
11. Fortescue EB, Shin AY, Greenes DS, Mannix RC, Agarwal S, Feldman BJ, Shah MI, Rifai N, Landzberg MJ, Newburger JW, Almond CS. Cardiac troponin increases among runners in the Boston marathon. *Ann Emerg Med*. 2007;49:137–143, 143.e1.
12. Eijsvogels TM, Hoogerwerf MD, Maessen MF, Seeger JP, George KP, Hopman MT, Thijssen DH. Predictors of cardiac troponin release after a marathon. *J Sci Med Sport*. 2015;18:88–92.
13. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol*. 2001;37:153–156.
14. Stewart GM, Yamada A, Haseler LJ, Kavanagh JJ, Chan J, Koerbin G, Wood C, Sabapathy S. Influence of exercise intensity and duration on functional and biochemical perturbations in the human heart. *J Physiol*. 2016;594:3031–3044.
15. Skadberg O, Kleiven O, Orn S, Bjorkavoll-Bergseth MF, Melberg TH, Omland T, Aakre KM. The cardiac troponin response following physical exercise in relation to biomarker criteria for acute myocardial infarction; the north sea race endurance exercise study (NEEDED) 2013. *Clin Chim Acta*. 2018;479:155–159.
16. Ungerer JP, Tate JR, Pretorius CJ. Discordance with 3 cardiac troponin I and T assays: implications for the 99th percentile cutoff. *Clin Chem*. 2016;62:1106–1114.

17. Mehta R, Gaze D, Mohan S, Williams KL, Sprung V, George K, Jeffries R, Hudson Z, Perry M, Shave R. Post-exercise cardiac troponin release is related to exercise training history. *Int J Sports Med*. 2012;33:333–337.

18. R foundation for statistical computing. R: a language and environment for statistical computing. Vienna, Austria, 2019. Available at: https://www.R-roject.org.

19. Vassalle C, Masotti S, Lubrano V, Basta G, Prontera C, Di Cecco P, Del Turco S, Sabatino L, Pingitore A. Traditional and new candidate cardiac biomarkers assessed before, early, and late after half marathon in trained subjects. *Eur J Appl Physiol*. 2018;118:411–417.

20. Weil BR, Suzuki G, Young RF, Iyer V, Canty JM Jr. Troponin release and reversible left ventricular dysfunction after transient pressure overload. *J Am Coll Cardiol*. 2018;71:2906–2916.

21. Ben Yedder N, Roux JF, Paredes FA. Troponin elevation in supraventricular tachycardia: primary dependence on heart rate. *Can J Cardiol*. 2011;27:105–109.

22. Donaldson JA, Wiles JD, Coleman DA, Papadakis M, Sharma R, O'Driscoll JM. Left ventricular function and cardiac biomarker release-the influence of exercise intensity, duration and mode: a systematic review and meta-analysis. *Sports Med*. 2019;49:1275–1289.

23. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med*. 2005;142:786–791.

24. Lara B, Salinero JJ, Gallo-Salazar C, Areces F, Ruiz-Vicente D, Martinez M, Del Coso J. Elevation of cardiac troponins after endurance running competitions. *Circulation*. 2019;139:709–711.

25. Skretteberg PT, Grundvold I, Kjeldsen SE, Engeseth K, Liestol K, Erikssen G, Erikssen J, Gjesdal K, Bodegard J. Seven-year increase in exercise systolic blood pressure at moderate workload predicts long-term risk of coronary heart disease and mortality in healthy middle-aged men. *Hypertension*. 2013;61:1134–1140.

26. Legaz-Arrese A, George K, Carranza-Garcia LE, Munguia-Izquierdo D, Moros-Garcia T, Serrano-Ostariz E. The impact of exercise intensity on the release of cardiac biomarkers in marathon runners. *Eur J Appl Physiol*. 2011;111:2961–2967.

SUPPLEMENTAL MATERIAL

Table S1. Basic model.

Linear Multiple regression calculated by using ENTER method. Full model showing all variables of the Basic model without adding heart rate variables. Abbreviations: Cardiac Troponin I (cTnI), cardiac Troponin T (cTnT), Body Mass Index (BMI), estimated glomerular filtration rate (eGFR), Low-Density Lipoprotein (LDL).

3 hours following race	Unstandardized coefficients		Standardized coefficients		
Ln cTnI (R^2=0.19)	B	Std Error	Beta	T	Sig
Ln cTnI Baseline	0.25	0.09	0.22	2.94	0.00
BMI	0.01	0.03	0.02	0.29	0.78
Age	-0.03	0.01	-0.23	-1.77	0.08
Sex	-0.73	0.21	-0.31	-3.43	0.00
Race duration	-0.42	0.14	-0.27	-3.06	0.00
Resting heart rate	0.00	0.01	0.01	0.13	0.89
Systolic blood pressure baseline	0.01	0.00	0.13	1.62	0.11
eGFR	0.01	0.01	0.15	1.86	0.06
LDL-cholesterol	0.03	0.09	0.03	0.36	0.72
Framingham Risk Score	0.07	0.04	0.22	1.75	0.08
Ln cTnT (R^2=0.17)					
Ln cTnT Baseline	0.45	0.13	0.26	3.42	0.00
BMI	-0.01	0.02	-0.04	-0.47	0.64
Age	-0.02	0.01	-0.23	-1.77	0.08
Sex	-0.40	0.15	-0.23	-2.57	0.01
Race duration	-0.34	0.10	-0.30	-3.42	0.00
Resting heart rate	0.00	0.01	0.01	0.12	0.90
Systolic blood pressure baseline	0.01	0.00	0.15	1.94	0.05
eGFR	0.00	0.00	0.06	0.78	0.44
LDL-cholesterol	0.03	0.06	0.04	0.48	0.63
Framingham Risk Score	0.05	0.03	0.21	1.60	0.11
24 hours following race					
Ln cTnI (R^2=0.37)	B	Std Error	Beta	T	Sig
Ln cTnI Baseline	0.65	0.08	0.52	7.93	0.00
BMI	0.02	0.03	0.05	0.64	0.52
Age	-0.01	0.01	-0.09	-0.74	0.46
Sex	-0.56	0.20	-0.21	-2.73	0.01
Race duration	-0.27	0.13	-0.16	-2.08	0.04
Resting heart rate	0.00	0.01	0.01	0.20	0.84
Systolic blood pressure baseline	0.01	0.00	0.16	2.37	0.02
eGFR	0.01	0.01	0.11	1.50	0.14
LDL-cholesterol	0.09	0.08	0.08	1.12	0.26
Framingham Risk Score	0.07	0.04	0.19	1.69	0.09
Ln cTnT (R^2=0.26)					
Ln cTnT Baseline	0.66	0.12	0.40	5.55	0.00
BMI	0.00	0.02	0.01	0.12	0.90
Age	-0.02	0.01	-0.20	-1.61	0.11
Sex	-0.11	0.14	-0.07	-0.78	0.44
Race duration	-0.24	0.09	-0.23	-2.73	0.01
Resting heart rate	0.00	0.00	-0.02	-0.25	0.80
Systolic blood pressure baseline	0.01	0.00	0.19	2.55	0.01
eGFR	0.00	0.00	0.04	0.52	0.60
LDL-cholesterol	0.06	0.05	0.08	1.03	0.31
Framingham Risk Score	0.05	0.03	0.22	1.80	0.07

Table S2. Time > 150 bpm.

Full model, multiple regression ENTER method, containing the heart rate variable that reached the highest level of significance and prediction values at all time-points. Abbreviations: Cardiac Troponin I (cTnI), cardiac Troponin T (cTnT), Body Mass Index (BMI), estimated glomerular filtration rate (eGFR), Low-Density Lipoprotein (LDL).

3 hours following race					
Ln cTnI (R^2=0.24)	B	Std Error	Beta	T	Sig
Ln cTnI Baseline	0.27	0.08	0.24	3.29	0.00
BMI	0.01	0.03	0.04	0.46	0.64
Age	-0.02	0.01	-0.19	-1.54	0.12
Sex	-0.74	0.21	-0.31	-3.60	0.00
Race duration	-0.44	0.13	-0.28	-3.29	0.00
Resting heart rate	-0.01	0.01	-0.07	-0.83	0.41
Systolic blood pressure baseline	0.01	0.00	0.14	1.79	0.07
eGFR	0.01	0.01	0.12	1.57	0.12
LDL-cholesterol	-0.01	0.09	-0.01	-0.12	0.90
Framingham Risk Score	0.09	0.04	0.27	2.20	0.03
Time > 150 bpm	0.25	0.07	0.27	3.44	0.00
Ln cTnT (R^2=0.21)					
Ln cTnT Baseline	0.48	0.13	0.28	3.76	0.00
BMI	-0.01	0.02	-0.03	-0.34	0.73
Age	-0.02	0.01	-0.20	-1.57	0.12
Sex	-0.41	0.15	-0.24	-2.73	0.01
Race duration	-0.35	0.10	-0.31	-3.64	0.00
Resting heart rate	0.00	0.01	-0.06	-0.77	0.44
Systolic blood pressure baseline	0.01	0.00	0.17	2.15	0.03
eGFR	0.00	0.00	0.04	0.51	0.61
LDL-cholesterol	0.00	0.06	0.01	0.07	0.94
Framingham Risk Score	0.06	0.03	0.25	1.98	0.05
Time > 150 bpm	0.16	0.05	0.25	3.08	0.00
24 hours following race					
Ln cTnI (R^2=0.40)	B	Std Error	Beta	T	Sig
Ln cTnI Baseline	0.67	0.08	0.53	8.25	0.00
BMI	0.02	0.03	0.06	0.78	0.43
Age	-0.01	0.01	-0.06	-0.53	0.59
Sex	-0.57	0.20	-0.22	-2.82	0.01
Race duration	-0.29	0.13	-0.17	-2.22	0.03
Resting heart rate	0.00	0.01	-0.04	-0.54	0.59
Systolic blood pressure baseline	0.01	0.00	0.17	2.51	0.01
eGFR	0.01	0.01	0.09	1.26	0.21
LDL-cholesterol	0.06	0.08	0.05	0.74	0.46
Framingham Risk Score	0.08	0.04	0.23	2.02	0.04
Time > 150 bpm	0.19	0.07	0.19	2.66	0.01
Ln cTnT (R^2=0.29)					
Ln cTnT Baseline	0.68	0.12	0.41	5.85	0.00
BMI	0.00	0.02	0.02	0.24	0.81
Age	-0.01	0.01	-0.18	-1.43	0.15
Sex	-0.12	0.14	-0.07	-0.88	0.38
Race duration	-0.25	0.09	-0.24	-2.90	0.00
Resting heart rate	0.00	0.00	-0.08	-1.00	0.32
Systolic blood pressure baseline	0.01	0.00	0.20	2.73	0.01
eGFR	0.00	0.00	0.02	0.29	0.77

LDL-cholesterol	0.04	0.05	0.05	0.68	0.50
Framingham Risk Score	0.06	0.03	0.26	2.11	0.04
Time > 150 bpm	0.13	0.05	0.20	2.62	0.01

Table S3. Percent of race duration > 150 bpm.

Full model, multiple regression ENTER method, containing the heart rate variable that reached the highest level of significance and prediction values at all time-points. Abbreviations: Cardiac Troponin I (cTnI), cardiac Troponin T (cTnT), Body Mass Index (BMI), estimated glomerular filtration rate (eGFR), Low-Density Lipoprotein (LDL).

3 hours following race					
Ln cTnI (R^2=0.24)	B	Std Error	Beta	T	Sig
Ln cTnI Baseline	0.27	0.08	0.24	3.27	0.00
BMI	0.01	0.03	0.04	0.48	0.63
Age	-0.02	0.01	-0.20	-1.61	0.11
Sex	-0.73	0.21	-0.31	-3.54	0.00
Race duration	-0.24	0.14	-0.15	-1.71	0.09
Resting heart rate	-0.01	0.01	-0.07	-0.85	0.40
Systolic blood pressure baseline	0.01	0.00	0.14	1.80	0.07
eGFR	0.01	0.01	0.12	1.56	0.12
LDL-cholesterol	-0.01	0.09	-0.01	-0.13	0.89
Framingham Risk Score	0.09	0.04	0.29	2.29	0.02
Percent of race > 150 bpm	0.96	0.29	0.29	3.38	0.00
Ln cTnT (R^2=0.21)					
Ln cTnT Baseline	0.48	0.13	0.28	3.75	0.00
BMI	-0.01	0.02	-0.03	-0.32	0.75
Age	-0.02	0.01	-0.21	-1.64	0.10
Sex	-0.40	0.15	-0.24	-2.68	0.01
Race duration	-0.23	0.10	-0.20	-2.17	0.03
Resting heart rate	0.00	0.01	-0.06	-0.80	0.43
Systolic blood pressure baseline	0.01	0.00	0.17	2.15	0.03
eGFR	0.00	0.00	0.04	0.50	0.62
LDL-cholesterol	0.00	0.06	0.00	0.06	0.96
Framingham Risk Score	0.06	0.03	0.26	2.07	0.04
Percent of race > 150 bpm	0.63	0.21	0.26	3.05	0.00
24 hours following race					
Ln cTnI (R^2=0.40)	B	Std Error	Beta	T	Sig
Ln cTnI Baseline	0.67	0.08	0.53	8.27	0.00
BMI	0.02	0.03	0.06	0.81	0.42
Age	-0.01	0.01	-0.07	-0.58	0.56
Sex	-0.56	0.20	-0.21	-2.79	0.01
Race duration	-0.13	0.14	-0.08	-0.96	0.34
Resting heart rate	0.00	0.01	-0.04	-0.61	0.54
Systolic blood pressure baseline	0.01	0.00	0.17	2.52	0.01
eGFR	0.01	0.01	0.09	1.24	0.22
LDL-cholesterol	0.06	0.08	0.05	0.71	0.48
Framingham Risk Score	0.08	0.04	0.24	2.12	0.04
Percent of race > 150 bpm	0.77	0.28	0.21	2.77	0.01
Ln cTnT (R^2=0.30)					
Ln cTnT Baseline	0.68	0.12	0.41	5.87	0.00
BMI	0.00	0.02	0.02	0.27	0.79
Age	-0.01	0.01	-0.18	-1.48	0.14
Sex	-0.11	0.14	-0.07	-0.84	0.40
Race duration	-0.15	0.09	-0.14	-1.61	0.11
Resting heart rate	-0.01	0.00	-0.08	-1.07	0.29
Systolic blood pressure baseline	0.01	0.00	0.20	2.75	0.01

eGFR	0.00	0.00	0.02	0.27	0.79
LDL-cholesterol	0.03	0.05	0.05	0.64	0.52
Framingham Risk Score	0.06	0.03	0.27	2.22	0.03
Percent of race > 150 bpm	0.52	0.19	0.22	2.74	0.01

Table S4. Extended Basic Model with Time > 150 bpm.

Full model, multiple regression ENTER method, containing the heart rate variable that reached the highest level of significance and prediction values at all time-points. In addition to the variables in Basic model, Extended Basic Model contains Years of Endurance training as a separate variable. Abbreviations: Cardiac Troponin I (cTnI), cardiac Troponin T (cTnT), Body Mass Index (BMI), estimated glomerular filtration rate (eGFR), Low-Density Lipoprotein (LDL).

3 hours following race					
Ln cTnI (R^2=0.30)	**B**	**Std Error**	**Beta**	**T**	**Sig**
Ln cTnI Baseline	0.28	0.09	0.24	3.23	0.00
BMI	0.01	0.03	0.04	0.44	0.66
Age	-0.02	0.01	-0.22	-1.68	0.10
Sex	-0.82	0.21	-0.34	-3.83	0.00
Years of endurance training	-0.01	0.01	-0.11	-1.32	0.19
Race duration	-0.51	0.14	-0.32	-3.60	0.00
Resting heart rate	-0.01	0.01	-0.13	-1.60	0.11
Systolic blood pressure baseline	0.01	0.00	0.17	2.21	0.03
eGFR	0.01	0.01	0.11	1.42	0.16
LDL-cholesterol	0.03	0.10	0.02	0.27	0.79
Framingham Risk score	0.10	0.04	0.31	2.36	0.02
Time > 150 bpm	0.25	0.08	0.26	3.06	0.00
Ln cTnT (R^2=0.26)	**B**	**Std Error**	**Beta**	**T**	**Sig**
Ln cTnT Baseline	0.51	0.13	0.30	3.86	0.00
BMI	-0.01	0.02	-0.02	-0.25	0.80
Age	-0.02	0.01	-0.25	-1.87	0.06
Sex	-0.49	0.16	-0.29	-3.14	0.00
Years of endurance training	-0.01	0.01	-0.17	-2.00	0.05
Race duration	-0.39	0.10	-0.34	-3.81	0.00
Resting heart rate	-0.01	0.01	-0.12	-1.45	0.15
Systolic blood pressure baseline	0.01	0.00	0.20	2.45	0.02
eGFR	0.00	0.00	0.03	0.32	0.75
LDL-cholesterol	0.03	0.07	0.03	0.37	0.71
Framingham Risk score	0.08	0.03	0.32	2.35	0.02
Time > 150 bpm	0.15	0.06	0.22	2.53	0.01
24 hours following race					
Ln cTnI (R^2=0.47)	**B**	**Std Error**	**Beta**	**T**	**Sig**
Ln cTnI Baseline	0.68	0.08	0.56	8.46	0.00
BMI	0.03	0.03	0.07	0.95	0.34
Age	-0.01	0.01	-0.06	-0.53	0.60
Sex	-0.64	0.20	-0.25	-3.18	0.00
Years of endurance training	-0.01	0.01	-0.09	-1.33	0.19
Race duration	-0.37	0.13	-0.21	-2.76	0.01
Resting heart rate	-0.01	0.01	-0.10	-1.42	0.16
Systolic blood pressure baseline	0.01	0.00	0.19	2.74	0.01
eGFR	0.01	0.01	0.07	0.98	0.33
LDL-cholesterol	0.05	0.09	0.04	0.56	0.58
Framingham Risk score	0.09	0.04	0.25	2.14	0.03
Time > 150 bpm	0.20	0.08	0.19	2.59	0.01
Ln cTnT (R^2=0.35)	**B**	**Std Error**	**Beta**	**T**	**Sig**
Ln cTnT Baseline	0.73	0.12	0.45	6.28	0.00
BMI	0.01	0.02	0.04	0.44	0.66
Age	-0.02	0.01	-0.20	-1.61	0.11
Sex	-0.20	0.14	-0.13	-1.44	0.15

Years of endurance training	-0.01	0.00	-0.12	-1.51	0.13
Race duration	-0.29	0.09	-0.27	-3.21	0.00
Resting heart rate	-0.01	0.00	-0.14	-1.79	0.08
Systolic blood pressure baseline	0.01	0.00	0.25	3.28	0.00
eGFR	0.00	0.00	0.00	0.06	0.95
LDL-cholesterol	0.04	0.06	0.05	0.65	0.51
Framingham Risk score	0.06	0.03	0.28	2.15	0.03
Time > 150 bpm	0.11	0.05	0.17	2.13	0.03