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ORIGINAL RESEARCH

Determinants of Interindividual Variation in Exercise-Induced Cardiac Troponin I Levels

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BACKGROUND: Postexercise cardiac troponin levels show considerable interindividual variations. This study aimed to identify the major determinants of this postexercise variation in cardiac troponin I (cTnI) following 3 episodes of prolonged high-intensity endurance exercise.

METHODS AND RESULTS: Study subjects were recruited among prior participants in a study of recreational cyclists completing a 91-km mountain bike race in either 2013 or 2014 (first race). In 2018, study participants completed a cardiopulmonary exercise test 2 to 3 weeks before renewed participation in the same race (second race). Blood was sampled before and at 3 and 24 hours following all exercises. Blood samples were analyzed using the same Abbot high-sensitivity cTnI STAT assay. Fifty-nine individuals (aged 50±9 years, 13 women) without cardiovascular disease were included. Troponin values were lowest before, highest at 3 hours, and declining at 24 hours. The largest cTnI difference was at 3 hours following exercise between the most (first race) (cTnI: 200 [87–300] ng/L) and the least strenuous exercise (cardiopulmonary exercise test) (cTnI: 12 [7–23] ng/L; $P<0.001$). The strongest correlation between troponin values at corresponding times was before exercise ($r=0.92$, $P<0.0001$). The strongest correlations at 3 hours were between the 2 races ($r=0.72$, $P<0.001$) and at 24 hours between the cardiopulmonary exercise test and the second race ($r=0.83$, $P<0.001$). Participants with the highest or lowest cTnI levels showed no differences in race performance or baseline echocardiographic parameters.

CONCLUSIONS: The variation in exercise-induced cTnI elevation is largely determined by a unique individual cTnI response that is dependent on the duration of high-intensity exercise and the timing of cTnI sampling.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02166216.

Key Words: biomarkers ■ exercise physiology ■ troponin

Elevated cardiac troponin (cTn) is a marker of myocardial damage, and high levels are associated with an adverse prognosis in both patients with and without known coronary artery disease.[1,2] It has been known for >3 decades that prolonged strenuous exercise causes an increase in the cTn values in healthy individuals. The exercise-induced cTn elevation in healthy individuals is considered a benign response to exercise.[3] However, recent studies found independent associations between exercise-induced cTn elevation, adverse cardiovascular events, and obstructive coronary artery disease.[4,5] These findings suggest a potential diagnostic role for postexercise cTn assessment. However, no cTn level cutoffs to differentiate a benign from a pathologic cTn elevation have been identified. This is possibly because of the considerable interindividual variations in cTn values, and a limited understanding of the mechanisms causing exercise-induced troponin elevation in healthy individuals. A better understanding of the determinants of the exercise-induced cTn elevation might pave the way for the potential use

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CLINICAL PERSPECTIVE

What Is New?

- The magnitude of exercise-induced troponin elevation is largely determined by a reproducible, unique individual troponin response.
- This individual response is not related to alterations in physical performance or baseline echocardiographic parameters.

What Are the Clinical Implications?

- The individual troponin response needs to be included in the interpretation of individual exercise-induced troponin values.
- These large physiological interindividual variations in the exercise-induced troponin response requires the establishment of individual troponin reference values if the response is to be used for diagnostic purposes.

Nonstandard Abbreviations and Acronyms

CPX	cardiopulmonary exercise test
cTn	cardiac troponin
cTnI	cardiac troponin I
RPP	rate pressure product

of exercise-induced cTn elevation in a diagnostic setting.

Previous studies have identified baseline cTn, exercise intensity, and duration of exercise as predictors of the exercise-induced cTn elevation.[6–9] Recent studies suggest that the duration of elevated heart rate and blood pressure before exercise might be predictors of the exercise-induced cTn response.[10] However, the current prediction models only explain part (<36%) of the physiological cTn variation,[9] underlining the possibility that other individual factors play a more important role. This is the first study to evaluate the individual reproducibility of exercise-induced cTn elevation following physical efforts separated by >4 years. The aim of this study was to identify the major determinants of individual variation in the cTn response to exercise, with a particular focus on the impact of the individual cTn response in relation to workload and timing of cTn sampling following exercise.

METHODS

In 2018, study individuals were recruited from a pool of previous participants in the NEEDED (North Sea Race Endurance Study) in either 2013 or 2014.[9,11] All participants had participated in the 91-km leisure sport mountain bike race (the North Sea Race) in either 2013 or 2014 (T0). In 2018, the recruited study participants were examined by a cardiopulmonary exercise (CPX) test (T1), 2 to 3 weeks before a renewed participation in the North Sea Race (T2). There was a comprehensive measurement of physiological parameters during the 2018 race (T2). Blood was sampled at similar time points (before and at 3 and 24 hours following the race) and analyzed using the same high-sensitivity cardiac troponin I (cTnI) assay at the 2 races (T0 and T2) and the CPX test (T1). Coronary computed tomography angiography was performed following T2 to ensure that no individual had obstructive coronary artery disease. The present study complies with the Declaration of Helsinki, all participants signed informed consent forms before the study, and the regional ethics committee approved the study (REK no. 2013/550 and no. 2018/63). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Subjects and Baseline Measurements

Only healthy subjects without obstructive coronary artery disease on coronary computed tomography angiography in 2013 or 2014 were eligible for the present study.[12] Only data from individuals participating in all 3 exercises were included in the final analysis (Figure 1). All study subjects underwent a thorough examination at inclusion in 2018, including a detailed history, blood investigations, ECG, blood pressure, and

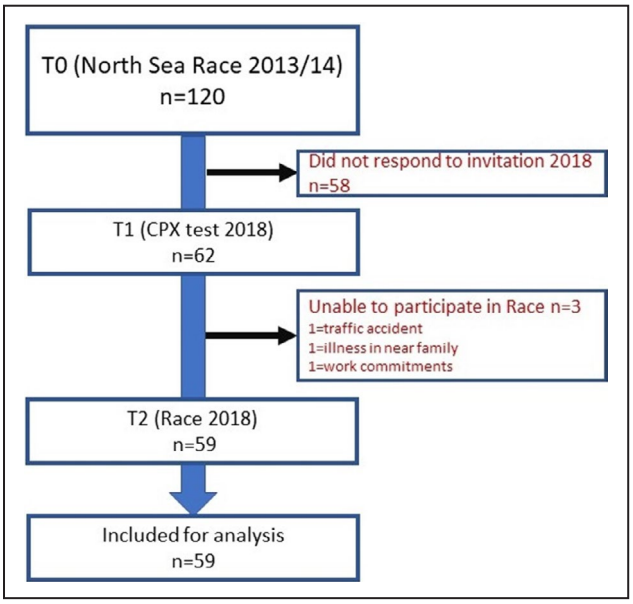

Figure 1. Flowchart of the study.
CPX indicates cardiopulmonary exercise; T0, recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

echocardiographic examination. Twelve-lead ECGs were taken at baseline and at 3 and 24 hours after exercise. Each participant answered questionnaires about symptoms after all exercises at all 3 time points. Noninvasive blood pressure was measured 3 times in a sitting position with an automated blood pressure monitor. The average of the 2 last measurements was used to calculate blood pressure. For an assessment of the amount of daily exercise, the International Activity Questionnaire was used.[13] The data from the International Activity Questionnaire were used to calculate the metabolic equivalent hours per week for each participant.

Estimation of Total and Cardiac Work

Except for the time taken to complete the race, there were no data about the total and cardiac work from the recruitment race (T0). During both the CPX test (T1) and the 2018 race (T2), power meters were used to assess the total work performed. Work during the CPX test (T1) was measured by a Cyclus 2 electronically braked ergo trainer (RBM Elektronik-Automation, Leipzig, Germany).[14] Each participant used their own bikes fitted to the Cyclus2 during the CPX test. Work performed during the 2018 race (T2) (n=40) was measured continuously with Stages power meters (StagesPower, Boulder, CO).[15] The Stages power meters were mounted on the bikes by replacing the original crank arm of the left side with a crank arm with a Stages power sensor. The rate pressure product (RPP) was used to estimate cardiac work during the exercise.[16] RPP was calculated as either mean or maximal RPP. Mean RPP was calculated as mean systolic blood pressure during exercise multiplied by mean heart rate, whereas maximum RPP was calculated as the highest measured systolic blood pressure multiplied by the maximal heart rate. Both during the CPX test (T1) and the 2018 race (T2), heart rate was measured continuously by chest straps and similar heart rate monitors in all the study subjects (Garmin Forerunner 935; Garmin, Olathe, KS). During the CPX test (T1), blood pressure was measured automatically using a Tango M2 Stress test monitor (Suntech Medical, Morrisville, NC). During the 2018 race (T2), blood pressure was measured manually on the right arm with a Heine G5, G7, or XXL LF-T (Heine, Herrsching, Germany) at 4 pit stops at the maximum and minimum anticipated efforts at the top and bottom at the 2 largest hills of the race after 34, 41, 69, and 76 km (Figure S1). A detailed description of the CPX test can be found in Data S1.

Blood Sampling

Blood was sampled at similar time points for all 3 exercises (T0, T1, and T2): the day before (baseline) the exercise and at 3 and 24 hours following the exercise. Blood samples were taken from the antecubital vein in a sitting position after a resting period of >5 minutes. Blood samples were stored at 4 ºC and analyzed within 24 hours of sampling.

Troponin Measurements

The same high-sensitivity cTnI assay (STAT) from Abbott Diagnostics was used for the measurement of troponin during all 3 events: T0, T1, and T2. The assay was analyzed on an Architect SR2000i (Abbott) for all sampling points. In 2013/2014 (T0) and 2018 (T1 and T2), the reported results were at or more than the limit of detection (1.6 ng/L) and limit of blank (0.9 ng/L). The cTnI assay had a total coefficient of variation of 10% at 6 ng/L, 7% at 27 ng/L, and 5% at 140 ng/L. Overall 99th percentile was 26 ng/L (men: 34 ng/L and women: 16 ng/L).[17]

Echocardiographic Assessment

Two GE Vivid E 95 systems (Vingmed, Horten, Norway) were used for the echocardiographic assessment performed at inclusion (T1). Comprehensive imaging protocols were applied, with complete coverage of both atria and ventricles, including parasternal and apical views, and adequate high frame rates to allow high-quality postprocessing, including speckle tracking and both global and regional strain analysis. An experienced medical doctor, blinded to the clinical data and exercise information, performed off-line post-processing on a GE EchoPAC (GE Healthcare, Horten, Norway). All parameters were calculated according to the recommendations of the European Association of Cardiovascular Imaging.[18]

Statistical Analysis

Normally distributed continuous variables are reported as mean±standard deviation, whereas continuous variables with markedly skewed distributions are reported as the median and interquartile range (25th–75th percentile). The Shapiro-Wilk test was used to test for normality. For changes over time, a paired *t* test or Wilcoxon signed rank test was used as appropriate. Spearman correlation was used to study bivariate associations. A 2-tailed *P* value <0.05 was considered significant. A linear mixed effects model with random intercept was used for estimation of between-group differences. Differences were estimated at each time point (baseline, +3 hours, and +24 hours) among the 3 groups, T0, T1, and T2. Multiple linear regression with a backward elimination was used with postexercise cTnI values at 3 and 24 hours after the CPX test and the race in 2018 as dependent values. Age, sex, duration of exercise, and systolic blood pressure at baseline were selected a priori.[9,19,20] Because of markedly skewed distribution, troponin values were transformed using

a natural logarithm. Based on the correlation analysis with cTnI as the dependent variable, explanatory variables with $P<0.05$ were included in the models. The same variables of effort were selected for both T1 and T2. Corresponding values from T0 and T1 or T2 were added to investigate if these variables would have a different influence on exercise-induced cTn. The statistical software programs SPSS version 26 (IBM, Armonk, NY) and GraphPad Prism 9 (GraphPad Software, San Diego, CA) were used for statistical analysis and generating the graphs.

RESULTS

Data from a total of 59 healthy cyclists (aged 50±9 years, 13 women) were included in the present analysis. There were no major abnormal echocardiographic findings at baseline (Table 1), and there was no obstructive coronary artery disease on coronary computed tomography angiography following T2. None of the participants reported symptoms or had ECG findings suggestive of cardiac disease.

Exercise Characteristics

There were significant differences in exercise workload between the CPX test (T1) and the 2018 race (T2) (Table 2). The exercise workload was higher in the 2018 race (T2) compared with the CPX test (T1); the duration of high-intensity exercise was longer in the race, and the mean heart rate, peak power output, the peak and mean systolic blood pressure, and the peak and mean RPP were all higher in the race (T2). In contrast, there was no difference in maximal heart rate, and the mean power output and mean systolic pressure were lower during T2 compared with T1 (Table 2).

For the recruitment race (T0), the only measurement of exercise intensity was the duration of the race. The duration was shorter ($P<0.001$) in T0 (3.6 [3.4–4.0] hours) than in T2 (4.2 [3.6–4.6] hours), at least partly because of interrupted exercise because of the four 2-minute pit stops to assess the blood pressure. The race course and the weather conditions were the same during T0 and T2, reflected by the same race duration for all participants in the race: mean 4.2 hours in 2018 (n=2650) compared with mean 4.1 hours in 2013/2014 (n=8763).

Exercise-Induced cTnI Profile

The cTnI values had the same profile following all 3 rounds of exercise (T0, T1, and T2): the lowest cTnI levels were at baseline, the highest at 3 hours after exercise, with declining values at 24 hours (Figure 2). The 3-hour exercise-induced cTnI levels were higher after T2 (77 [37–128] ng/L) than after T1 (12 [7–23] ng/L), and were highest after T0 (200 [87–300] ng/L) ($P<0.001$). A similar pattern was seen for the 24-hour values, T1 (5 [3–9] ng/L), T2 (16 [8–32] ng/L), and T0 (34 [18–85] ng/L) ($P<0.001$).

Table 1. Baseline Characteristics and Physical Measurements During the CPX Test and the 2018 Race

Physical Characteristics and Training Status	Value	Minimum–Maximum
Male sex, n (%)	46 (74%)	
Age, y	50.3±9.6	31–77
Body mass index, kg/m^2	24.9 (23.3–27.1)	21.4–33.6
Systolic blood pressure, mm Hg	135 (122–146)	110–175
Diastolic blood pressure, mm Hg	81 (74–89)	61–104
Resting heart rate, bpm	60±10	41–92
Waist circumference, cm	86 (81–93)	72–107
Years of endurance training	10 (7–21)	0–50
Total MET h, MET h/wk	61 (47–102)	15–359
CPX test, T1		
Vo2Max, mL/min per kg	41.3±8.3	24.0–57.1
Power at lactate threshold, W	200±47	80–300
Heart rate lactate threshold, bpm	162±13	134–200
Echocardiographic findings at baseline		
LV measurements		
LV mass index, 2D, g/m^2	87.1±14.2	63.0–129.0
LV septum, mm	10.4±1.1	7.0–13.0
LV volume, 3D, mL/m^2		
Diastole	84.4±18.2	59.7–129.5
Systole	35.3±8.3	19.4–57.4
E/A ratio	1.4±0.4	0.9–2.5
LV ejection fraction, 3D, %	58.3±3.7	51.0–67.0
LV GLS, %	20.2±2.2	15.9–25.5
RV measurements		
RV volume, mL/m^2, 3D		
Diastole	75.3±14.7	51.0–116.0
Systole	40.2±9.8	24.0–69.0
RV 3 segment GLS, %	26.8±3.8	14.4–34.3

Normally distributed values are reported as mean±SD and markedly skewed values are reported as median (25th–75th percentile) unless indicated otherwise. CPX indicates cardiopulmonary exercise; GLS, global longitudinal strain; LV, left ventricle; MET, metabolic equivalent; RV, right ventricle; Vo2Max, maximum oxygen consumption; 2D, two-dimensional; and 3D, three-dimensional

Correlation Between Physical Measurements and Exercise-Induced cTnI Values

There was no correlation between baseline echocardiographic parameters and cTnI levels, and no correlation between cTnI levels and duration of exercise above the heart rate and power thresholds. A summary of the main findings and the basic parameters are presented in Table 2. RPP was found to have a significant correlation with exercise-induced cTnI value at both T1 and T2. Peak systolic pressure was significantly correlated

Table 2. Correlation Between cTnI and Exercise Data in CPX Test 2018 and Race 2018

Exercise Variables	T1, CPX Test 2018	T2, race 2018	*P* Value, T1 vs T2	Correlation T1 cTnI, +3 h, ρ/*P* Value	Correlation T1 cTnI, +24 h, ρ/*P* Value	Correlation T2 cTnI, +3 h, ρ/*P* Value	Correlation T2 cTnI +24 h, ρ/*P* Value
Duration of exercise, min	43 (40–45)	230 (210–245)	*P*<0.001	0.13/0.32	−0.14/0.30	−0.14/0.30	−0.21/0.11
HR peak, bpm	177±12	175±12	NS	0.08/0.56	−0.07/0.61	0.08/0.55	−0.03/0.83
HR mean, bpm	132±12	154±10	*P*<0.001	0.13/0.31	−0.06/0.65	0.16/0.23	0.09/0.51
Power peak, W	301 (242–342)	655 (502–759)	*P*<0.001	0.07/0.56	−0.07/0.61	0.27/0.55	0.20/0.07
Power mean, W	225±51	172±51	*P*<0.001	0.05/0.70	0.14/0.30	0.15/0.37	0.16/0.33
Work total, W×min	8650±1778	40289±7714	*P*<0.001	0.02/0.90	0.10/0.48	0.11/0.51	0.15/0.36
Work/kg total, W×min/kg	107±21	496±65	*P*<0.001	0.06/0.66	0.07/0.60	0.05/0.77	0.07/0.68
SBP peak, mm Hg	201 (181–216)	230 (210–245)	*P*<0.001	0.23/0.09	**0.29/0.003**†	0.21/0.12	0.25/0.06
SBP mean, mm Hg	183±14	166±15	*P*<0.001	0.13/0.33	0.11/0.42	0.20/0.14	0.22/0.09
DBP peak, mm Hg	83 (68–94)	100 (90–110)	*P*<0.001	−0.03/0.78	−0.08/0.57	0.06/0.64	0.09/051
DBP mean, mm Hg	83±9	84±8	NS	−0.11/0.42	−0.17/0.20	0.06/0.64	0.09/0.51
RPP peak, bpm×mm Hg	31594±4822	34416±4173	*P*<0.05	**0.32/0.02***	**0.30/0.03***	**0.26/0.045***	**0.29/0.03***
RPP mean, bpm×mm Hg	26511±2783	25319±2843	*P*<0.05	0.22/0.10	0.09/0.51	**0.27/0.04***	0.24/0.06
Weight reduction, kg	0.4 (0.2–0.6)	1.3 (0.8–1.8)	*P*<0.001	0.01/0.94	−0.01/0.92	0.02/0.88	0.15/0.26
Delta creatinine 3 h, µmol/L	2.7±4.5	11.0±12.7	*P*<0.001	0.17/0.20	0.23/0.09	0.26/0.05	**0.29/0.03***

Comparison is between variables of effort and biochemical variables after the 2 exercises in 2018. Skewed variables reported as median (25th–75th quartile) and normally distributed variables reported as mean±SD. Differences between the sample points were analyzed using the Wilcoxon signed rank or a paired-samples *t* test when appropriate. Work during the race (W) was assessed continuously by power meters in a subset of 40 study subjects. Normally distributed values are reported as mean±SD, and markedly skewed values are reported as median (25th–75th percentile). Bivariate correlation was analyzed with the Spearman rank method. Significant correlations are highlighted in bold letters. CPX indicates cardiopulmonary exercise; cTnI, cardiac troponin I; DBP, diastolic blood pressure; HR, heart rate; NS, not significant; RPP, rate pressure product; SBP, systolic blood pressure; T0, recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

*P<0.05.

†P<0.01.

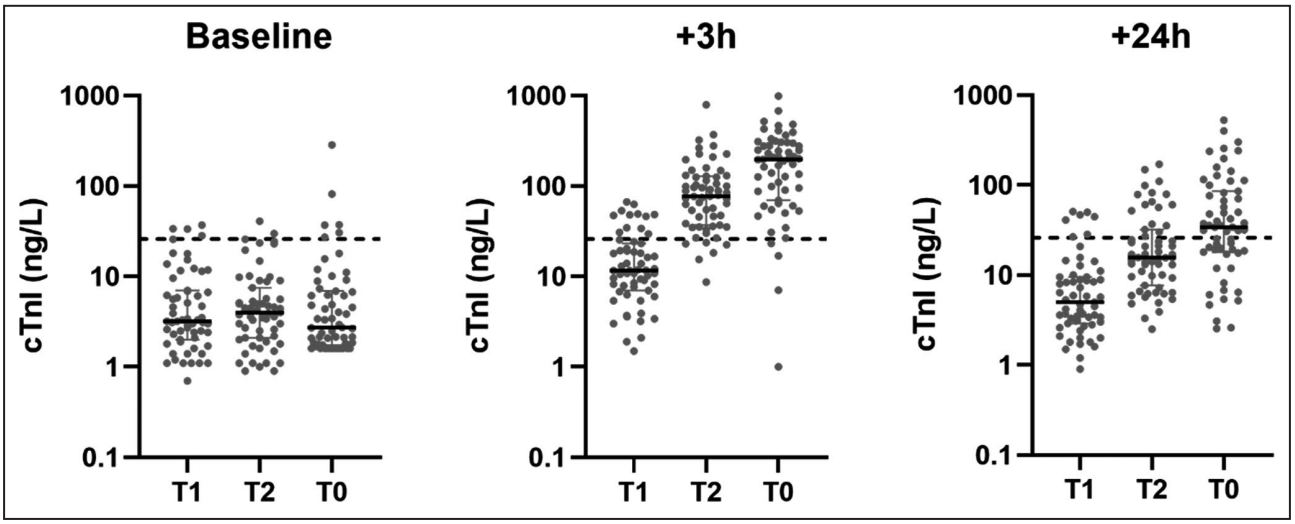

Figure 2. Cardiac troponin I (cTnI), at baseline, 3 h, and 24 h, after the cardiopulmonary exercise test in 2018 (T1), the North Sea Race in 2018 (T2), and the North Sea Race recruitment race in either 2013 or 2014 (T0).
Scale is log10-transformed. Dotted lines indicate the 99th percentile of the high-sensitivity cTnI assay (26 ng/L).

with the exercise-induced cTnI value at 24 hours following the CPX test (r=0.29, P=0.003) and reached borderline significance at 24 hours following the race (T2) (r=0.25, P=0.06).

Low- Versus High-cTnI Responders

Figure 3 displays the consistency in the rankings of cTnI values following the 2 races T0 and T2. Individuals were either classified as low- or high-cTnI responders depending on their cTnI value 3 hours after exercise in the recruitment race (T0). Low responders were defined as individuals with a cTnI level within the first quartile after T0, whereas high responders were defined as individuals with a cTnI level in the highest quartile in T0. There was no difference in the physical performance or echocardiographic parameters after the 2018 race

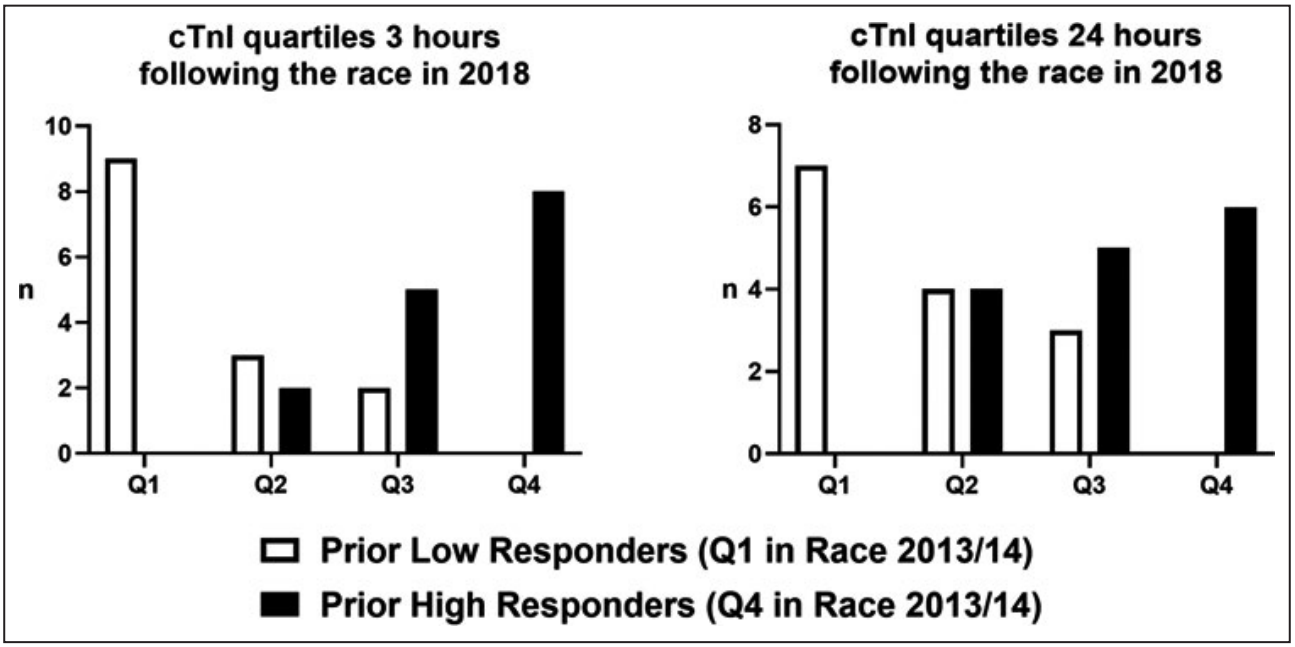

Figure 3. Consistency in ranking of cardiac troponin I (cTnI) values following the recruitment race (the North Sea Race in either 2013 or 2014) and the 2018 North Sea Race.
Low responders are defined as individuals with a cTnI value within the first quartile (Q1) of the recruitment race (T0), whereas high responders are defined as individuals with a cTnI value within the highest quartile (Q4) of the recruitment race (T0). The graph displays the number of individuals in each of the 4 quartiles based on the cTnI values achieved in the 2018 race (T2). T0 indicates recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

between low- and high-cTnI responders. Following the race in 2018, none of the low responders in the recruitment race (T0) were classified as high responders in the second race (T2), and none of the high responders were classified as low responders in the second race (T2).

Correlation Between cTnI Levels at Corresponding Time Points During the 3 Exercises

In the individual subjects, there were strong correlations between cTnI values from the 2 races (T0 and T2) and the CPX test (T1) at all corresponding time points (Figure 4). The strongest correlations between cTnI values were observed at baseline (ie, 24 hours before the exercise). Following exercise, the strongest correlation at 3 hours was between the 2 races (r=0.72, P<0.001) and at 24 hours between the CPX test and the second race (r=0.83, P<0.001). The weakest correlations were between the recruitment race (T0) and the CPX test (T1) at both 3 and 24 hours following exercise.

Linear Mixed Effects

Differences between expected values are presented in Table 3. The largest difference in expected values

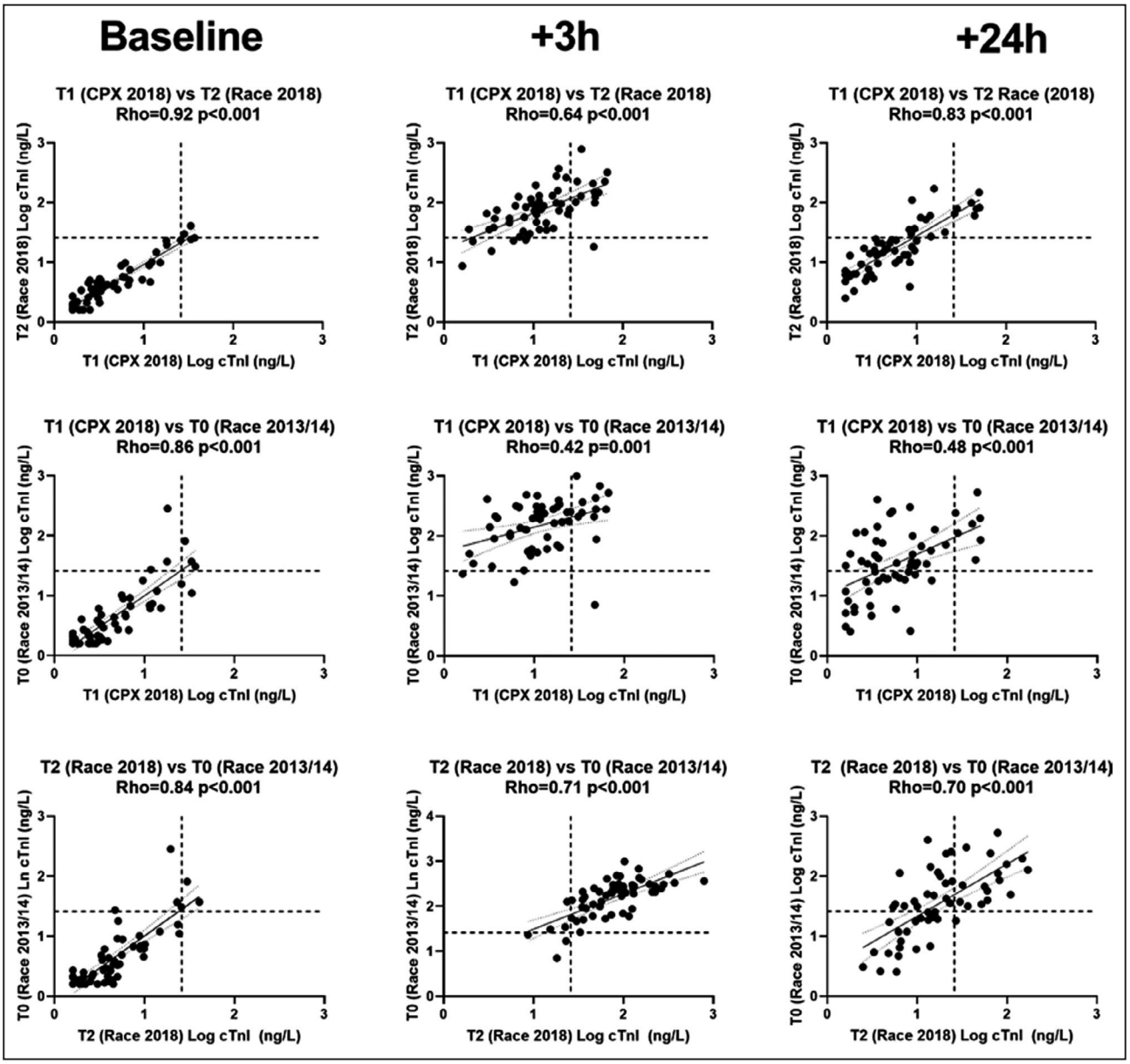

Figure 4. Scatterplot shows individual cardiac troponin I (cTnI) response at baseline, 3 h, and 24 h after the cardiopulmonary exercise (CPX) test in 2018 (T1), the 2018 race (T2), and the recruitment race in either 2013 or 2014 (T0).
Spearman bivariate correlations were used to assess the correlations between time points. Dotted lines indicate the 99th percentile of the high-sensitivity cTnI assay (26 ng/L).

Table 3. Linear Mixed Effects

Comparison Between Groups	Expected Difference	*P* Value	95% CI
Baseline			
T0–T1	5.1	0.18	−2.4 to 12.6
T0–T2	5.4	0.16	−2.1 to 12.9
T1–T2	0.3	0.95	−7.2 to 7.8
3 h after exercise			
T0–T1	199.4	<0.0005	159.9 to 238.9
T0–T2	108.1	<0.0005	68.6 to 147.6
T1–T2	−91.3	<0.0005	−130.8 to −51.8
24 h after exercise			
T0–T1	63.8	<0.00005	43.3 to 84.3
T0–T2	44.3	<0.00005	23.8 to 64.8
T1–T2	−19.5	0.06	−40.0 to 1.0

All 3 exercises (T1, T2, and T0) compared with a random intercept linear mixed-effects model. Expected differences with *P* value and 95% CI at corresponding time points between T0, T1, and T2. T0 indicates recruitment race; T1 cardiopulmonary exercise test 2018; and T2, 2018 race.

were found at 3 hours between T0 and T1. The smallest difference was at baseline between T1 and T2. Differences were highly significant at 3 hours among all groups ($P<0.00005$). At 24 hours, there was a significant difference between T0 and T1 and T0 and T2, but not between T1 and T2.

Multiple Regression Models

Multiple regression models were used to identify the predictors of the postexercise cTnI values after T1 and T2 (Table 4). Following the CPX test (T1), baseline cTnI, maximal RPP, and maximal systolic blood pressure were independent predictors of cTnI elevation at 3 hours. Following the race in 2018 (T2), baseline and cTnI response at identical time points of the race in 2013/2014 (T0) were the strongest predictors of the exercise-induced cTnI levels at both 3 and 24 hours. Duration of the race was an independent predictor of cTnI levels at 24 hours after the race but not at 3 hours.

DISCUSSION

This study demonstrates that the exercise-induced cTnI elevation is specific to each individual and that the individual cTnI level is strongly related to the workload and timing of sampling. These findings underscore that the exercise-induced cTn response needs to be interpreted in relation to the subject-specific response

Table 4. Multiple Regression Analysis

cTnI 3 h After CPX Test (T1), R^2=0.69	Nonstandardized Coefficients		Standardized Coefficients		
	B	SE	β	*t*	*P* Value
Ln cTnI baseline T1	0.53	0.09	0.58	5.97	<0.001
Ln cTnI 3 h T2	0.34	0.10	0.32	3.29	<0.001
Systolic blood pressure maximum	−0.01	0.00	−0.35	−2.12	0.04
Peak RPP	0.00	0.00	0.48	2.94	0.005
Duration of test	−0.03	0.02	−0.18	−2.17	0.03
cTnI 24 h after CPX test (T1) R^2=0.87					
Ln cTnI baseline T1	0.72	0.10	0.73	7.53	<0.001
Ln cTnI 24 h T2	0.21	0.10	0.21	2.14	0.04
Male sex	0.21	0.11	0.10	1.88	0.07
cTnI 3 h after race 2018 (T2) R^2=0.65					
Ln cTnI 3 h T1	0.40	0.08	0.43	5.0	<0.001
Ln cTnI 3 h T0	0.48	0.08	0.54	6.28	<0.001
cTnI 24 h after race 2018 (T2) R^2=0.83					
Ln cTnI baseline T2	0.40	0.15	0.39	2.72	0.009
Ln cTnI 24 h T0	0.20	0.05	0.26	3.66	0.001
Ln cTnI 24 h T1	0.37	0.14	0.37	2.65	0.01
Male sex	−0.26	0.15	−0.12	−1.76	0.08
Duration of the race	−0.18	0.09	−0.13	−2.09	0.04

The table presents the multiple linear regression models using the backward elimination method. The models included predefined variables (age, sex, systolic blood pressure baseline, metabolic equivalent, hours, duration of exercise, cTnI at baseline), variables with a bivariate correlation *P* value <0.05 (Table 2), and the cTnI values at corresponding timepoints at CPX test 2018 (T1), 2018 race (T2), and the recruitment race (T0). CPX indicates cardiopulmonary exercise; cTnI, cardiac troponin I; Ln cTnI, natural logarithm of cardiac troponin I; and RPP, rate pressure product.

to exercise, exercise workload, and timing of sampling following the exercise. These findings have implications for both clinical interpretation and future scientific studies exploring the exercise-induced cTn response. The present findings are particularly important for the differentiation between a physiological and pathological response, emphasizing that knowledge of the prior exercise-induced cTn response and precise information about workload (exercise intensity and duration) are necessary to generate reliable prediction models. These findings underscore the limitations in the interpretation of cTn increase following exercise in a clinical setting, wherein information about prior cTn response and exercise workload are rarely available.

The increase in troponin following exercise has been demonstrated by numerous studies.[3] In line with the previous studies, the present study demonstrates that cTnI levels relate to baseline cTn concentration, exercise intensity, and duration of exercise.[10,21,22] However, the precise relationship between workload and cTn elevation remains obscure. Figure 2 demonstrates the close relationship between troponin response and exercise intensity and duration, with the lowest postexercise cTnI levels following the CPX test (T1), higher following the race in 2018 (T2), and highest following the recruitment race (T0). The difference in cTnI levels following the 2 races (T0 and T2) reflects the higher exercise intensity in the recruitment race (T0) than in the 2018 race (T2). The race duration was shorter in the recruitment race (T0) than in the 2018 race (T2), indicating a longer duration of high-intensity exercise in the recruitment race than in the 2018 race. The primary reason for this difference in race duration relates to the study-related interference during the 2018 race. In 2018, all study individuals were stopped 4 times for blood pressure measurements during the race. Although each pit stop lasted <2 minutes, most riders waited to join other riders coming up from behind. Because there was a ranking of participants in the race, subsequent groups were slower, thereby further reducing the duration of high-intensity exercise. This is underlined by the findings from the linear mixed-effects models. The expected differences in cTnI values increase with increasing exercise intensity and duration; the largest differences were at 3 hours after exercise between the first race, the second race, and the CPX test. These findings underscore the impact of exercise intensity and duration on the cTnI response both at 3 and 24 hours following exercise. Although race duration is a surrogate for the duration of high-intensity exercise, it is a complex parameter that needs careful interpretation. Because there were no accurate measurements of heart rate or work during the first race, it is not possible to evaluate differences in the physical performance in study participants between the recruitment race and the 2018 race (T0 and T2) accurately. Future studies need to incorporate repeated exercise with accurate measurements of workload to allow a better prediction of the relationship between repeated exercise and cTn release.

Both during the CPX test and the 2018 race, there was a univariate correlation between cTnI and peak RPP following exercise. However, in multiple regression models, RPP remained an independent predictor of cTnI elevation only at 3 hours following exercise in the CPX test. When interpreting these results, it should be noted that peak RPP measurements from the 2018 race have a drawback of uncertainty because blood pressure was measured at only 4 time points during the race. The use of more accurate tools, allowing more frequent monitoring of blood pressure during exercise, preferably without the need to interrupt the exercise, might provide better insights into the relationship between increased cardiac workload during exercise and exercise-induced cTn response.

Few studies have used multiple regression models to predict the exercise-induced cTn response.[9,23–25] Several variables have been identified as independent predictors of the cTnI response, including age,[23] duration of exercise,[24] the intensity of exercise,[8,22] changes in creatinine,[26] exercise experience,[27] and systolic blood pressure.[9] However, no study has used information from a previous exercise-induced cTn response in the models. A common finding from the multiple regression models is that the models explain only a small proportion of the total variation in the cTn response to exercise, with an R^2 ranging from 9% to 44%.[23,24] Compared with the previous studies, the present study found multiple regression models with far larger explanatory (R^2) values ranging from 65% to 87%. The model fit after adding information about the previous cTnI value (T0) in the multiple regression models was more evident following the race in 2018 (T2) than following the CPX test (T1). This might, in part, be explained by lesser exercise-induced cTnI elevation following the CPX test than the cTnI elevation following the 2 races (T0 and T2) (Figure 2).

The physiological mechanisms causing troponin release during exercise are largely unknown. It has been proposed that cTn elevation might be because of an increase in preload, causing increased myocardial stretch and integrin-mediated transportation of cTn molecules across the intact myocyte membranes.[28] However, in the present study, no difference in the echocardiographic parameters was observed, and markers of dehydration (creatinine) did not explain the variation in the exercise-induced cTnI response in the multiple regression models. Circulating troponins levels are influenced by posttranslational modifications such as proteolytic degradation, phosphorylation, glycation, and acetylation.[29] Individual differences in these changes might

alter the circulating cTn molecules and influence the detection of cTn molecules by current assays. Notably, a recent study demonstrated the presence of smaller cTnT molecules released in healthy runners after a marathon, compared with larger cTnT molecules released after acute myocardial infarction.[30] This finding suggests that there might be changes in the molecular structure of circulating troponins when comparing exercise with ischemic injury. It remains to be determined whether there are also changes in the molecular structure of cTnI that can explain the large individual differences in the exercise-induced cTnI response.

Strengths and Limitations

The strengths of this study are the extensive data and the measurement of high-sensitivity cTnI at different exercise loads and time points separated by >4 years. Normal echocardiographic findings and the absence of coronary pathology on repeated coronary computed tomography angiography ensured that the cause of cTnI elevation was not related to the abnormal cardiac function or obstructive coronary artery disease. Although the study subjects were well-trained participants from a selected cohort, age, sex, and physical characteristics are representative of an average recreational athlete. The recruitment of well-trained subjects in the present study ensures that exercise-performance was not limited by factors such as muscular capacity or technical skills.

Several limitations apply to the present study. First, this is an observational study with study subjects reflecting a highly selective cohort. Second, as discussed above, there are no additional data except the race duration to evaluate exercise intensity from the recruitment race (T0). Hence, it is not possible to make an accurate comparison of difference in race intensity between the recruitment (T0) and the 2018 race (T2). The exercise-induced cTnI response was only followed for 24 hours. We have previously reported that prolonged release of cTnI might be associated with a pathological cTnI response.[5] It would be of interest to study the reproducibility of the duration of the cTnI elevation beyond 24 hours following exercise.

CONCLUSIONS

The present study shows that there are large but reproducible differences in the magnitude of the exercise-induced cTnI responses among individuals. The exercise-induced cTnI response reflects exercise intensity and duration in a person-specific manner. This finding underscores the need to consider both workload, timing of sampling, and earlier cTnI response when attempting to differentiate physiological from a pathological cTnI response to exercise. These findings have important implications for the interpretation of postexercise cTnI values and for the future design of studies evaluating the exercise-induced cTnI response.

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Disclosures

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Supplementary Material

Data S1
Figure S1

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Supplemental Material

Data S1.

Supplemental Methods

Cardiopulmonary exercise (CPX) test

All study participants were tested on their personal bikes fitted to a Cyclus 2 electronically braked ergotrainer (RBM elektronik-automation; Leipzig, GER)[14]. Each participant performed a 10-minute warm-up before exercise tests, resistance was kept low and was guided by the test-leader. The lactate threshold test was executed as a 4-minute incremental load stepwise test. The workload was based on previous training history and results from warm-up (min 50w – maximum 220w). The workload was increased with fixed individualized (min 15w – maximum 30w) steps every fourth minute. Lactate was measured in capillary blood from the participants' index finger on the Lactate Scout+ (EKF Diagnostic, Cardiff, GB). Gas exchange was measured breath by breath on a Jaeger Vyntus CPX (Carefusion, Hoechberg, GE). Lactate threshold was defined as a lactate value > 1.5 mmol/l above mean value from step 1 and 2 or a RER > 1.0. For each step, including rest and warm-up, the following variables were collected; Work (watt), blood pressure (mmHg), VO_2 (ml/min/kg), RER, Lactate, and heart rate (bpm). Following the stepwise determination of lactate threshold, participants were allowed a maximum of 5-minute cooldown, before performing the VO_{2max} test. The VO_{2max} test was a ramp protocol started at 70-250 (min-max) watts with an increase in the workload of 15-32 (min-max) Watt/min until exhaustion. The VO_{2max} test was performed to reach maximum effort between 5 and 10 minutes. Pre-test blood pressure was obtained at the start of the test and maximal blood pressure was obtained immediately after the end of the test with the participant still seated on the bike. VO_{2max} was defined as the point where VO_2 reached a plateau despite increasing resistance. Peak power and peak heart rate were the maximum value achieved during this test.

Figure S1. Race profile, altitude outlined.

Points of blood pressure measurements marked. Diagram exported from the Garmin Connect website (copyright Garmin International, KS, US).