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The relationship between workload and exercise-induced cardiac troponin elevations is influenced by non-obstructive coronary atherosclerosis

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Abstract

The relationship between exercise-induced troponin elevation and non-obstructive coronary artery disease (CAD) is unclear. This observational study assessed non-obstructive CAD's impact on exercise-induced cardiac Troponin I (cTnI) elevation in middle-aged recreational athletes. cTnI levels of 40 well-trained recreational athletes (73% males, 50 ± 9 years old) were assessed by a high-sensitive cTnI assay 24 h before, and at 3 and 24 h following two high-intensity exercises of different durations; a cardiopulmonary exercise test (CPET), and a 91-km mountain bike race. Workload was measured with power meters. Coronary computed tomography angiography was used to determine the presence or absence of non-obstructive (<50% obstruction) CAD. A total of 15 individuals had non-obstructive CAD (Atherosclerotic group), whereas 25 had no atherosclerosis (normal). There were higher post-exercise cTnI levels following the race compared with CPET, both at 3 h (77.0 (35.3–112.4) ng/L vs. 11.6 (6.4–22.5) ng/L, $p < 0.001$) and at 24 h (14.7 (6.7–16.3) vs. 5.0 (2.6–8.9) ng/L, $p < 0.001$). Absolute cTnI values did not differ among groups. Still, the association of cTnI response to power output was significantly stronger in the CAD versus Normal group both at 3 h post-exercise (Rho = 0.80, $p < 0.001$ vs. Rho = −0.20, $p = 0.33$) and 24-h post-exercise (Rho = 0.87, $p < 0.001$ vs. Rho = −0.13, $p = 0.55$). Exercise-induced cTnI elevation was strongly correlated with exercise workload in middle-aged athletes with non-obstructive CAD but not in individuals without CAD. This finding suggests that CAD influences the relationship between exercise workload and the cTnI response even without coronary artery obstruction.

KEYWORDS

atherosclerosis, biomarkers, cardiac troponin, exercise

1 | INTRODUCTION

The health benefits of physical activity in individuals with cardiovascular disease have been demonstrated,[1,2] and increased physical activity is recommended as one of the most critical risk reduction interventions in cardiovascular disease, both as primary and secondary prevention.[3] Patients with symptoms and signs of ischemia have an increased risk of myocardial infarction and sudden cardiac death,[4] and CAD is the most common cause of sudden cardiac death during physical exercise in individuals >35 years of age.[5] The increased risk is also evident in non-obstructive CAD individuals.[5] Indeed, 60% of individuals suffering a sudden cardiac death during physical activity were asymptomatic before the event.[6] Predictors of increased risk of adverse events in physically active individuals with asymptomatic non-obstructive CAD are currently lacking. Prolonged high-intensity endurance exercise causes increased cardiac troponin (cTn) levels in both individuals with and without CAD.[7] Post-exercise cTn levels in healthy individuals often exceed the limits defining myocardial injury.[8] The clinical interpretation of the exercise-induced cTn response is therefore challenging.[9] Recent studies have reported an association between post-exercise cTn levels, adverse cardiac events,[10] and obstructive coronary artery disease.[11]

Several mechanisms have been suggested as potential causes of exercise-induced cTn elevation: reversible, apoptotic, and necrotic injury.[7] Exercise-induced cTn is thought to originate from increased cardiomyocyte permeability due to cell wounds and bleb-formation or higher cardiomyocyte turnover, apoptosis or necrosis.[7] Previous studies have shown a relationship between exercise intensity, duration of exercise and exercise-induced cTn.[7] Indeed, higher post-exercise values have been found in patients with silent obstructive coronary artery disease.[11,12] Previous work from our study group suggests a potential link between increased blood pressure[8] and the duration of high heart rate and exercise-induced cTn elevation.[13] These findings suggest a link between exercise-induced cTn elevation and myocardial injury in susceptible individuals with underlying coronary artery disease (CAD). A major challenge with previous studies is a lack of accurate workload assessment during exercise, particularly in field studies.

This study hypothesized that non-obstructive CAD would alter the cTn response to increased workloads. This study used power meters to assess workload accurately and to determine the individual exercise-induced cTnI response following laboratory exercise testing and a field study of prolonged high-intensity endurance exercise.

2 | MATERIALS AND METHODS

The study population comprised asymptomatic, well-trained middle-aged recreational athletes without known cardiovascular disease. Participants were recruited among athletes without obstructive CAD assessed by coronary computer tomography angiography (CCTA) in the prior NEEDED studies in 2013/14.[8] Following enrollment, participants were exposed to two high-intensity exercises: a cardiopulmonary exercise test (CPET) and a recreational 91-km mountain bike race (Figure 1). These tests were conducted in 2018. Following the final exercise (the North Sea Race in 2018), a new CCTA scan was performed to determine the presence or absence of coronary atherosclerosis (Figure 1). According to the CCTA findings following the race in 2018, all individuals were categorized as either with or without coronary atherosclerosis. CCTA images were acquired using a Siemens Somatom Definition Flash

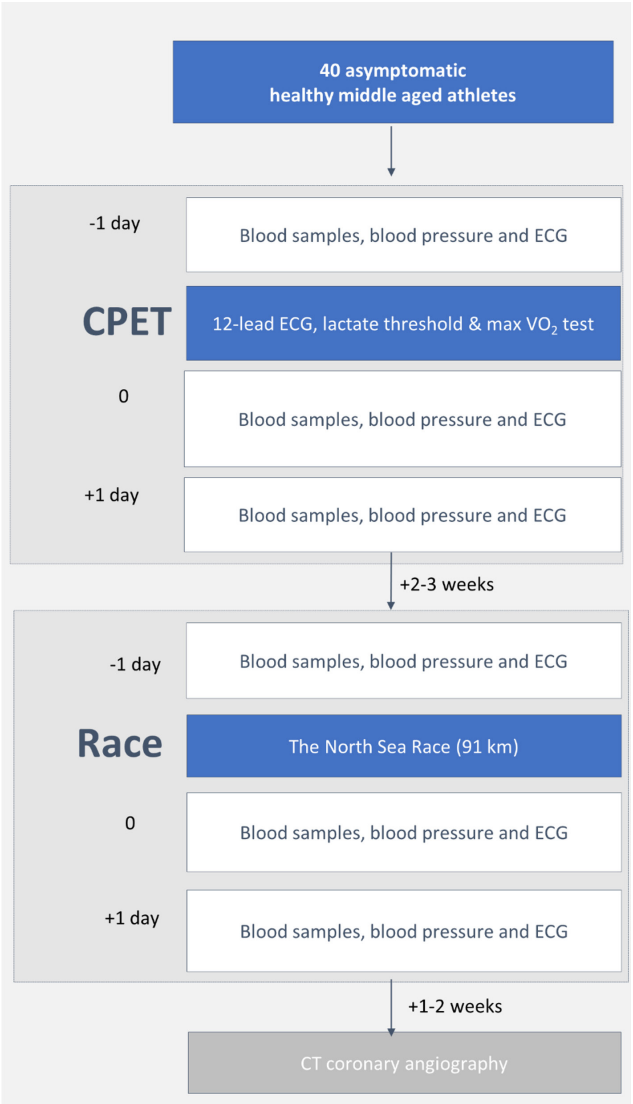

FIGURE 1 Study chart. CPET, cardiopulmonary exercise test.

Dual Source. The Normal group was defined as individuals without any evidence of soft or calcified plaques or any other coronary abnormality. The Atherosclerotic group was defined as individuals with at least one atherosclerotic plaque with less than 50% luminal stenosis in any of the three main coronary arteries, a diagonal or marginal branch. Individuals with obstructive CAD were excluded from this study. Two experienced radiologists independently assessed examinations, blinded to the cTnI findings. Rate pressure product (RPP) was used to determine cardiac work.[14] Mean RPP was calculated as mean systolic blood pressure during exercise multiplied by mean heart rate.

The study complies with the Declaration of Helsinki. All participants signed informed consent forms before the study, and the study was approved by the Regional Ethics Committee (REK nr 2013/550). The data supporting this study's findings are available from the corresponding author upon reasonable request.

2.1 | Baseline measurements

Baseline screening and noninvasive blood pressure, height, weight, and waist circumference were measured by experienced healthcare professionals before the CPET. Repeated measurements and clinical assessments were performed 24 h before, 3 and 24 h after both exercises. After 5 min of rest, blood pressure was measured sitting. A 12-lead ECG was taken before the test as recommended by the pre-participation consensus statement.[15] Questionnaires on prior training history, medical history, demographics and symptoms were answered at baseline screening and after the race. The total amount of weekly exercises before the race was assessed using the International Activity Questionnaire (IPAQ).[16] The data from the IPAQ was used to calculate the metabolic equivalent hours (MET-h) per week for each participant.

2.2 | Blood samples and cardiac troponin I (cTnI) analysis

Blood was sampled 24 h prior, 3 and 24 h after the CPET and the race. Blood samples were stored at 4°C and analyzed within 24 h by a hs-cTnI STAT assay at Architect SR2000i (Abbott Diagnostics, Abbot Park, IL, USA) with a lower detection limit of 1.6 ng/L and an overall 99th percentile of 26 ng/L.

2.3 | The cardiopulmonary exercise test

The CPET included a 12-lead ECG to monitor potential ischemia and arrhythmia, blood pressure measurements, a lactate threshold assessment and a VO_{2max} measurement. All study participants were tested on their bikes fitted to a Cyclus 2 electronically braked ergo trainer (RBM Elektronik-Automation; Leipzig, GER).[17] Each participant performed a 10-min warm-up before the exercise test. Resistance was kept low and guided by the test leader. The lactate threshold test was executed as a 4-min incremental load stepwise test using fixed individualized steps (min 15 W–max 30 W). The choice of workload was based on previous training history and the warm-up (min 50 W–max 120 W). Lactate was measured in capillary blood from the participant's index finger on the Lactate Scout+ (EKF Diagnostic, Cardiff, UK). Gas exchange was measured breath by breath on a Jaeger Vyntus CPET (Carefusion, Hoechberg, Germany). The lactate threshold was defined as a lactate value >1.5 mmol/L above the mean value from steps 1 and 2 or an RER >1.0. At the end of each 4-min step (including rest and warm up), the following variables were collected: Workload (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-min cool down before performing the VO_{2max} test. The VO_{2max} test was a ramp protocol started at 70–240 W (min–max) with an increased workload of (min–max) 15–30 W/min until exhaustion. The VO_{2max} test was performed to reach maximum effort between 5 and 10 min following the onset of exercise. Pre-test blood pressure was obtained at the start of the test. Maximal blood pressure was obtained immediately after the test's end while the participants were still seated on the bike. VO_{2max} was the point where VO_2 reached a plateau despite increasing resistance. Peak power (averaged over 30 s) and peak heart rate were the maximum value achieved. Mean power was calculated from the LT and VO_{2max} test readings.

2.4 | Measurements during the race

The North Sea Race 2018 is a 91 km long mountain bike race between Egersund and Sandnes in southwestern Norway. Blood pressure was measured at the start and finish of the race and four prespecified points during the race. These points were placed at the top and bottom of the two most strenuous hills (after 34 and 69 km) to test the response to strenuous exercise during the race and the ability to recover after the increased work. The study participants were stopped to measure blood pressure on the right arm. Stops were arranged as a pit stop to keep time away from the race as low as possible. Measurements were made manually with a Heine G5, G7 or XXL LF-T (Heine,

Herrsching, Germany). Bodyweight was measured at the start and immediately following the race's finish using the same calibrated scale for all measurements (Seca, Chino, USA). All subjects were supplied with the same sports watch (Garmin Forerunner 935, Garmin, Kansas, USA). GPS coordinates, altitude, speed, distance, and heart rate were sampled every second. Heart rate was collected with a Garmin chest strap. Work performed during the race was assessed by continuous measurement with a Stages power meter (Stagespower, Colorado, USA)[18] mounted on the participant's bike. All power meters were calibrated before the race. Study participants were blinded for power measurements during the race.

2.5 | Statistical analysis

Normally distributed continuous variables are reported as mean ± SD, while continuous variables with markedly skewed distributions are reported as median and interquartile range (25th–75th percentile). The Shapiro–Wilk test was used to test for normality. For continuous variables, The Mann–Whitney *U* test or a Student *t*-test was used to compare groups, as appropriate. For categorical variables, a chi-square test was performed. A Paired Student *t*-test or a Wilcoxon signed-rank test assessed differences between sampling points. A two-tailed *p*-value <0.05 was considered significant. For bivariate correlation, we used Spearman analysis. Regression analysis was used to estimate the slope coefficients between power output and exercise-induced cTn for both groups in both Race and CPET. Comparisons between exercises within groups imply possible dependencies due to repeated measurements. Bootstrap was used to assess differences in the steepness of the regression lines between CPET and Race. We have used a 95% BCa interval based on 100 000 bootstrap samples.[19] The regression slope for the Race and the CPET data must be computed for each bootstrap sample. The difference between these two slopes is the statistic of interest. The dependence between the two calculated slopes stems from the fact that the same individuals have produced both the Race and the CPET data. This structure is preserved by bootstrapping the same individuals from both data sets. The statistical software programs SPSS version 24, GraphPad Prism 8, and R[20] were used for statistical analyses.

3 | RESULTS

3.1 | Baseline characteristics

A total of 40 athletes (30 males) were recruited for this study (Figure 1). At the CCTA scan after the last exercise, 15 participants had non-obstructive CAD (Atherosclerotic group). None of the participants had obstructive CAD (>50% obstruction). The remaining individuals ($n = 25$) had normal coronary arteries without detectable coronary atherosclerosis (Normal group).

Individuals with atherosclerosis were older and had a higher Framingham Risk Score and HbA1c, but they were more physically active than participants without coronary atherosclerosis (Table 1). The participants with and without coronary atherosclerosis had no significant differences in other baseline risk parameters, such as BMI, blood pressure, waist circumference, total cholesterol, LDL, HDL cholesterol or triglycerides between the participants with and without coronary atherosclerosis. Detailed characteristics of participants with atherosclerosis can be found in Table S1.

3.2 | CPET and race performance

There were no significant pathological changes to the 12-lead ECGs during the CPET or any significant ECG findings after the two exercises. The duration of the race was significantly ($p < 0.001$) longer than the CPET (Race: 236 (214–268) min, CPET: 43 (40–45) min), and the total workload was significantly ($p < 0.001$) higher during the race compared with the CPET (Race: 499 ± 6 mean W/kg × min, CPET: 159 ± 35 mean W/kg × min).

There were no between-group differences in peak VO_2 or peak power between individuals with and without CAD, neither during the CPET test nor during the Race (Table 2). There were no differences in mean systolic blood pressure during the race. However, there were significant differences in systolic ($p = 0.001$) and diastolic blood pressure ($p = 0.002$) measured at the top of the most strenuous hill, with higher values among subjects with CAD.

3.3 | Cardiac Troponin I

There was a significant increase in post-exercise cTn levels in all participants (Figure 2). The highest post-exercise cTnI values were at 3 h following both exercises. The post-exercise cTnI values were significantly higher after the race compared with the CPET, both at 3 h (77.0 (35.3–112.4) ng/L vs. 11.6 (6.4–22.5) ng/L, $p < 0.001$) and at 24 h (14.7 (6.7–16.3) ng/L vs. 5.0 (2.6–8.9) ng/L, $p < 0.001$).

There was no significant ($p = 0.12$) difference in pre-exercise cTnI before the CPET, comparing the Normal group with the Atherosclerotic group: 3.0 (1.7–6.8) ng/L versus 5.1 (2.9–6.9) ng/L. In contrast, before the race, the Normal group had significantly ($p = 0.04$) lower cTnI values than the Atherosclerotic group: 2.6 (1.6–4.8) ng/L

TABLE 1 Baseline characteristics.

Baseline	Normal ($n=25$)	Atherosclerosis ($n=15$)	p
Male(%)	19 (76)	11 (73)	0.85
Age (years)	46.7 (±8.0)	54.4 (±8.9)	**0.007**
BMI (kg/m^2)	24.9 (23.3–26.0)	25.1 (23.2–27.6)	0.44
Former smoker (%)	14 (56)	6 (40)	0.33
Systolic blood pressure (mmHg)	133 (±16)	139 (±13)	0.25
Diastolic blood pressure (mmHg)	81 (±11)	86 (±9)	0.12
Waist circumference (cm)	85.0 (80.5–87.3)	88.0 (82.0–101.0)	0.11
MET hours per week (METh)	50.6 (33.4–88.3)	68.6 (64.0–101.7)	0.03
Resting heart rate (bpm)	59 (±11)	57 (±6)	0.41
Total cholesterol (mmol/L)	5.0 (±0.9)	5.0 (±0.8)	0.94
LDL-cholesterol (mmol/L)	3.0 (±0.8)	3.2 (±0.7)	0.62
HDL-cholesterol (mmol/L)	1.6 (±0.3)	1.4 (±0.4)	0.15
Triglycerides (mmol/L)	1.1 (0.9–1.8)	1.3 (0.8–1.7)	0.77
Framingham risk score	1.1 (0.5–7.3)	3.0 (1.1–9.1)	0.03
HbA1c (%)	5.4 (±0.2)	5.6 (±0.2)	**0.002**
BNP (pg/mL)	10.0 (0.0–17.8)	15.8 (10.0–25.1)	0.09
Creatinine (μmol/L)	75.5 (±12.4)	74.4 (±11.4)	0.79

Note: Baseline characteristics of the group of individuals with normal coronary arteries (normal, $n=25$) compared with those with non-obstructive coronary artery disease (atherosclerosis, $n=15$). Normally distributed values are reported as mean ± SD. Variables with markedly skewed observations are reported as median (25th–75th percentile). Student t-tests or the Mann–Whitney U test analyze the groups' differences as appropriate. Atherosclerotic group highlighted in shades. Significant p-values highlighted in bold.

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalents.

versus 4.5 (3.4–8.8) ng/L. Following 3 h race, the same proportion (92% vs. 93%, $p=0.88$) of participants exceeded the 99th percentile of the cTnI assay. There were no significant differences at 24 h between the two groups, neither following the CPET test nor the race.

Significant differences were found between the normal and the Atherosclerotic groups in the relationship between workload and post-exercise cTnI levels (Table 3). Strong and significant correlations existed between the total workload assessed by power meters and the post-exercise cTnI levels following CPET and Race among participants in the Atherosclerotic group. In contrast, these associations were absent in the Normal group (Figure 3). Similar observations were made for the association between myocardial workload assessed by RPP and post-race cTnI levels (Figure 4). In the Atherosclerotic group, there were significant differences in the steepness of the regression lines both at 3 h (CPET: $B_1=22.4$ (±6.8) vs. Race: 111.6 (±34.2), $p<0.0001$) and at 24 h (CPET: $B_1=7.1$ (±6.0) vs. Race 28.4 (±10.3), $p<0.001$) between CPET and Race data. The strongest correlation was found at 24 h post-race ($r=0.87$, $p<0.001$) (Figure 5). These findings were evident and significant even when adjusting for age and Hba1c in the same model.

The participant with the highest workload in the Atherosclerotic group achieved a mean workload of 2.73 W/kg over the entire race. The highest achieved mean value in the Normal group was 3.24 W/kg. When comparing individuals from the Atherosclerotic group ($n=9$) with the most increased workload (W/kg between 2.0 and 3.0) to Normal individuals ($n=14$) within the same range of workload, cTnI levels were significantly higher in the Atherosclerotic group at 3 h (130.0 ng/L vs. 70.1 ng/L, $p=0.036$), but not at 24 h (30.0 ng/L vs. 11.6 ng/L, $p=0.21$).

4 | DISCUSSION

This study found increased post-exercise cTnI levels in response to increased workloads in both groups of individuals with and without coronary atherosclerosis. More importantly, this is the first study to report a strong correlation between power output and post-exercise cTnI levels in asymptomatic individuals with non-obstructive coronary atherosclerosis, which was completely absent

TABLE 2 Physiological variables during exercise comparing the normal and atherosclerotic groups.

	Normal ($n=25$)	Atherosclerosis ($n=15$)	p-value
CPET test			
Duration (min)	43.2 ± 5.3	42.9 ± 5.1	0.86
Mean heart rate (bpm)	133 ± 12	129 ± 12	0.39
Maximum heart rate (bpm)	181 ± 10	174 ± 13	0.05
Mean power (W)	239 ± 48	223 ± 56	0.34
Mean Power Index (W/kg)	3.0 ± 0.5	2.7 ± 0.5	0.11
Maximum power (W)	313 ± 65	293 ± 76	0.37
Maximum Power Index (W/kg)	3.9 ± 0.7	3.6 ± 0.8	0.17
Peak VO_2 (mL/min/kg)	43.5 ± 9.1	40.0 ± 8.8	0.91
Maximum systolic blood pressure (mmHg)	188 ± 27	203 ± 34	0.14
Maximum diastolic blood pressure (mmHg)	75 ± 23	85 ± 23	0.18
Rate pressure product (mmHg × bpm)	25 967 ± 2474	26 049 ± 3440	0.93
Race			
Duration (h)	3.9 (3.5–4.5)	4.1 (3.6–4.5)	0.53
Mean heart rate (bpm)	156 ± 8	151 ± 12	0.10
Maximum heart rate (bpm)	179 ± 11	174 ± 12	0.21
Mean power (W)	176 (132–203)	177 (135–189)	0.92
Mean Power Index (W/kg)	2.2 ± 0.6	2.0 ± 0.5	0.40
Maximum power (W)	668 (517–799)	640 (487–682)	0.43
Maximum Power Index (W/kg)	8.7 (6.9–9.5)	7.4 (6.9–9.7)	0.46
Mean systolic blood pressure (mmHg)	164 ± 17	171 ± 14	0.17
Maximum systolic blood pressure (mmHg)	219 ± 26	241 ± 14	**0.001**
Mean diastolic blood pressure (mmHg)	82 ± 8	86 ± 7	0.10
Maximum diastolic blood (mmHg)	95 ± 13	107 ± 8	**0.002**
Rate pressure product (mmHg × bpm)	25 570 ± 2931	25 842 ± 2877	0.78

Note: Physiological variables measured during the cardiopulmonary exercise (CPET) test and the race in the group of individuals with normal coronary arteries (normal, $n=25$) compared with the group of individuals with non-obstructive coronary artery disease (atherosclerosis, $n=15$). Values with a normalized distribution reported as mean ± SD, Student t-test analyses group differences. Values with a markedly skewed distribution are reported as median (25th–75th percentile), the difference between the groups analyzed with the Mann–Whitney U test. Atherosclerotic group highlighted in shades. Significant p-values highlighted in bold.

Abbreviations: CPET, cardiopulmonary test; Race, 91-km mountain bike race.

in healthy peers. A strong correlation was consistently present following the CPET and race, with a significantly steeper relationship following the race probably attenuated by a longer exercise duration. This finding suggests an increased myocardial sensitivity to increased workloads in individuals with atherosclerosis, even in the absence of obstructive CAD.

Similar to other studies, there was no difference in the mean post-exercise troponin values when comparing the two groups.[21] In this study, the mean values of the two groups hide the individual differences in the cTnI response to workload. Both groups, with and without atherosclerosis, had a similar mean increase of TnI levels in response to the increased exercise duration after the race compared

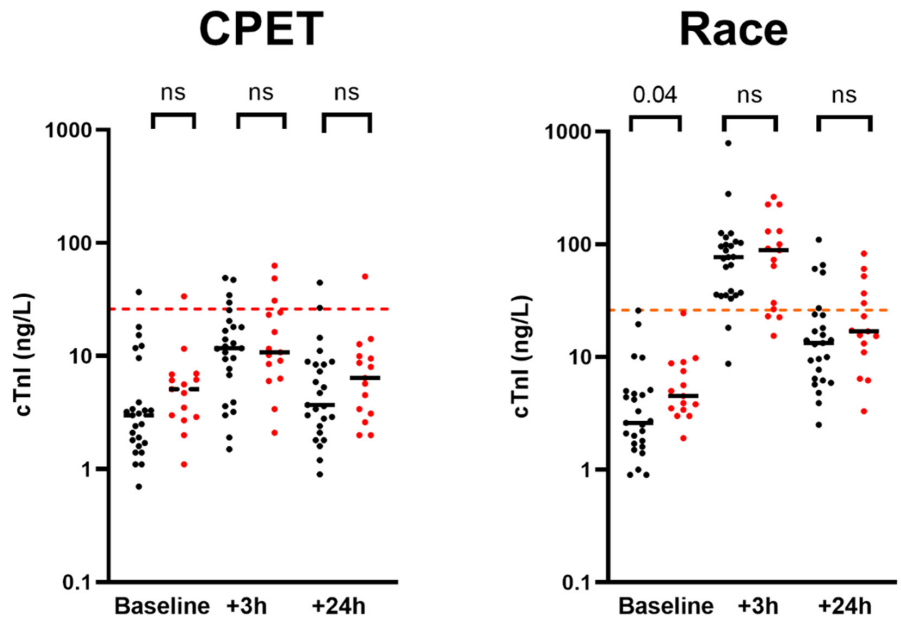

FIGURE 2 Cardiac Troponin I Kinetics. Individual values of cTn at baseline, +3 h and 24 h following exercise. Horizontal lines represent median values. The dotted red line represents the 99 percentile of normal cTnI values. The *y*-axis Log transformed—differences between groups were analyzed with the Mann–Whitney *U* test. Atherosclerotic patients are in red dots, and normal patients are in black dots—median values indicated in black horizontal bars.

with the CPET. However, when adding accurate workload power meter measurements, there was a reproducible difference in the association between power output and cTnI elevation comparing individuals with and without coronary atherosclerosis. The atherosclerotic individuals with a low workload had lower cTnI values than the normal individuals. In contrast, atherosclerotic individuals had higher cTnI values at 3 h than normal individuals in the same power range (w/kg between 2.0 and 3.0). These findings may suggest a more sensitive myocardial response to increasing workload in individuals with coronary atherosclerosis, potentially allowing an individual adjustment of the cTnI response using power meter measurements during exercise.

When comparing individuals in the same power range (w/kg between 2.0 and 3.0), atherosclerotic participants had higher cTnI values at 3 h but not 24 h. This contradicts an earlier study finding an association with coronary stenosis and cTnI at 24 h, potentially evidence of myocardial necrosis.[11] A recent study finds an association between cTnI and myocardial oedema, evident in cardiovascular magnetic resonance after cycling.[22] Comparable to our group, both oedema and cTnI normalized after 24 h. Even though there were no signs of myocardial injury, a recent editorial speculates that these increased physiological responses in some individuals could indicate subclinical cardiovascular disease.[23]

Cardiac troponin elevation is an essential marker of myocardial ischemia and long-term cardiovascular prognosis.[24,25] Myocardial ischemia may be present in individuals with coronary atherosclerosis, even without obstructive CAD, due to arterial stiffness and microvascular and endothelial dysfunction.[26–28] Furthermore, non-obstructive CAD can generate an intracoronary pressure drop at the site of the atherosclerotic plaque, causing myocardial ischemia.[29] The present study found higher exercise-induced cTnI values in individuals with coronary atherosclerosis exposed to the highest workloads (Figure 3). Furthermore, the increased gradient of the regression line after the race suggests an exaggerated troponin response to workload in individuals with coronary atherosclerosis.

Our atherosclerotic participants had a higher blood pressure at the top of the most strenuous hill, indicative of a higher cardiac load than their normal counterparts. The elevated cTnI in our group is probably not due to myocardial necrosis but is indicative of increased cardiomyocyte stress. Notably, the assessment of cardiac work by RPP indicates that these findings are related to an increased troponin response to increased cardiac workload. The same relationship is found in the study by Lanza et al., where post-exercise cTn in patients with suspected unstable angina is related to exercise intensity and systolic blood pressure during exercise.[30] Our findings support an association between subclinical myocardial disease and the myocardial response seen during increased myocardial workload in individuals with coronary atherosclerosis.

TABLE 3 Correlations between cardiac troponin after exercise and physical measurements in CPET and Race.

	Normal ($n=25$)				Atherosclerosis ($n=15$)			
	cTnI 3-h		cTnI 24-h		cTnI 3-h		cTnI 24-h	
	Rho	*p*-value	Rho	*p*-value	Rho	*p*-value	Rho	*p*-value
CPET test								
Duration CPET test (min)	−0.06	0.77	−0.06	0.80	0.21	0.46	0.27	0.34
Mean power (W)	−0.20	0.35	−0.13	0.55	**0.63**	**0.01**	**0.58**	**0.02**
Mean Power Index (W/kg)	−0.22	0.28	−0.18	0.38	**0.78**	**<0.001**	**0.62**	**0.01**
Mean HR (bpm)	0.02	0.94	−0.02	0.93	0.44	0.11	0.34	0.23
Power at max VO_2 (W)	−0.12	0.56	−0.05	0.81	**0.68**	**0.01**	**0.60**	**0.02**
Power index at max VO_2 (W/kg)	−0.19	0.37	−0.17	0.43	**0.69**	**0.005**	**0.52**	**0.05**
Peak HR (bpm)	0.18	0.39	0.15	0.47	0.48	0.07	0.47	0.08
Peak VO_2 (mL/min/kg)	−0.08	0.71	−0.06	0.78	0.48	0.07	0.28	0.32
Maximum systolic blood pressure (mmHg)	0.15	0.50	0.10	0.63	0.34	0.22	0.17	0.56
Maximum diastolic blood pressure (mmHg)	0.12	0.56	0.03	0.90	−0.15	0.60	−0.16	0.57
Rate pressure product (bpm × mmHg)	−0.06	0.78	−0.12	0.57	0.41	0.13	0.36	0.19
Race								
Race duration (h)	0.13	0.55	0.10	0.64	**−0.80**	**<0.001**	**−0.85**	**<0.001**
Mean heart rate (bpm)	0.24	0.25	0.27	0.20	0.49	0.07	**0.61**	**0.02**
Maximum heart rate (bpm)	0.26	0.21	0.27	0.20	0.25	0.36	0.33	0.23
Mean power (W)	−0.18	0.39	−0.08	0.70	**0.66**	**0.007**	**0.71**	**0.003**
Mean Power Index (W/kg)	−0.20	0.33	−0.13	0.55	**0.80**	**<0.001**	**0.87**	**<0.001**
Maximum power (W)	0.08	0.69	0.15	0.49	**0.52**	**0.05**	**0.59**	**0.02**
Maximum Power Index (W/kg)	0.12	0.58	0.15	0.47	**0.70**	**0.004**	**0.80**	**<0.001**
Duration of race with power > LT (min)	−0.06	0.77	0.11	0.62	−0.16	0.58	−0.27	0.33
Duration of race with power > max VO_2 (min)	−0.04	0.86	−0.01	0.96	0.13	0.64	0.09	0.75
Duration of race with HR > HR at LT (min)	0.23	0.27	0.43	0.03	−0.11	0.69	−0.05	0.87
Mean systolic blood pressure (mmHg)	0.13	0.55	0.17	0.42	**0.66**	**0.01**	**0.56**	**0.03**
Mean diastolic blood pressure (mmHg)	0.18	0.40	0.24	0.25	−0.11	0.69	−0.11	0.69
Maximum systolic blood pressure (mmHg)	0.37	0.07	0.34	0.09	0.49	0.06	0.50	0.06
Maximum diastolic blood pressure (mmHg)	0.23	0.26	0.32	0.12	0.14	0.62	−0.12	0.67
Rate pressure product (bpm × mmHg)	0.20	0.33	0.28	0.17	**0.76**	**0.001**	**0.75**	**0.002**
Weight reduction during race (kg)	−0.19	0.35	−0.03	0.90	**0.59**	**0.02**	**0.62**	**0.01**

Note: Correlations between cardiac Troponin I (cTnI) 3 and 24 h after exercise and physiological variables measured during exercise. Correlations are analyzed with a Spearman bivariate correlation test, and significant correlations are highlighted in bold letters. Atherosclerotic group highlighted in shades.

Abbreviations: CPET, cardiopulmonary test; HR, heart rate; LT, lactate threshold; Race, 91-km mountain bike race.

The increased troponin response to high-intensity exercise in individuals with coronary arteriosclerosis aligns with recent studies, demonstrating an increased progression of coronary atherosclerosis and calcification in individuals with the highest exercise intensities.[31] Importantly, as shown by Figure 3, individuals with atherosclerosis that did not exceed a high-power output remained at a relatively low cTnI level. In a recent study on exercise-induced cTn in participants with and without atherosclerosis, the researchers found no difference in cTn levels between the groups after work-out.[21] However, heart rate was the primary marker of intensity. The strong relationship in our study between exercise-induced cTnI and work assessed by power meters underscores the importance of directly measuring the work performed. The relationship between workload and cTnI response was reproducible following the CPET test and the race, arguing against a chance finding within this cohort. Other studies measuring troponin release

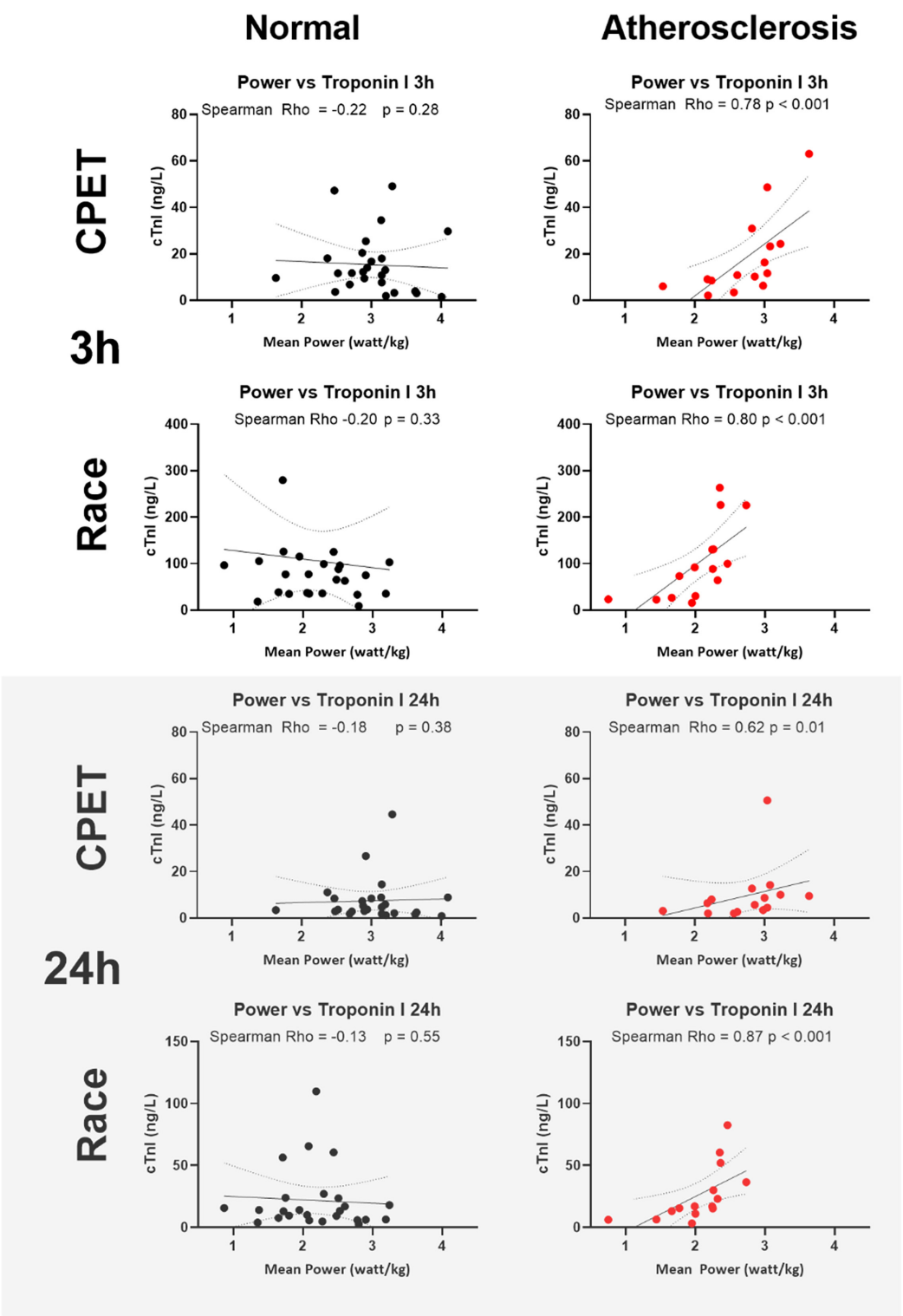

FIGURE 3 Correlations between power output and exercise-induced troponin after cardiopulmonary exercise test (CPET) and race. Scatter plot of power output during exercise versus cTnI at 3 and 24 h between participants with atherosclerosis (red dots) and participants without atherosclerosis (black dots). Power is indexed relative to weight and expressed as W/kg—bivariate correlations analyzed with Spearman Rho. Complete lines indicate regression lines with error bars in stapled lines.

after exercise have mainly been done on marathons, using heart rate as an intensity marker. As such, they have not measured the muscular workload. In addition, participants were not divided based on the findings of CAD, which may explain some of the heterogeneity in the data reported from these studies.[7]

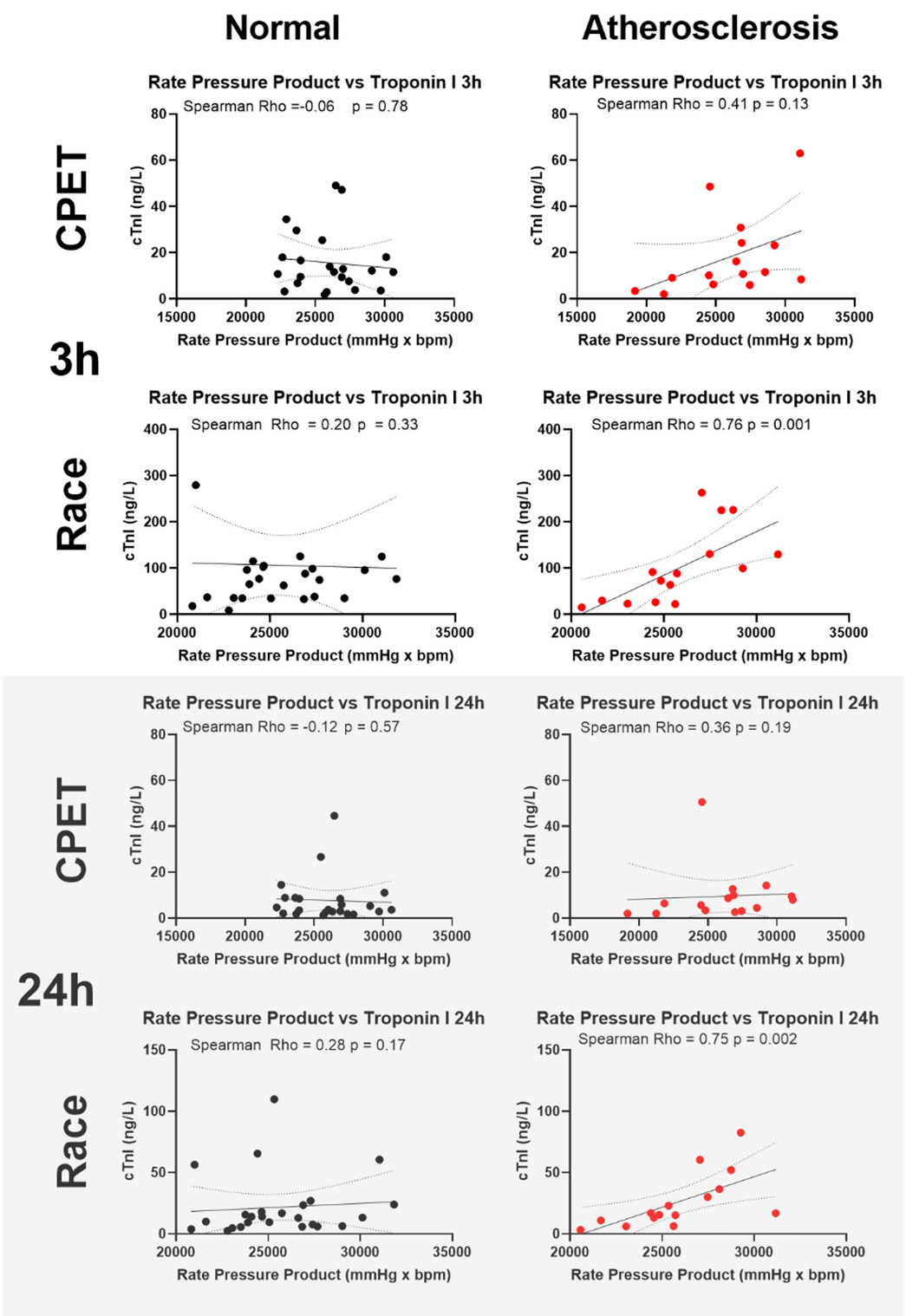

FIGURE 4 Correlations between rate-pressure-product (RPP) and exercise-induced cardiac troponin after cardiopulmonary exercise test (CPET) and race. Bivariate correlations (Spearman) between RPP and exercise-induced troponin in participants with atherosclerosis (red dots) and participants without atherosclerosis (black dots). RPP is calculated as mean systolic blood pressure during exercise multiplied by mean heart rate. Complete lines indicate regression lines with error bars in stapled lines.

4.1 | Strength

This is the first study to explore the relationship between direct power output measurements and exercise-induced cTn elevation. This study used the same bikes during both the CPET and the race, allowing a direct comparison between the power output during both exercises. The study demonstrates

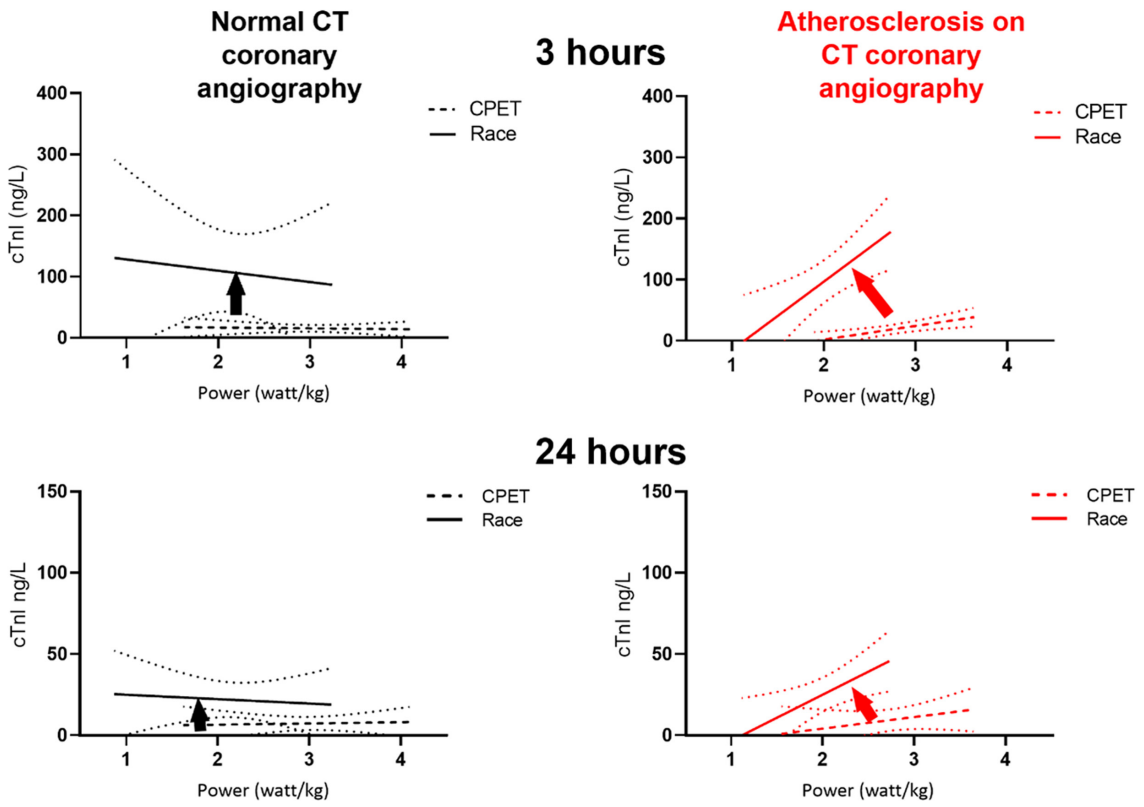

FIGURE 5 Differences in cTnI kinetics depend on workload and coronary artery disease. The difference in cTnI kinetics between participants with (red) and without (black) established atherosclerosis. Dotted lines represent the Cardiopulmonary exercise test (CPET), while complete lines represent the race. Error bars are indicated in small dots. Significant differences were found in the Atherosclerotic group in the steepness of the regression lines both at 3 h (CPET: $B_1 = 22.4$ (±6.8) vs. Race: 111.6 (±34.2), $p < 0.0001$) and at 24 h (CPET: $B_1 = 7.1$ (±6.0) vs. Race 28.4 (±10.3), $p < 0.001$), highlighting the effect of duration on cTnI kinetics; Race (atherosclerosis: 4.1 (3.6–4.5) h vs. normal: 3.9 (3.5–4.5), CPET (atherosclerosis: 42.9 ± 5.1 min vs. normal 43.2 ± 5.3 min).

strong correlations between exercise-induced cTnI and power output following both exercises, showing that these findings are reproducible when accurate power output measurements are used.

The present study assessed RPP during the race, allowing field assessment of cardiac work during prolonged high-intensity exercise. These findings provide valuable insights into potential mechanisms causing the increased cTnI response to workloads in individuals with coronary atherosclerosis.

4.2 | Limitations

There are several limitations of this study. Due to the small population size, there is an increased risk of chance findings. Any statistical analysis of such a small sample size should be interpreted cautiously. We did not find any significant difference between the two groups. However, due to a small sample size, this could be a type 2 error. In addition, the study population consisted of a highly selected population of well-trained recreational athletes, and the results are restricted to this population. However, these middle-aged, well-trained athletes represent a vital risk group among recreational athletes. Due to their combination of high physical capacity and CAD may generate larger myocardial energy demand/supply mismatches compared to less well-trained individuals, increasing the risk of exercise-induced myocardial ischemia. Thus, the findings are important in describing the myocardial response to high workloads in individuals with atherosclerosis. The response in less well-trained individuals needs to be determined by future research. Only 10 women were included, so results on women should be interpreted cautiously.

5 | PERSPECTIVE

The present findings have several important potential clinical implications. First, the results suggest an exaggerated workload impact on cTn elevation in individuals with non-obstructive coronary atherosclerosis. At the same time, individuals with atherosclerosis and

low workloads had cTnI levels comparable to normal individuals. This contradicts a recent study that found no difference in cTn response between participants with or without coronary atherosclerosis.[21]

Our findings indicate that modification of exercise intensity may prevent the exercise-induced cTnI response in individuals with CAD. In cycling, external load shows higher variation depending on whether you are in the front of a group, in the slipstream, or going up or downhill. Direct power output measurements using power meters provide a more comprehensive workload assessment than heart rate. These findings suggest that direct power output measurements may be a potent tool to guide exercise intensity in recreational athletes with coronary atherosclerosis. Future studies need to explore the potential role of power output monitoring during exercise in guiding exercise intensity in individuals with CAD. These findings align with studies demonstrating a strong prognostic impact of power measurements in cardiac stress tests.[32] This study involved participants accustomed to high exertion levels over long periods without restrictions on their blood pressure or exercise intensity. The study included continuous power meter measurements and blood pressure recording during exercise, allowing more precise assessments of the participants' efforts during exercise. This study underlines the need for accurate global and cardiac workload recordings when assessing the implications of exercise-induced troponin elevation in future studies.

6 | CONCLUSION

This is the first study to demonstrate that workload is associated with post-exercise cTnI levels in patients with non-obstructive CAD. A solid and reproducible relationship was found between these parameters following prolonged physical activity. In contrast, no association between power output and cTnI was present in individuals with normal coronary arteries despite significant increases in cTnI levels after the Race and CPET. These findings underscore the importance of cardiovascular health status and accurate workload measurements when interpreting post-exercise cTn values.

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CONFLICT OF INTEREST STATEMENT

MBB, ØK, CBE, TW, BA, TMHE, and SØ have no disclosures to declare. ØS has received lecture fees from Abbott Diagnostics. KMA has served on the advisory board for Roche Diagnostics and SpinChip, consultant honoraria from CardiNor, lecturing honorarium from Siemens Healthineers and Snibe Diagnostics and research grants from Siemens Healthineers and Roche Diagnostics; she is Associate Editor of Clinical Biochemistry and Chair of the IFCC Committee of Clinical Application of Cardiac Biomarkers.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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