Occult obstructive coronary artery disease is associated with prolonged cardiac troponin elevation following strenuous exercise

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Abstract

Background: Sudden cardiac death among middle-aged recreational athletes is predominantly due to myocardial ischemia. This study examined if measuring cardiac troponin I and T (cTnI and cTnT) after strenuous exercise could identify occult obstructive coronary artery disease (CAD).

Design: Prospective observational study

Methods: Subjects were recruited from 1002 asymptomatic recreational cyclists completing a 91-km mountain bike race (North Sea Race Endurance Exercise Study). No subject had known cardiovascular disease or took cardiovascular medication. Blood samples were collected within 24 h before and 3 and 24 h after the race. Coronary computed tomography angiography (CCTA) was performed in 80 participants with the highest post-exercise cTnI and in 40 reference subjects with moderately elevated cTnI values.

Results: Study subjects (n=120) were 45 (36-52) years old and 74% were male. There were similar demographics in the High-cTnI and the Reference group. The cTn concentrations were highest at 3 h post-race: cTnI, 224 (125-304) ng/L; cTnT, 89 (55-124) ng/L. Nine subjects had obstructive CAD on CCTA, eight of whom were High-cTnI responders. Two subjects had myocardial bridging, both High-cTnI responders. Troponin concentrations at 24 h post-race were higher in subjects with obstructive CAD than the rest of the cohort (n=109): cTnI, 151 (72-233) ng/L vs. 24 (19-82) ng/L, p=0.005; cTnT, 39 (25-55) ng/L vs. 20 (14-31) ng/L, p=0.002. The ROC-AUCs for predicting obstructive CAD were 0.79, p=0.005 (cTnI) and 0.82, p=0.002 (cTnT).

Conclusion: In subjects with occult obstructive CAD there was a prolonged elevation of cTn following strenuous exercise.

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Introduction

Myocardial ischemia is the major cause of sports-related sudden cardiac death in recreational athletes ≥ 35 years of age [1 2]. Most individuals suffering from sports-related sudden cardiac death are asymptomatic or fail to recognize warning symptoms prior to the event [3]. Therefore, the identification of these subjects is challenging. Elevated resting cardiac troponin (cTn) levels are associated with an increased risk of an adverse cardiovascular (CV) event [4-6]. Thus, it is reasonable to assume that exercise-induced cTn levels may be used to evaluate CV risk during exercise. However, following strenuous physical exercise, there is a physiological increase in cTn levels in healthy individuals [7-11]. This physiological increase may mask a pathological response and preclude the use of exercise-induced cTn elevation as a risk marker. Thus, the clinical interpretation of post-exercise cTn levels is problematic.

Recently, we published a pilot study demonstrating that the highest exercise-induced cTn levels were present in asymptomatic subjects with obstructive coronary artery disease (CAD) [12]. However, only 13 subjects were assessed by coronary computed tomography angiography (CCTA) in that study. The present study explores the potential diagnostic role of cTn assessment following strenuous exercise in a larger subset of presumably healthy individuals included in the North Sea Race Endurance Exercise Study 2014 [13]. The main aim of the present study was to compare the exercise-induced cTn profiles in presumably healthy recreational cyclists with and without coronary artery obstruction identified by CCTA.

Methods

Design and study population

The current study used CCTA to identify obstructive CAD in a subset of 120 subjects participating in the NEEDED 2014 main-study (n=1002) [13]. All study participants were asymptomatic, recreational cyclists participating in the 91-km North Sea mountain bike race. Screening and patient inclusion are presented in Figure 1. Inclusion and exclusion criteria have been reported previously[13]. Blood samples, clinical assessments, blood pressure measurements, and ECGs were obtained the day before (baseline) and at 3 and 24 h following the race. The study complied with the Declaration of Helsinki and was approved by the Regional Ethics Committee (REK 2013/550). All participants signed informed consent forms prior to enrollment into the study.

Selection of subjects for coronary computed tomography angiography

Study subjects were selected for the present sub-study based upon their maximal cardiac troponin I (cTnI) value following the race. Two different subcohorts were studied. The first cohort (High-cTnI group) consisted of the 80 subjects with the highest cTnI values (from the total NEEDED 2014 population, n=1002) at any time-point following the race. This cohort was assessed by CCTA within a few weeks following the race. The second cohort consisted of a Reference group of 40 subjects with maximal cTnI values that reflected the values of the remaining NEEDED 2014 population (n=922). The reference population selection was based on a representative 20/80% (Female/Male) sex-distribution, with each subject matched from the NEEDED 2014 population according to age. The reference group was assessed by CCTA within a year following the race.

Blood samples

Venous blood samples were drawn from the antecubital vein at baseline and at 3 and 24 h after the race. Cardiac TnI (serum) was analyzed within 24 h at Stavanger University Hospital on an Architect i2000SR using the high-sensitive cTnI STAT assay, which has a lower limit of detection of 1.6 ng/L and a 99th percentile of 26 ng/L (Abbott Diagnostics, IL USA) [14]. Serum was frozen at -80 °C until thawed and analyzed for cardiac troponin T (cTnT) on a Cobas e601; this assay has a limit of blank of 3 ng/L and a 99th percentile of 14 ng/L (Roche Diagnostics, Switzerland) [14].

Coronary computed tomography angiography

Coronary calcification and CCTA were obtained using a Siemens Somatom Definition Flash Dual Source. Obstructive CAD was defined as ≥ 50% luminal stenosis in the left coronary artery, the right coronary artery, the circumflex artery, or a diagonal or marginal branch. The CCTA examinations were independently assessed by two experienced radiologists, blinded to the cTn findings. Non-obstructive CAD was defined as a luminal narrowing of 1-50%. Subjects with obstructive CAD on CCTA were referred for conventional coronary angiography and treated with percutaneous coronary intervention or coronary artery bypass grafting, as determined by the cardiologist performing the angiography.

Statistical analysis

Normally distributed continuous variables are reported as the mean ±SD, while continuous variables with markedly skewed distributions are reported as the median and interquartile range (25th percentile-75th percentile). The Shapiro-Wilk test was used to test for normality. The Chi-Square test, Fisher's Exact test, Student t-test, or Mann-Whitney U test was used for comparison of groups, as appropriate. A two-tailed p-value < 0.05 was considered significant. For statistical analyses, the statistical software programs SPSS version 24, "R", and GraphPad Prism 7 were used.

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Results

Participants were 45.4 (36.3-52.3) years old and 74.2% were male. The race duration was 3.6 (3.4-4.1) h. Subjects in the High-cTnI and the Reference groups had similar ages, gender and body mass indexes (Table 1). None of the subjects reported CV symptoms during or following the race. The CCTA identified nine subjects with obstructive CAD, who all had normal ECGs at baseline and 3 h after the race. However, at 24 h following the race, two subjects had new T-wave inversions (V2/V4-6) and one had high precordial T-waves. Two subjects in the High-cTnI group had myocardial bridging, and were excluded from the analysis due to the uncertain clinical implication of this finding. Their characteristics are, however, included in Table 2.

Troponin profiles

High-cTnI subjects had maximum cTnI concentration after the race ranging from 196-7919 ng/L (Supplementary Figure 1). Most High-cTnI subjects achieved maximum cTnI values at 3h following the race (n=78, 97.5%). The Reference group had a maximum cTnI range of 7-189 ng/L (Supplementary Figure 1). All Reference group subjects achieved maximum cTnI concentrations at 3 h following the race. Overall, cTnI concentrations increased markedly from baseline (2.7 [1.6-6.9] ng/L) to 3 h after the race (224 [125-304] ng/L), declining at 24 h after the race (39 [19-102] ng/L). Similarly, cTnT increased from baseline (3.1 [3.0-5.1] ng/L) to 3 h after the race (89 [55-124] ng/L), followed by a decline at 24 h after the race (23 [15-38] ng/L). The cTnI values exceeded the 99th percentile (26 ng/L) in 95.8% of study subjects at 3 h and 63.3% at 24 h following the race. The cTnT values exceeded the 99th percentile (14 ng/L) in 98.3% of study subjects at 3 h, and 75.8% at 24 h following the race.

Coronary computed tomography angiography findings

In total, 80 of the 120 subjects (67 %) had normal coronary arteries, two had myocardial bridging (1.7 %), and 39 had CAD (32.5 %, this number includes one subject who also had myocardial bridging, Figure 2). Non-obstructive CAD was present in 15 subjects in the High-cTnI group (18.8 %), including one with myocardial bridging, and in 15 subjects (37.5 %) in the Reference group. A total of eight subjects (10.0%) had obstructive CAD in the High-cTnI group; whereas, one subject (2.5%) had obstructive CAD in the Reference group.

The median CAC score of the High-cTnI group was 0 (0-0) Agatston Units, vs 0 (0-11) Agatston Units in the Reference group, p=0.132. When only subjects with CAD were assessed, the CAC scores were 36 (2-187) Agatston Units in the High-cTnI group vs 18 (4-71) Agatston Units in the Reference group, p=0.72. One subject (Subject F) was only imaged by conventional coronary angiography and was not included in this analysis.

The odds ratio (OR) for obstructive CAD between the two cohorts was: 4.46 (95% CI: 0.54-37.0), p=0.17.

Troponin concentrations in relation to coronary anatomy and pathology

Both cTnI and cTnT levels were significantly higher 24 h following the race in subjects with obstructive CAD compared with the rest of the cohort (Figure 3, Supplementary Table 1): cTnI: p=0.005, cTnT: p=0.002 (n=118). There was no between-group difference in the cTn values at baseline or at 3 h following the race. Within the High-cTnI group, subjects with obstructive CAD (n=8) still had significantly higher cTn values at 24 h after the race than the rest of the group (cTnI: p=0.006, cTnT: p=0.004, Supplementary Table 2).

Only cTn values at 24 h after the race significantly predicted the presence of obstructive CAD: cTnI: area under the curve (AUC) of 0.78, p=0.005; cTnT: 0.82, p=0.002 (Figure 4).

Discussion

This study has several novel and important findings: First, both cTnI and cTnT levels were significantly higher 24 h following the race in subjects with obstructive CAD compared with those without coronary artery obstruction. Second, there was no difference in cTn levels between subjects with and without coronary artery obstruction prior to or 3 h following the race. Third, none of the subjects with obstructive CAD reported symptoms suggestive of CAD during or following the race. Our findings are in line with the pilot study but add to previous data suggesting that subjects with obstructive CAD have a different cTn profile than the physiological cTn response, with a prolonged cTn release resembling an ischemic injury pattern. These findings, however, need to be confirmed by future studies before they can be used in a clinical context.

Troponin profiles in subjects with and without obstructive CAD

A total of nine subjects with obstructive CAD were identified in the present study, eight of whom were in the High-cTn group (Table 2). Additionally, two persons with myocardial bridging, both in the High-cTn group, were excluded from the analysis due to the unclear implications of this characteristic in this setting (23). Physiological exercise-induced cTn elevation is thought to be due to increased myocardial stress generating a leakage of loosely bound cTn into the blood stream by cytoplasmic blebbing, release of microparticles, increased membrane permeability, or activation of apoptosis of cardiomyocytes [11, 15, 16]. Exercise-induced cTn elevation peaks at 3-6 h (cTnI) and 2-5 h (cTnT) following exercise [11, 17, 18]. These peaks differ from the later rise in cTn levels following myocardial infarction. After myocardial infarction, there is a release of structural cTn due to cellular necrosis, with a rapid increase in cTn levels, reaching maximum values 11-12 h following revascularization [19, 20].

The later peak in cTn levels following myocardial infarction reflects a slower release of structural cTn due to destruction of cellular components and a prolonged washout [20]. In the present study, the prolonged elevation of cTn levels in subjects with obstructive CAD may suggest a different mechanism of cTn release than the short-term physiological cTn response. Although no additional determination of myocardial ischemia was performed in the present study, it is possible that the prolonged cTn elevation following exercise in subjects with obstructive CAD is due to the development of demand ischemia during exercise. This is in line with the findings of Kim et al. who found demand ischemia to be the most frequent mechanism of sport-related sudden cardiac arrest [21]. This important finding warrants further investigation into the relationship between demand ischemia and the cTn response following strenuous exercise.

The absence of ischemic symptoms during strenuous exercise

Preventing deaths due to myocardial ischemia in recreational athletes is challenging, both due to the low event rate and the frequent lack of recognizable warning symptoms prior to the event [3, 22, 23]. In the study by Smallmann et al., only 17 % of subjects > 35 years of age who suffered a sport-related cardiac death had reported chest pain in the 6 months leading up to the event, despite the fact that most of these deaths were attributed to atherosclerotic heart disease[2].

During strenuous exercise, there are alterations in pain perception that may suppress symptoms and preclude an early clinical diagnosis [24-26]. In the present study, none of the subjects reported chest pain during the consultation with the cardiologists at 3 or 24 hours following the race. At 24 hours after the race, Subject F had new T-wave inversions in leads V2-3 and highly elevated cTnI. He was admitted to hospital for a conventional coronary angiography and during the hospitalization he retrospectively reported some chest discomfort during the race,

despite having finished the race faster than expected. His case underscores the challenges related to the symptom-based CV evaluation strategy of athletes.

The use of regular training or competitive events to determine the risk of demand ischemia

Most previous studies have not been able to demonstrate a significant difference in the cTn response between subjects with and without evidence of ischemia using standardized stress- or perfusion tests [27, 28]. During prolonged strenuous exercise, there are major changes in hemodynamics, neuro-endocrine activation, acid-base status, and metabolism that may induce demand ischemia [21, 29]. These factors are not addressed by current routine exercise or stress tests that are mostly of short duration with limited exposure to high intensity work. The present study suggests there is diagnostic potential for using field-data in the detection of obstructive CAD in asymptomatic individuals. Recreational athletes perform numerous sessions of prolonged, high-intensity exercise both during training and competitive events that may be used to evaluate risk. During these sessions, athletes are exposed to far more vigorous exercise than in traditional stress tests assessing ischemia. Also, repeated assessments of the exercised-induced cTn response in connection with exercise sessions may lead to personal exercise cTn profiles that may be used to monitor the athlete.

A major challenge in the use of real-life data is the need for sufficiently accurate quantification of the amount physical work performed. Future studies need to clarify the relationship between exercise-induced cTn release and exercise intensity and duration by direct measurement of work. Failure to perform enough work to induce demand ischemia may possibly explain the low 24 h cTn levels of subject C and I in the present study (Table 2).

Limitations

For logistic reasons, it was only possible to examine 80 individuals with CCTA within the first weeks following the race. The 40 subjects in the Reference population were examined later. There was one subject with obstructive CAD in the Reference population (Subject C). Due to the late CCTA assessment of this subject (almost a year following the race), it is not possible to determine if the coronary artery stenosis was present at the time of the race.

Due to logistic challenges with the large sample size of the original study (n=1002), blood sampling was limited to 24 h before and 3 and 24 h after the race.

Long-term follow-up is needed in order to assess the association between exercise-induced cTn elevation and future CV events. Follow-up studies are planned for the entire NEEDED 2014 cohort (n=1002) at 5, 10 and 20 years after the race to determine the long-term prognostic role for prolonged cTn elevation. The results of this study need to be confirmed by future studies before specific recommendations regarding the clinical use of exercise-induced troponin elevation can be made.

Conclusion

In this prospective observational study, cTn levels 24 h after strenuous exercise were higher in asymptomatic subjects with obstructive CAD compared with subjects with no coronary artery obstruction. The diagnostic role of delayed post-exercise cTn elevation remains to be determined in future studies.

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Figure 1

Study recruitment and flow; CAD = coronary artery disease, CCTA = coronary computed tomography angiography, CV = cardiovascular, STEMI = ST-segment elevation myocardial infarction.

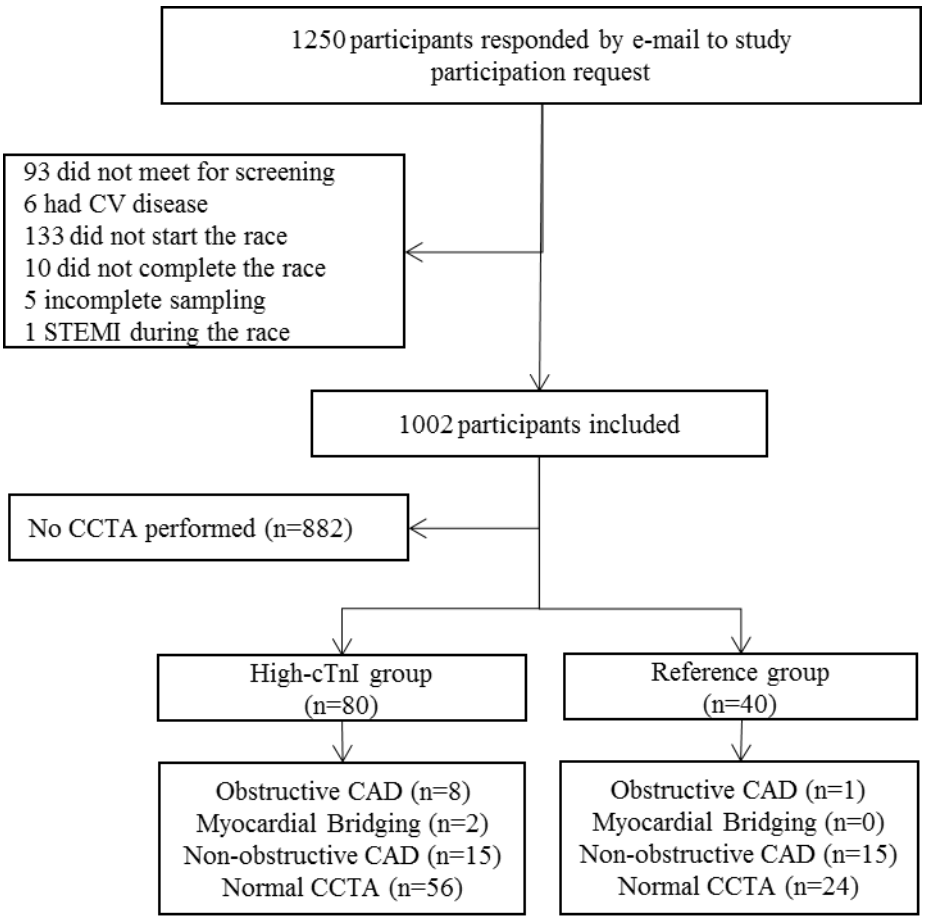


Figure 2

Illustration of a) normal coronary arteries on coronary computed tomography angiography (CCTA), b) myocardial bridging of the left anterior descending artery on CCTA (Subject A), c) obstructive CAD of the right coronary artery on conventional angiography (Subject E), d) non-obstructive CAD of the left anterior descending artery on CCTA (small white spot in the proximal portion of the left anterior descending artery).

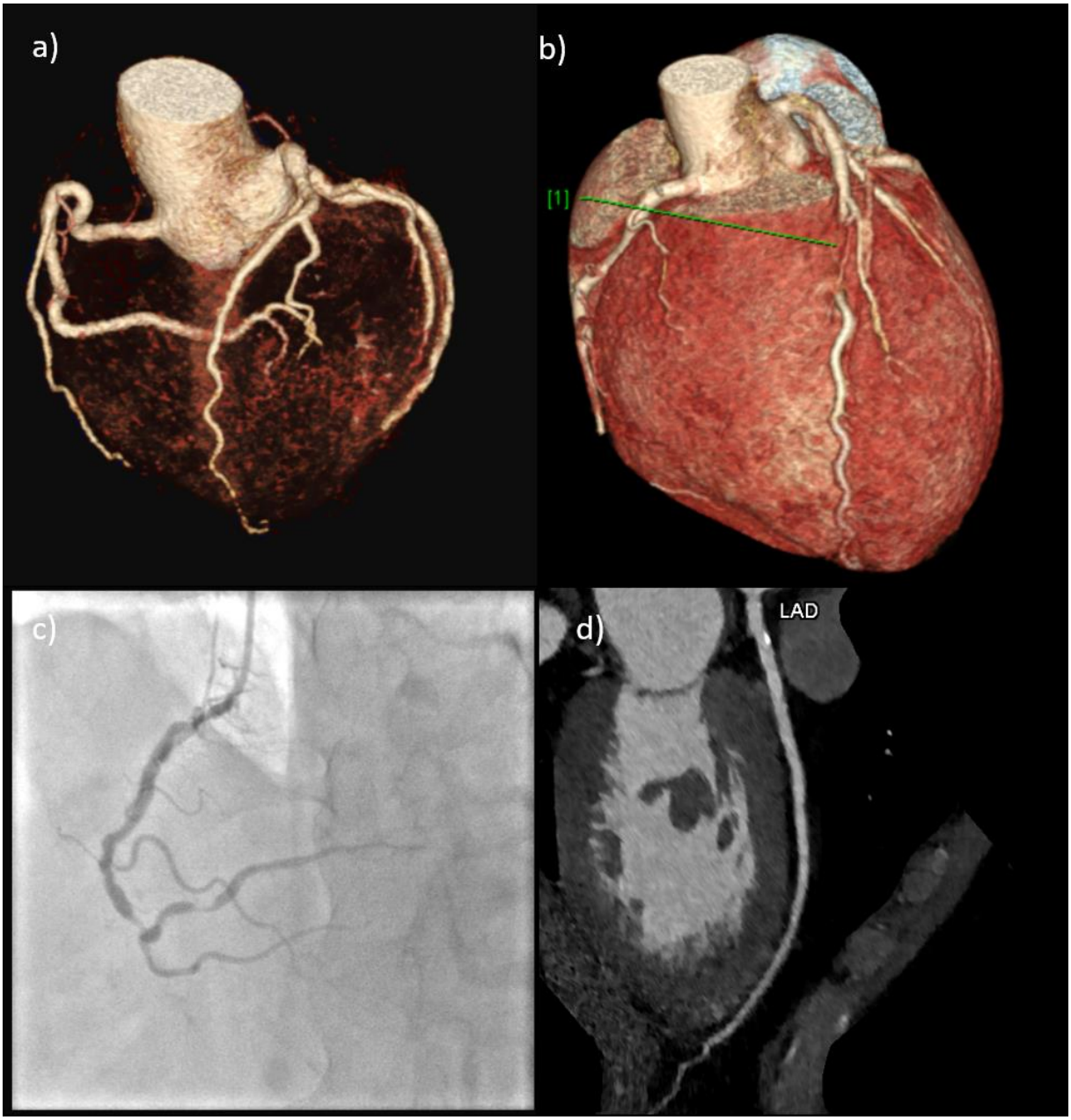


Figure 3

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) concentrations in subjects assed by coronary computed tomography angiography (n=118). Green columns represent subjects without coronary artery obstruction (n=109). Blue bars represent subjects with obstructive coronary artery disease (CAD, n=9). The dotted horizontal line represents the 99th percentile of each assay.

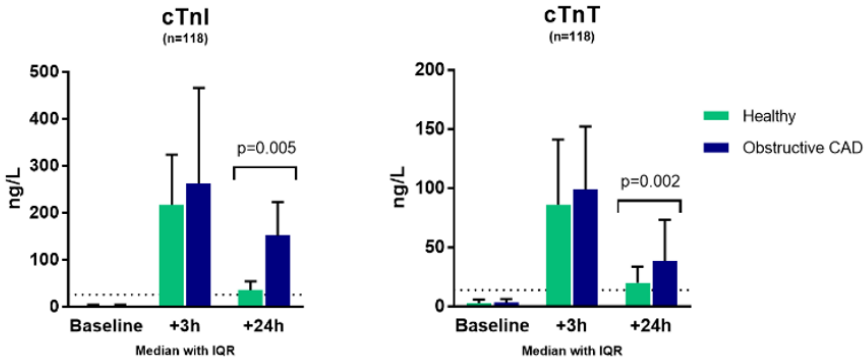
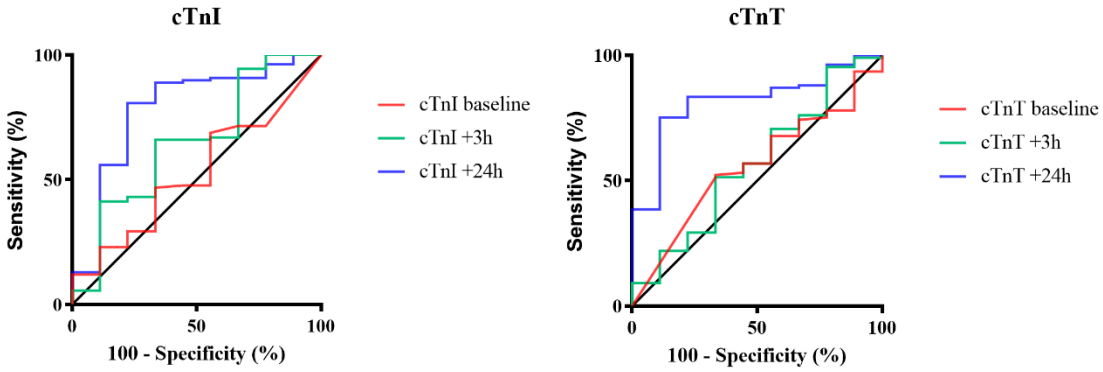


Figure 4

Receiver operating characteristic (ROC) curves for predicting obstructive CAD (n=9) in a total of 118 subjects assessed by coronary computed tomography angiography. The two subjects with myocardial bridging were excluded from this analysis; cTnI = cardiac troponin I, cTnT = cardiac troponin T.



	AUC	95 % CI	p-value
cTnI baseline	0.48	0.29-0.66	0.80
cTnI +3h	0.65	0.45-0.95	0.14
cTnI +24h	0.79	0.61-0.96	0.005
cTnT baseline	0.56	0.38-0.73	0.57
cTnT +3h	0.57	0.36-0.77	0.10
cTnT +24h	0.82	0.70-0.94	0.002

Table 1

Baseline characteristics of subjects included in the study. P-value signifies differences between the High-cTnI group and the Reference group. The two subjects with myocardial bridging in the High-cTnI group were not included.

	High-cTnI group (n=78)	**Reference group (n=40)**	**p-value**
Age, years	44.6±10.8	45.8±10.8	0.67
Males, %	57 (73.1%)	31 (77.5%)	0.60
BMI, kg/m^2	25.0 (23.4-26.9)	25.0 (24.1-30.1)	0.60
Body weight, kg	81.8 (72.6-90.0)	80.6 (71.9-86.6)	0.81
Waist circumference, cm	85.0 (80-92)	84.0 (79-90)	0.71
Systolic blood pressure, mmHg	142.0 (127.5-152.0)	135.5 (124-145)	0.12
Diastolic blood pressure, mmHg	81.0 (74-88)	79.3 (73-79)	0.30
Resting HR, beats/min	58.0 (53.0-66.5)	57.5 (53.0-67.0)	0.86
Current smokers, n (%)	1 (1.3%)	0 (0)	1.00
Framingham risk score, %[*]	1 (0-5)	1 (0-5)	0.78
MET hours per week [†]	48.2 (31.7-83.0)	65.2 (44.6-89.3)	0.037
Number of races past 5 y, n	5 (2-10)	13 (5-30)	<0.001
Self-reported maximal HR, bpm	190 (184.5-195.5)	185 (177.5-190.0)	0.10
Race performance			
Race duration, h	3.7 (3.3-4.0)	3.5 (3.3-4.0)	0.70
Maximal HR during race, bpm	183.1±12.2	179.3±13.0	0.12
Maximal HR of estimated maximal HR, %	100.8 (98.7-107.6)	100.4 (97.1-104.8)	0.30
Mean HR during race, bpm	164.0 (156.0-168.0)	158.5 (150.0-165.3)	0.06
Mean HR of estimated maximal HR, %	90.8 (88.0-93.4)	88.7 (85.5-92.8)	0.13
Blood samples at baseline			
cTnI, ng/L [‡]	3.8 (1.8-8.6)	1.7 (1.6-2.9)	0.001

cTnT, ng/L [§]	3.8 (3.0-5.5)	3.0 (3.0-3.1)	<0.001
BNP, pg/mL	13.1 (10.0-21.0)	12.6 (10.0-21.0)	0.60
CRP, mg/L	0.7 (0.4-1.1)	0.7 (0.4-1.5)	0.16
Creatinine, umol/L	82.8 ± 13.5	82.2 ± 11.7	0.63
eGFR, mL/min/1.73m^2	92.8 ± 14.6	93.5 ± 12.5	0.76
LDL, mmol/L	3.1 (2.6-4.1)	3.0 (2.3-3.5)	0.07
HDL, mmol/L	1.5 (1.3-1.8)	1.5 (1.3-1.8)	0.93
Hemoglobin, g/dL	14.3 ± 1.0	14.4 ± 0.8	0.76

[*] Framingham risk score: 10-year risk of death or myocardial infarction.
[†] MET = Metabolic equivalents (3.5 ml O^2/kg/min). Estimated by IPAQ-SF
[‡] 27.5 % had cTnI values ≤ 1.6 ng/L (limit of detection)
[§] 49.2 % had cTnT values ≤ 3.0 ng/L (limit of blank)
BMI = body mass index, HR = heart rate, cTnI = cardiac troponin I, cTnT = cardiac troponin T, BNP = B-type natriuretic peptide, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, LDL = low-density lipoproteins, HDL = high-density lipoproteins.

Table 2

Individual characteristics of the nine subjects with obstructive CAD and two with myocardial bridging.

	Age (years)	Gender	Race duration (h)	Framingham risk score (%)	cTnI baseline (ng/L)	cTnI +3hr (ng/L)	cTnI +24hr (ng/L)	High-cTnI group/ Reference group	Findings on angiography
Subject A	27	M	3.4	0	4.7	1002	110	High-cTnI	Myocardial bridging LAD
Subject B	55	F	4.9	1	7.6	443	181	High-cTnI	Myocardial bridging LAD, diffuse CAD
Subject C	62	M	3.4	10	1.7	28	8	Reference	Obstructive lesion LAD (FFR 0.78)
Subject D	42	M	4	1	1.6	260	169	High-cTnI	Obstructive lesion RCA (80%), CAD also in LAD
Subject E	69	M	4.9	20	2.8	999	269	High-cTnI	Obstructive lesions (80-90%) in all major vessels
Subject F	58	M	3.5	8	17.4	5026	7919	High-cTnI	Obstructive lesions in LAD (80%) and diffuse CAD
Subject G	58	M	3.5	8	7.2	269	196	High-cTnI	Obstructive lesion 1. obtuse marginal (90%), diffuse CAD
Subject H	47	M	3.8	2	2.8	206	102	High-cTnI	Obstructive lesion RCA (80%), diffuse CAD
Subject I	66	F	4.9	5	1.6	263	41	High-cTnI	Obstructive lesion LAD (90%), diffuse RCA
Subject J	57	M	4	10	1.7	200	137	High-cTnI	Obstructive lesion LAD (70%), diffuse CAD
Subject K	50	M	4.1	3	4.9	545	151	High-cTnI	Obstructive lesion 2.diagonal (80%), diffuse CAD

cTnI = cardiac troponin I, M = male, LAD = Left anterior descending artery, F = female, CAD = Coronary artery disease, FFR = Fractional flow reserve, RCA = Right coronary artery.