Clinica Chimica Acta 479 (2018) 155–159

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

The cardiac troponin response following physical exercise in relation to biomarker criteria for acute myocardial infarction; the North Sea Race Endurance Exercise Study (NEEDED) 2013

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ARTICLE INFO

Keywords:
Endurance exercise
Dynamics
Healthy
Reference interval
Release
Cardiac biomarker

ABSTRACT

Background: The aim of this study was to investigate troponin (cTn) dynamics for both genders, compared the different release patterns to the gender specific 99th percentile and to current biomarker criteria for diagnosing myocardial infarction (MI).

Methods: Serum was collected from 97 recreational cyclists 24 h before and immediately, 3 and 24 h following a 91-km bike race. hs-cTnI (Abbott) and hs-cTnT (Roche) were measured. Conventional or CT coronary angiography was performed in the 13 participants with the highest hs-cTnI (> 140 ng/L). Three subjects with obstructive coronary artery disease were excluded from the statistical analysis.

Results: There was a significant ($p < 0.001$) post-race increase in cTnI and cTnT; cTnT peaked immediately, cTnI peaked after 3 h. Relative to the gender specific 99th percentile values, women had the largest increase. The biomarker criteria for MI were met in 76–87% for hs-cTnI, and 96–95% for hs-cTnT (p value < 0.05), within the first 3 h post-race.

Conclusion: Post-race cardiac troponin concentrations exceeded diagnostic criteria for MI in the majority of subjects, more often for hs-cTnT than for hs-cTnI, and more pronounced in women than in men. The current biomarker criteria for MI discriminate poorly between an exercise induced troponin increase and acute MI.

1. Introduction

Cardiac troponins (cTn) are released into the bloodstream following acute myocardial necrosis, and an elevated cTn level is an obligate criterion for the diagnosis of myocardial infarction (MI) [1,2]. Increased cTn concentrations are also commonly seen following strenuous physical activity [3–9]. Although there is limited long-term clinical data, the exercise associated cTn response in healthy individuals is considered a physiological phenomenon [9,10]. Conflicting data exist in patients with coronary artery disease (CAD); most studies show an exaggerated exercise-induced cTn response in patients with imaging evidence of myocardial ischemia [8,11–14], but commonly not sufficiently large to demonstrate a satisfactory diagnostic power to discriminate between groups. Accordingly, the differentiation between a physiological and pathological cTn response following exercise remains a challenge [15].

The underlying mechanisms causing the exercise related cTn increase remain to be established. In 1998 Bleier et al. showed that similar amounts of total myocardial cTnI and cTnT (8.3% for cTnI vs 7.5% for cTnT) were present in soluble forms in the cytosol of cardiomyocytes [16] and a recent paper from Majot et al. show that equal amount of cTnI and cTnT are released in vitro per μg of human myocardium [17]. The dominating contemporary theory suggests that strenuous physical activity temporarily increases the permeability of

Abbreviations: CAD, coronary artery disease; MI, myocardial infraction; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T

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https://doi.org/10.1016/j.cca.2018.01.033
Received 1 December 2017; Received in revised form 19 January 2018; Accepted 19 January 2018

the cell membrane, leading to the release of the soluble cTn molecules from the small cytosolic pool [9,10]. In contrast, following MI, large amounts of myofilament-bound troponins are released into the circulation due to myocyte necrosis [18–20]. Today's cTn assays are not capable of distinguishing between cytosolic and complex-bound troponin, which might complicate the interpretation of cTn results following strenuous exercise. Even though it has been known for years that cTn increases following strenuous physical activity, there is limited information on how gender, the timing of blood sampling and use of different high sensitivity cTn assays influence the increase and the number of subjects exceeding the diagnostic criteria for acute MI. We therefore sought to investigate these relationships in a large cohort of healthy individuals of both genders, using serial sampling for 24 h before and following strenuous exercise.

2. Methods

2.1. Study population

The current study is part of the North Sea Race Endurance Exercise Study (NEEDED) conducted in 2013, extending the previous study by including an additional analysis of cTnT. Time dependent cTnI concentrations have been presented earlier, but are included in this report for clarification and for comparison with the ESC NSTEMI criteria [1,2]. Details regarding the study design and data collection have been described earlier [8,21]. Briefly, the present study assessed cardiac troponin levels serially before and after a 91-km bike race for recreational cyclists of both genders, mostly middle aged, with different physical fitness levels. The study conforms to the ethical standards given in the Declaration of Helsinki and was approved by the Regional Ethics Committee (2013/550/REK vest). A total of 97 cyclists provided informed written consent and were included in the study. Blood samples were collected 24 h before the race, immediately (i.e. within 15 min), 3 and 24 h following completion. Serum samples were stored at 4 degrees Celsius and analysed within 24 h utilizing a hs-cTnI STAT assay at Architect i2000SR (Abbott Diagnostics, Illinois, USA) with a lower limit of detection of 1.6 ng/L and overall 99th percentile of 26 ng/L, (package insert). Additional serum was frozen immediately at −80 degrees Celsius until hs-cTnT were analysed on Cobas e602 (Roche Diagnostics, Switzerland), with a limit of blank of 3 ng/L and overall 99th percentile of 14 ng/L (package insert) [22].

No study participant had signs or symptoms of CAD before, during or following the race. However a few subjects developed unexpectedly high cTnI concentrations up to 24 h post-race. Based on the assumption that the individuals with the highest post-race cTn concentrations had the highest risk of CAD; conventional invasive coronary angiography or coronary computer tomography (CT) angiography were performed in the 13 subjects who had the highest cTnI concentration (i.e. > 140 ng/L). Angiographically significant CAD was detected in three of these subjects [8]. Data from the three participants with CAD are presented separately and excluded from all calculations of physiological cTn dynamics (n = 94).

2.2. Data analysis

Continuous variables are reported as mean (SD) or median (IQR), if distributions were markedly skewed. The distributions of most variables were markedly skewed. We therefore chose to use non-parametric statistical tests. Significant differences between genders were evaluated by Mann-Whitney *U* test (continuous variables) or Pearson Chi-Square test (categorical variables). McNemars test were used for paired nominal data. Associations between variables were assessed by Spearman rank correlation. A p-value of < 0.05 was considered statistically significant.

For evaluation of relative cTn increases we adjusted the concentrations by dividing by the 99th percentile of the assays that were defined by Ungerer et al. [23]. We used this 99th percentile since that study defined the 99th percentile for both assays in a large cohort (N = 1352) of blood donors below the age of 50 years, which we found largely resembled our population of moderately fit presumably healthy exercisers with a mean age of 43 years. The 99th percentile was 26 ng/L (females; 22 ng/L and males; 28 ng/L) for hs-cTnI and 14 ng/L (females; 10 ng/L and males; 16 ng/L) for hs-cTnT [23].

The biochemical criteria for myocardial infarction were defined in accordance with the recommendations of the European Society of Cardiology, i.e. at least one concentration above the 99th percentile and a 20–50% increase (i.e. 20% if the first concentration was above the 99th percentile and 50% if it was below the 99th percentile of the assay) in two consecutive cTn concentrations measured 3 h apart [1,2].

Statistical analyses were performed using SPSS version 23.0.

Table 1
Baseline characteristics of the study participants (n = 97), absolute numbers (% in brackets), mean ± SD or median and inter quartile range (IQR) for markedly skewed distributions.

Gender (male, %)	74 (76.3)
Age (yrs)	42.8 ± 9.6
Weight (kg)	83.4 ± 14.0
Body mass index (kg/m^2)	25.3 (23.4–28)
Blood pressure (mmHg)	
Systolic	138 (129–152)
Diastolic	77 (71–85)
Family history of CV disease (n, %)	25 (26)
Smoker (n, %)	
Never	49 (51)
Stopped	39 (40)
Current	4 (4)
No data	5 (5)
Baseline blood tests	
HbA1c (%)	5.3 ± 0.27
Total cholesterol (mmol/L)	4.9 (4.4–5.5)
HDL (mmol/L)	1.3 (1.1–1.6)
LDL (mmol/L)	3.2 ± 0.84
eGFR (ml/min/1,73 m^2)	94 ± 13.9
Training history	
No. of endurance competitions past 5 years	7 (2–16)
Hours of training per week past 3 months	7.0 (5–10)

3. Results

3.1. Participant characteristics

Participant characteristics are described in Table 1. Women had significantly lower cTn concentrations compared to men at baseline; cTnI 2.6 ng/L vs. 4.3 ng/L, ($p = 0.002$) and cTnT 3.5 ng/L vs. 5.2 ng/L ($p < 0.001$).

3.2. Troponin kinetics following prolonged strenuous exercise

Time dependent concentration changes for the two cTn assays are shown in Fig. 1. The peak concentration of cTnT was observed immediately post-race, and after 3 h for cTnI. Woman had significantly lower cTnT concentrations 3 and 24 h after the race compared to men; 31.6 ng/L vs. 40.8 ng/L at 3 h ($p = 0.04$) and 16.2 ng/L vs. 9.2 ng/L at 24 h ($p = 0.001$), respectively. However, when concentrations were related to the appropriate 99th percentile, the largest relative increase was seen in women (Fig. 2).

Following the race were the absolute cTn concentrations similar or higher for cTnI compared to cTnT (Supplemental data, Fig.1). The correlation between the two cTn assays ranged from $r = 0.54$ ($p < 0.01$) at baseline, to $r = 0.89$ ($p < 0.01$) acquired immediately following the race. The largest numerical differences between cTnI and cTnT concentrations were seen at the highest cTn concentrations.