Cardiac troponins and physical exercise. It's time to make a point

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Abstract

The timely diagnosis of acute coronary syndrome (ACS), in particular myocardial infarction (MI), is still one of the most challenging issues in medicine. The introduction into routine laboratory practice of assays for measuring the cardiospecific troponins has dramatically revolutionized the diagnostic approach and the recent development of methods with improved analytical sensibility (i.e., highly sensitivity [HS] assays), has further contributed to improve the negative predictive value of troponin testing but, contextually, has substantially lowered the clinical specificity of these markers. In particular, clinical studies have demonstrated the existence of an exercise-related increase of HS-troponins, with measurable values detectable in up to 94% of athletes undergoing endurance sports. This measurable amount of troponin in blood would mirror an increased membrane permeability and early troponin release rather than reflecting a clinically threatening myocardial injury. As such, the measurable amount of cardiac troponins as assessed with the novel HS assays requires major clinical focus (i.e., serial measurement of cardiac biomarkers, detailed clinical history-taking, integration with ECG and imaging findings) to prevent misdiagnosis of ACS and/or MI in otherwise healthy persons.

Key words: sports; biomarkers; acute myocardial infarction; cardiac injury; troponin

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The timely diagnosis of acute coronary syndrome (ACS), in particular myocardial infarction (MI), is still one of the most challenging issues in medicine. Despite the relentless introduction of novel biomarkers of myocardial injury over the past decades, the "Holy Grail" seems to be missing as yet. Although the development and introduction into routine laboratory practice of assays for measuring the cardiospecific troponins (namely Troponin I and T) has dramatically revolutionized the diagnostic approach to the patients with chest pain and suspected ACS, the main drawback of cardiac troponins testing has been represented for years by the relative lack in clinical sensitivity, in that up to 50% of the patients with an ACS had non-diagnostic values on admission (1,2). The recent introduction of methods with improved analytical sensibility (i.e., low limit of detection, LOD), traditionally referred to as "highly sensitivity troponins" (HS-Tns) assays, has substantially contributed to improve the negative predictive value of troponin testing but, contextually, has substantially lowered the clinical specificity of these markers (3). Despite the accurate selection of the normal reference population for calculation of reliable cut-off values (i.e., the 99th percentile limit of the reference value distribution [99th URL] obtained with assays with CV <10% at those levels), there are still several analytical, physiological and pathological conditions where troponin value is measurable in the absence of a clear ischemic myocardial injury (Table 1) (4,5). Physical exercise, especially when strenuous, must be indeed listed among these causes.

Table 1. Main sources of elevations of cardiac troponins in blood.

Analytical
Heterophilic antibodies
Rheumatoid factor
Microparticles
Fibrin clots in the sample
Hemolyzed, lipaemic of icteric samples
Analytical failure
Clinical (cardiac)
Myocarditis and pericarditis
Pathologies of cardiac valves
Hypertrophic cardiomyopathy
Severe arrhythmias
Severe heart failure
Cardiac trauma
Chemotherapy toxicity
Cardiac amiloidosis and sarcoidosis
Rejection of heart transplantation
Clinical (extra-cardiac)
Pulmonary embolism
Acute pulmonary oedema
Severe hypertension or hypotension
Chronic renal failure
Hypothyroidism
Stroke
Sepsis
Snake venom
Sickle Cell Disease
Physical exercise
Ketoacidosis
Carbon monoxide poisoning

A variety of clinical studies have now clearly demonstrated the existence of an exercise-related increase of HS-Tns (6), with measurable values (i.e., either above the LOD or the 99th URL) being detected in up to 94% of athletes undergoing endurance exercise (Table 2) (7-30). A recent meta-analysis pooling sixteen studies of 939 participants also showed that there were only 6 pre-marathon cTn elevations (0.6%) but as much as 579 post-race elevations (62%) (31). Odds ratio for converting from a normal pre-race to an elevated post-race cTn was 51.8 (95% CI = 16-168; $P < 0.001$). Interestingly, age and gender were not associated with post-race increases, but publication date and assay sensitivity were indeed associated with cTn elevation. Cardiac TnI was also less commonly elevated versus cardiac TnT, which can be explained with the greater sensibility (i.e., low LOD) of the latter assay. As such, the pooled data of the current scientific literature are consistent with the hypothesis that cTn levels might frequently increase after strenuous endurance exercise.

This very frequent occurrence of post-exercise increases of HS-Tns has substantial clinical implications, because diagnostic values in plasma or serum might last for 24 to 36 hours after an acute bulk of physical exercise, and this, in turn if ignored, might dramatically decrease the diagnostic performance of troponin testing, especially in those patients admitted to the emergency department for suspected ACS (32).

Several hypotheses were put forward to explain the biology of troponin increase after physical exercise. Since the current knowledge of myocardial biology has led to definitely rule out that measurable amount of troponins in blood after physical exercise would reflect a clinically threatening myocardial injury, it is now assumed that they would instead mirror an increased membrane permeability and early troponin release (i.e., "leakage") from the unbound, cytosolic pool, which represents nearly 3-8% of the total cardiac troponin content (33,34). This hypothesis is supported by the fact that the anatomic variations observed in marathon runners only included dilation of the right atrium and right ventricle, reduction of right ventricular ejection fraction, but no morphological changes were observed in the left atrium or ventricle, nor evidence of ischemic injury to any chamber by late gadolinium enhancement could be detected (35). Similar morphological features were observed by Wilson *et al*., who concluded that biomarkers of cardiac sufferance after prolonged exercise are not associated with either systolic (i.e., stroke volume or ejection fraction) or diastolic (i.e., early diastolic filling [E], late diastolic filling [A], E/A, isovolumic relaxation time, E deceleration time) functional measures (36).

Besides a very low amount of troponin, which is now measurable using most of the novel HS assays and is mainly attributable to cardiac remodelling (i.e., turnover of cardiomyocytes), the stretch-indu-

Table 2. Clinical studies investigating the post-exercise increase of cardiac troponins in endurance sports.

Biomarker	Assay	URL	Study population*	Type of exercise	Distance or duration	Sampling	Outcome	Reference
cTnT	Elecsys cTnT (Elecsys-1010; Roche Diagnostics GmbH)	0.03 µg/L	24 (19M and 5F; age: 49±6) [1]	Running	Marathon (42 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in 50% of the athletes	7
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.01 µg/L	60 (41M and 19F; age: 41 yr [21-65])[3]	Running	Marathon (42 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in 60% of the athletes	8
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.03 µg/L	10 amateur endurance runners (All M; age: 52 yr [43-57])[2]	Running	Ultramarathon (216 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in none of the athletes	9
cTnI and cTnT	ACS:Centaur TnI (ACS:Centaur, Bayer Labs) and Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	cTnT: 0.01 µg/L; cTnI: 0.1 µg/L	482 amateur endurance runners (318M and 164F; age: 39±10 yr)[1]	Running	Marathon (42 km)	Baseline, immediately post-exercise	Post-exercise levels of either cTn exceeded the URL in 68% of the athletes	10
cTnI	AxSYM cTnI (AxSYM, Abbott Diagnostics)	0.16 µg/L	27 athletes (20 male, 7 female)	Triathlon	Ultra-endurance (3.8 km swim, 180 km cycle and 42.2 km run)	Baseline, immediately and 1 week post-exercise	Post-exercise levels exceeded the URL in 58% of the athletes	11
cTnI and cTnT	E170 cTnT (E170; Roche Diagnostics GmbH) and AxSYM cTnI (AxSYM ADV, Abbott Diagnostics)	cTnT: 0.01 µg/L; cTnI: 0.04 µg/L	13 amateur endurance runners (12M and 1F; age: 41 [23–54])[3]	Running	Downhill marathon (42 km and 795 m vertical difference)	Baseline, immediately and 24h post-exercise	Post-exercise levels exceeded the URL in 46% (cTnT) and 69% (cTnI) of the athletes	12
cTnI and cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH) and AccuTnI (Access; Beckman Coulter, Inc)	cTnT: 0.01 µg/L; cTnI: 0.06 µg/L	10 junior basketball players (All M; age: 15.0±1)[1]	Basketball	Preseason basketball game	Baseline, 2, 4 and 24 h post-exercise	Post-exercise levels exceeded the URL in 40% (cTnT) and 30% (cTnI) of the athletes	13
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.03 µg/L	99 Collapsed endurance runners (61M and 38F; age: 39±10 yr) [1]	Running	Marathon (42 km)	Baseline, immediately post-exercise	Post-collapse levels exceeded the URL in 8% of the athletes	14
cTnI	cTnI (Randox Laboratories)	0.18 µg/L	10 (All M; age: 47 [38-52])[3]	Running	Half-marathon (21 km)	Baseline, immediately and 3, 6, 24 h post-exercise	Post-exercise levels exceeded the URL in none of the athletes	15
cTnI	TnI-Ultra assay (Advia Centaur XP, Bayer Labs)	0.05 µg/L	15 nonelite runners (All M; age: 32±10 yr) [1]	Running	Marathon (42 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in 92% of the athletes	16

Biomarker	Assay	URL	Study population*	Type of exercise	Distance or duration	Sampling	Outcome	Reference
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.03 µg/L	17 (All M; age: 47 [37-64])[3]	Running	Half-marathon (21 km)	Baseline, immediately and 3, 6, 24 h post-exercise	Post-exercise levels exceeded the URL in none of the athletes	17.
cTnT	Elecsys cTnT (Roche Diagnostics GmbH)	0.01 µg/L	9 amateur endurance runners (All M, age unavailable)	Running	Marathon on motorized treadmill (42 km)	Baseline, at 30-min intervals during exercise, immediately, 3, 6, 12, and 24 h post-exercise	During and immediately post-exercise levels exceeded the URL in 100% and 89% of the athletes, respectively; 24h post-exercise levels exceeded the URL in 56% of the athletes	18
Hs-cTnI, Hs-cTnT and cTnT	cTnI (Architect i2000SR, Abbott Diagnostics); Elecsys cTnT STAT and hs-cTnT (Elecsys 2010, Roche Diagnostics GmbH)	Hs-cTnI: 0.013 µg/L; hs-cTnT: 0.016 µg/L; cTnT: 0.01 µg/L	85 amateur endurance runners (70M and 15F; age 47 [45–49])[4]	Running	Marathon (42 km)	Baseline, immediately and 24 h post-exercise	Post-exercise levels exceeded the URL in 81% (Hs-cTnI), 86% (Hs-cTnT) and 45% (cTnT) of the athletes	19
cTnT	Elecsys cTnT (Elecsys-1010; Roche Diagnostics GmbH)	0.01 µg/L	25 subjects (20M and 5 F; age 41±5 yr) [1]	Running	Ultramarathon (160 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in 20% of the athletes	20
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.01 µg/L	61 non-elite marathon runners (half-marathon; 40M and 21 F; age: 40±12 yr) 1 68 non-elite marathon runners (full marathon; 44M and 24 F; age: 42±14 yr) 1	Running	Half-marathon (21 km) and full marathon (42 km)	Baseline, immediately and 1 h post-exercise	Post-exercise levels exceeded the URL in 46% of the athletes (half-marathon) and in 53% of the athletes (full marathon)	21
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.01 µg/L	13 adolescent endurance runners (All M; 14±2 yr)	Running	Two 45-min and Two 90-min constant-load treadmill runs	Baseline, immediately and 5 h post-exercise	Post-exercise levels exceeded the URL in 15%, 62% and 92% of the athletes performing 90 min at 80% ventilatory threshold (Th_{vent}), 45 min at 100% Th_{vent} and 90 min 100% Th_{vent}	22

Biomarker	Assay	URL	Study population*	Type of exercise	Distance or duration	Sampling	Outcome	Reference
cTnI	cTnI (not specified)	0.1 µg/L	92 amateur endurance runners (65M and 27F; age: 43±10 yr)[1]	Running	Marathon (42 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in 32% of the athletes	23
Hs-cTnT	Hs-cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.012 µg/L	10 amateur endurance runners (all M; age: 52 [43-57])[2]	Running	Ultramarathon (216 km)	Baseline, immediately post-exercise	Post-exercise levels exceeded the URL in 40% of the athletes	24
cTnT	Elecsys cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.01 µg/L	14 amateur endurance runners (8M, 6F; age: 33±6 yr)[1]	Running	Marathon (42 km)	Baseline, immediately, 3 days and 1 week post-exercise	Post-exercise levels exceeded the URL in 100% of the athletes	25
Hs-cTnT	Hs-cTnT (Elecsys-2010; Roche Diagnostics GmbH)	0.010 µg/L	78M amateur endurance runners (all M; age: 53±14 yr) [1]	Running	Marathon (42 km)	Baseline and 20 min post-exercise	Post-exercise levels exceeded the URL in 39% of the athletes	26
cTnI	AccuTnI (Access; Beckman Coulter, Inc)	0.04 µg/L	91 elite cyclists (All M; age: 40±9 yr) [1]	Cycling	Cycle-touring event (206 km)	Baseline and 20 min post-exercise	Post-exercise levels exceeded the URL in 43% of the athletes	27
cTnT	Elecsys cTnT STAT (Elecsys-2010; Roche Diagnostics GmbH)	0.03 µg/L	185 amateur endurance runners (132M, age 62±5 yr; 53F, age: 59±4 yr) [1]	Running	Cross-country race (30 km)	Baseline and 45 min post-exercise	Post-exercise levels exceeded the URL in 41% of the athletes	28
cTnI	AccuTnI, (Access; Beckman Coulter Inc)	0.04 µg/L	21 amateur endurance runners (19M, age: 38±8 yr and 2F; age: 38±1 yr) [1]	Running	45, 90 and 180 min	Baseline and 30 min and 3h post-exercise	Post-exercise levels exceeding the URL non significantly different from the baseline (range: 0–9%)	29
HS-cTnT	HS cTnT assay (Roche Diagnostics GmbH)	0.013 µg/L	78 male marathon runners	Running		Baseline, immediately after and 2 weeks post-exercise	Post-exercise levels exceeded the URL in 94% of the athletes	30

ced release of troponin and its degradation products even in absence of a clear myocardial necrosis has been widely described in several extra-cardiac clinical conditions, such as those listed in table 1. The precise mechanisms of the cellular leakage probably involves a sequence of events, where cardiac ischemia interferes with the normal function of the plasma membrane so that plasma membrane bubbles (also defined "blebs") develop and gradually grow as a function of both severity and duration of ischemia. Transient or mild cardiac ischemic episodes, such as those occurring during physical exercise, might not be sufficient to produce an irreversible membrane injury, so that the blebs are either reabsorbed or shed into the circulation with their protein content, thus justifying the low (usually < 1.0 µg/L) and short-lasting (typically < 24-36 h) amount of troponin detectable with the new HS assays. Conversely, when re-oxygenation dose not occur timely and cardiac ischemia is thereby prolonged, the blebs at the surface of the plasma membrane tend to collapse rather than be shed into the circulation and the irreversible myocardial injury (i.e., cell necrosis) occurs (34,37). In this instance, the appearance of troponin in plasma is that typical of ACS or MI. As such, the exercise-induced myocardium sufferance can be completely repaired and it might even lead to supercompensation.

A further support for this elegant model has recently been provided with the data of O'Hanlon *et al*, who demonstrated a non significant relationship between cardiac troponins and measures of cardiac damage. In particular, the increase of troponins and other cardiac biomarkers were unrelated with any detectable myocardial damage (inflammation, oedema, hyperemia, or fibrosis) using current gold standard imaging modalities (i.e., cardiovascular magnetic resonance) (38). It is to mention however that the conclusions from Delayed Gadolinium Enhancement (DGE) studies, in which a lack of enhancement has been argued as evidence that myocardial necrosis does not occur, might be questionable inasmuch as the levels of cardiac troponins detectable in athletes is usually less than that defined as the sensitivity limits for necrosis detectable on DGE following percutaneous coronary intervention or myocarditis.

Cardiac abnormalities may be a major source of morbidity in a small number of endurance and recreational athletes. Neilan *et al* investigated noneli-

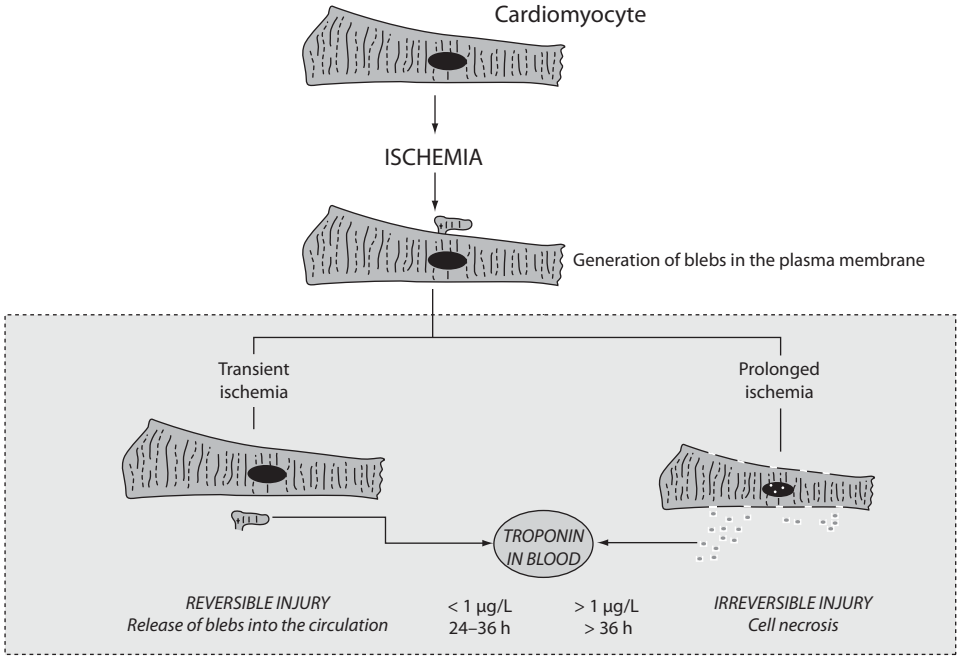

Figure 1. Biological basis underlying the ischemic release of measurable amount of cardiac troponins from cardiomyocites.

te participants before and after the 2004 and 2005 Boston Marathons with echocardiography and serum biomarkers (8). Sixty percent of participants had increased cTnT > 99th percentile of normal (> 0.01 ng/mL), whereas 40% had a cTnT level at or above the decision limit for acute myocardial necrosis (≥ 0.03 ng/mL) after the race. Interestingly these troponin increases significantly correlated with post-race diastolic dysfunction, increased pulmonary pressures, and right ventricular dysfunction, and inversely with training mileage. As such, exercise-induced cardiac dysfunction (e.g., right ventricular dysfunction) might be an additional biochemical evidence of cardiac injury after endurance sports, especially in participants with less training.

Recreational sports encompass activities where the primary purpose is participation, but that also hold the inherent goals of improved physical fitness, fun and social involvement. This kind of physical activity, which includes mostly amateur running and cycling, is typically less stressful, both physically and mentally, for the participants and it is also endorsed by health agencies and organizations such as the American Heart Association (AHA) and the American College of Sports Medicine (ACSM) for the substantial healthcare benefits, both physical and economical (i.e., reductions in the strain on public healthcare costs due to prevention of several pathologies such as cardiovascular disease, cancer and osteoporosis) (39). Nevertheless, the clear demonstration that even moderate amounts of physical exercise can increase the concentration of cardiac biomarkers, especially when measured with the novel HS assays, requires major clinical focus on this issue (i.e., serial measurement of cardiac biomarkers, detailed clinical history-taking, integration with ECG and imaging findings) to prevent misdiagnosis of ACS and/or MI otherwise healthy persons.

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Srčani troponini i tjelovježba

Sažetak

Pravovremeno dijagnosticiranje aktunog koronarnog sindroma, a posebice infarkta miokarda, još uvijek predstavlja jedan od najvećih izazova u medicini. Uvođenje testova za mjerenje srčanih troponina u rutinske laboratorijske pretrage znatno je poboljšalo dijagnostički pristup, a najnoviji razvoj metoda s poboljšanom analitičkom osjetljivošću (engl. *high-sensitive*, [HS]; visokoosjetljivi testovi) nadalje je doprinjelo poboljšanju negativne prediktivne vrijednosti kod određivanja koncentracije troponina. Međutim, to je istovremeno značajno snizilo kliničku specifičnost tih biljega.

Klinička su ispitivanja pokazala kod čak 94% sportaša koji se bave nekim od od sportova izdržljivosti (engl. *endurance sports*) mjerljivo povišenje koncentracije HS-troponina. Ta povišena koncentracija troponina u krvi ukazuje prije na povećanu propustljivost membrane te rano otpuštanje troponina, nego na klinički opasnu ozlijedu miokarda. Povećana bi koncentracija troponina određena visokoosjetljivim testovima trebala opširnu kliničku obradu (uzastopna mjerenja srčanih biomarkera, detaljno bilježenje kliničke povijesti bolesti, integracija nalaza elektrokardiograma i rezultata slikovne dijagnostičke obrade), kako bi se spriječile pogrešne dijagnoze aktunog koronarnog sindroma i infarkta miokarda kod inače zdravih osoba.

Ključne riječi: sport; biomarkeri; akutni infarkt miokarda; srčana ozljeda; troponin