Exercise-Induced Cardiac Troponin Release: Real-Life Clinical Confusion

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Abstract: Exercise training represents a successful and powerful strategy to prevent future cardiovascular disease. Paradoxically, performance of exercise is also associated with an increased risk of acute cardiac events. Accordingly, patients may present to hospital with cardiac symptoms following a bout of unaccustomed physical effort (e.g. exercise). Current guidelines for the identification of an acute myocardial infarction (AMI) importantly depend on the presence of cardiac troponin as a highly sensitive marker of cardiac damage. However, a number of studies have reported elevated cardiac troponin levels in asymptomatic, healthy subjects after endurance exercise (such as a marathon, prolonged cycling or prolonged walking). These observations indicate that elevated cardiac troponin levels can be the result of cardiac ischemia, and subsequent necrosis, but also may be related to strenuous exercise. In this paper, we present three different clinical cases of post-exercise elevations in cardiac troponins, each with a distinct clinical presentation. These case studies emphasize that a detailed assessment of all symptoms and a thorough patient-history are prerequisite for accurate interpretation of a positive cardiac troponin test following exercise.

Keywords: Cardiac biomarkers, acute myocardial infarction, endurance exercise, cardiovascular risk, troponin assay.

INTRODUCTION

Exercise training represents a successful strategy to prevent future cardiovascular disease in healthy subjects and reduces the risk for progression and/or development of secondary problems in those with established cardiovascular pathology [1-3]. Paradoxically, performance of exercise is also associated with an increased risk of acute cardiac problems, especially in those with an increased cardiovascular risk and who perform sudden unaccustomed bouts of exercise [4]. Following a suspected cardiac event, serum is analysed at admission for the presence of elevated cardiac troponin (cTn), either subunits T or I (cTnT and cTnI), as highly sensitive and specific markers of myocardial injury [5-7]. According to current guidelines, an acute myocardial infarction is diagnosed if cTn levels are above the 99th percentile of the upper reference limit, combined with evidence of myocardial ischaemia with at last one of the following: (1) symptoms of ischaemia; (2) ECG changes indicative of new ischaemia; (3) development of pathologic Q waves in the ECG; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [5, 8].

Interestingly, prolonged exercise in healthy, asymptomatic individuals has been shown to elevate cTn. Indeed, levels of cTn above the clinical cut-off used for the diagnosis of AMI have been shown following marathons, triathlons, cycling and/or walking events [9-13]. Despite the post-exercise elevation in cTn, previous studies have not reported (patho)physiological evidence or clinical signs of myocardial injury. This suggests that post-exercise cTn levels may be related to a physiological rather than a pathological response after the exercise stimulus [10]. Accordingly, the interpretation of elevations in cTn following unaccustomed exercise can be highly challenging and has important clinical implications. Differentiation between the physiological *versus* pathological release of cTn is important to avoid misdiagnosis. For example, a false-positive diagnosis could lead to unnecessary hospital admission and invasive investigations [14], while a false-negative diagnosis could be potentially life threatening for the patient. The recent development of even more sensitive cTn assays effectively reduces the incidence of false-negative tests in the *general* population. However, in individuals undertaking prolonged exercise, these new highly sensitive assays will better detect the small cTn release following exercise. In addition, relatively little is known about the challenging interpretation of cTn elevation in subjects after (strenuous) exercise, which may result in clinical confusion.

In this paper, we present three distinct case studies, each demonstrating elevation in cTn post-exercise, yet each presenting with different symptomatology. Discussion of these cases and recognition of the importance of other signs and symptoms may help clinicians and laboratories to improve the clinical management of "*positive*" cTn samples in people who have recently undertaken strenuous exercise.

CASE PRESENTATION

The most important information regarding the exercise characteristics, clinical symptoms and laboratory tests is summarised in Table **1**.

Case 1

A 59 year old male (1.86 m, 88 kg, BMI 25.4 km/m^2) participated in the Nijmegen Four Days Marches, which included 40 km of walking exercise per day for four consecutive days. The event was held under moderate climate conditions (maximum ambient temperature of 25.0°C). The subject had no history of smoking, cardiovascular disease, cardiovascular risk factors and was not using any medication. The subject reported to be physically active on at least five days per week for at least 30-minutes. As part of a previously published scientific study [15], blood was drawn the day before the march and following completion everyday thereafter. cTnI-level was 0.025 µg/L before the march, which is under the clinical cut-off value for AMI (0.040 µg/L) [16]. The subject walked for ~7.5 hours (5.4 km.hour^{-1}) and with an average heart rate of 160 beats per minute on each of the four days. Core body temperature was measured using a wireless telemetry system and increased to an average finish temperature of 38.4°C, indicating that he was not hyperthermic [17]. The subject did not report any physical complaints during or after the marches. Using a visual analogue scale (scale 0-10, with 10 as maximal effort), he rated the walking exercise as a 6. Post-exercise blood was taken 20-minutes after finishing each day. Analysis of stored serum samples, three-months after the event, revealed an increase in cTnI to 0.448 µg/L after day-1 and values of 0.314, 0.171 and 0.097 µg/L on the subsequent three days. As a final diagnosis, the elevation of cTnI-levels in this case were due to the preceding physical exercise.

Case 2

A 47 year old male (1.80 m, 72 kg, BMI 22.2 km/m^2) was admitted to the Radboud University Nijmegen Medical Centre (16:00

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Table 1. Characteristics of Three Cases with Elevated Cardiac Troponin Levels After Exercise with an Individual Score for the Presence (+) or Lack (-) for a Certain Marker for AMI

Parameter	Case 1	Case 2	Case 3
Exercise			
Type	*walking*	*running*	*walking*
Intensity	*moderate - high*	*high*	*moderate*
Duration	*~7.5 h*	*1 h 12 min*	*~10.5 h*
Cardiac troponins			
Assay	*cTnI*	*cTnI*	*cTnI*
cTn level (highest value)	*0.448 µg/L*	*17.40 µg/L*	*4.26 µg/L*
cTn > clinical cut-off	+	+	+
Physical complaints			
Chest pain	-	-	+
Sweating	-	-	-
Breathlessness	-	-	-
Nausea	-	+	-
Vomiting	-	-	-
Restlessness	-	-	-
Signs of ischemia			
ECG abnormalities	-	+	-
Cardiac imaging abnormalities	-	+	-
PCA	-	+	-

PCA: percutaneous coronary angiography, '-': not present, '+': present.

h.) after completing a 15-km run. The race was completed under cool climatic conditions (maximal air temperature 9 °C), and he finished the race in 1 hour 12 minutes (12.5 km.hour^{-1}). No (family) history of myocardial infarction, stroke or other cardiovascular diseases was reported. The patient used no medications, oral supplements or tobacco while he routinely performed 4 hours of moderate- to high-intensity exercise per week.

The patient experienced nausea after finishing the 15-km the race and after ~60 minutes he collapsed and lost consciousness. After successful application of basic life support combined with 3 shocks from an automated external defibrillator (AED), vital functions were stable (pulse and breathing), but he was still unconscious. After 10 minutes, an ambulance arrived and he was transferred to hospital after intubation for mechanical ventilation and administration of aspirin and heparin intravenously. On admission (16:15 h.), ECG showed sinus rhythm with maximum 2 mm ST-elevation in leads II-III-aVF and downsloping ST-segment depression in leads I, aVL, V2-V6, suggestive of an acute myocardial infarct. He was in sinus-tachycardia (110 bpm) and showed hypertension (160/114 mmHg). Cardiac auscultation was normal. Neurological examination revealed a Glasgow Coma Score of 1-2-tube. Laboratory tests immediately on admission showed cTnI below the detection limit (<0.2 µg/L). However, blood tests at 6.50 PM revealed cTnI-levels above this limit (0.82 µg/L), which demonstrated a further increase on subsequent days (5.82, 11.30, 17.40 and 16.60 µg/L, respectively). Creatine kinase was increased immediately after admission (172 µg/L), and increased to 400, 1392, 1908, 3010 and 3542 µg/L during subsequent laboratory tests at 18:50, 00:39, 0:52, 11:52 and 17.43 h., respectively. Shortly after admission (17:21 h.), he was taken for coronary angiography after administration of intravenous aspirin and 10,000 International Units (IU) of Heparin. Coronary angiography revealed an occlusion of the right coronary artery at the level of the right ventricular branch. After opening of the occlusion by primary stenting with a drug-eluting stent, a 70-80% stenosis at the origin of the right posterior descending artery partially consisting of dislodged thrombus became apparent. Balloon dilatation of this lesion in the posterior descending artery was subsequently performed. The left main coronary artery was normal, but significant proximal stenoses of the left anterior descending artery, the left circumflex artery and the left marginal artery were found. The patient was transported to the intensive care unit for mechanical ventilation, whole body cooling for 24 hours and pharmacological treatment, consisting of beta-blockade, ACE-inhibition, dual anti-platelet therapy (80 mg aspirin and 75 mg clopidogrel after a loading dose of 600 mg), heparin and a statin. Twelve days after admission, he was discharged from hospital. The final diagnosis for this case was an out-of-hospital cardiac arrest due to ventricular fibrillation in the setting of an acute myocardial infarction.

Case 3

A 31 year old male (1.86 m, 70 kg, 20.2 kg/m^2) was admitted to the Maasziekenhuis-hospital (18:30 h.) with a tight band feeling. He successfully completed four days of walking (50 km per day) during the Nijmegen Four Days Marches and reported no (family) history of myocardial infarction, stroke or other cardiovascular diseases. The patient used no medications, oral supplements, tobacco or caffeine. Furthermore, he was recreationally active (4 hours walking and 1 hour football per week) and frequently used a bicycle for transportation (3 hours per week). The walking march was held under mild to moderate climatic conditions (maximal temperatures 17-20 °C), and he walked with an average speed of 4.7 km.hour^{-1}.

The patient reported a tight band-feeling around his chest that started 1 hour prior to admission. The night before (03:30 h.), he experienced similar complaints, which disappeared after 45 min. On admission to a small community hospital, he was in sinus-bradycardia (58 bpm), exhibited normal breathing frequency and was normotensive (127/78 mmHg). He reported no shortness of breath, nausea, sweating, anxiety or chest pain. Auscultation and neurological examination revealed no abnormalities. ECG at admis-

sion did not show any signs of ischemia, pericarditis or right heart pressure overload (e.g. ST elevation or depression, T wave inversion, Q waves or PR depression). The tight band-feeling around his chest disappeared 30 min after admission. Laboratory tests showed elevated levels for creatine kinase-MB (32.0 μg/L) and cardiac troponin I (4.26 μg/L), while CRP levels were only mildly increased (12 mg/L) and the leukocyte concentration was normal ($5.6*10^9$/L). He was taken to the intensive care unit for (overnight) monitoring, while standard oral pharmacological treatment was started (80 mg acetylsalicylic acid, 75 mg clopidogrel, 2x0.8 mg enoxaparine, 2x40 mg atorvastatin, 4x25 mg metoprolol). The day after admission, new laboratory tests (03:00, 09:15 and 16:45 h.), revealed a decrease in creatine kinase-MB levels (29.3, 18.8 and 13.0 μg/L, respectively), but no change in cTnI (4.21 μg/L at 16:45 h.). Subsequently, pharmacological treatment was stopped. Two days after admission, a 12-lead ECG showed no abnormalities at rest or during a graded-maximal cycling test. In addition, echocardiography showed no abnormalities. Three days after admission, the patient was discharged from the hospital and pharmacological treatment was stopped. After 9 months, additional tests were performed to examine potential scarring of the cardiac tissue. His resting ECG and lipid levels showed no abnormalities (total cholesterol 3.8 mmol/L, triglycerides 0.74 mmol/L, low-density lipoproteins 2.65 mmol/L, high-density lipoproteins 0.82 mmol/L). Furthermore, a cardiac MRI-scan revealed normal left ventricular mass and volume, and no regional wall motion abnormalities were present. In addition, no abnormalities were found during first-pass early perfusion MRI, and there was no delayed enhancement of the ventricular walls using gadolinium contrast. A final diagnosis for this patient remains debatable as we found no signs for cardiac damage or ischaemia, whilst elevated troponin levels are unlikely explained by the prolonged, multiple day, exercise stimulus.

DISCUSSION

This paper presented 3 distinct clinical cases, each with an elevation in cTn following successful completion of a bout of prolonged moderate- to high intensity exercise. In this last section we will discuss the importance and recognition of the clinical symptoms in relation to changes in cTn. This information may help clinicians with decision making in relation to post-exercise elevations in cardiac troponins.

The first case reveals an increase in cTnI above the clinical cut-off value on 4 consecutive days when performing prolonged, moderate-intensity walking exercise. Nonetheless, this subject reported no physical complaints, clinical signs or specific symptoms of ischemia (Table **1**). Current guidelines indicate that clinical symptoms *as well as* a rise/fall of cTn must be present for the diagnosis of AMI [5, 18]. Since no accompanying symptoms were present in Case 1, the increase in cTn is likely related to a physiological response during the exercise stimulus. Although walking is not regarded as either strenuous or exhaustive exercise, this subject exercised for 7.5 hours with an average heart rate of 160 bpm. Two recent studies have shown that a significant proportion of participants in long-distance walking events demonstrate an increase in cTnI, with 6-11% exceeding the AMI clinical cut-off [10, 15]. These findings support a recent review that concluded that the exercise-induced increase in cTn in healthy individuals is a common phenomenon [19]. Although the exact mechanism behind the physiological release of cTn during exercise is unknown, recent studies have hypothesized an increased membrane permeability of the cardiomyocytes following strenuous exercise [20-23]. When the individual described in Case 1 was taken to hospital, assessment of blood cTn-levels could have caused confusion if clinicians had not appreciated the importance of the recent 'exercise history', such as has been described in previous case reports [14, 24]. It is worth noticing that only a mild increase in cTnI is observed in this subject after exercise. This "relatively" low cTnI, combined with a lack of clinical signs or symptoms suggestive for AMI, suggest a physiologic as opposed to a pathologic troponin release and as such does not warrant further medical attention.

On the other end of the spectrum, exercise can also act as a trigger for AMI. A crucial difference between Case 1 and 2 is the presentation of clinical symptoms that are strongly suggestive of AMI. According to a recently published algorithm for the differential diagnosis in participants who have recently completed unaccustomed exercise who then seek medical attention (Fig. **1**), cTn should be tested in this patient [19]. While cTn levels were normal directly after admission to the hospital, cTnI was significantly elevated above the 99th percentile of the upper reference limit after two hours [5]. In contrast to healthy subjects who usually demonstrate a direct increase in cTn post-exercise, it takes ~2 hours to detect elevated cTn levels in patients with ischemic cardiac injury. This characteristic delayed increase of cTnI highlights the importance of assessing clinical symptomatology alongside humoral markers [25]. Given the magnitude and kinetics of the subsequent cTnI release in Case 2, it is clear that this cannot be explained by the prior exercise alone, but is likely the direct result of cardiac damage. Indeed, we found classical clinical signs for AMI and characteristic changes in the 12-lead ECG, whilst percutaneous coronary angiography was necessary to open the right coronary artery. This case is, therefore, representative of an AMI, which in occurred after a bout of exercise.

Case 3 raises a number of questions, and exemplifies the difficulty of interpreting elevated cTn levels after prolonged exercise. Immediately after hospital admission, and also on subsequent days, cTn levels were above the clinical cut-off value. Furthermore, a "tight band feeling" was reported by the patient at admission. According to current guidelines [5, 8], the elevated cTn levels in combination with the clinical symptoms suggest the presence of an AMI. However, no signs of cardiac ischeamia or damage were found with additional testing. First, the clinical symptoms typical for a myocardial infarction (e.g. the "tight band feeling") were temporary and disappeared within 1 hour 30 minutes. Second, the clinical investigations that were performed after admission (ECG recordings and echocardiography), and play a central role in the final diagnosis of AMI, were all negative and did not reveal evidence of ischaemic cardiac injury. Third, additional analysis performed 9 months after admission (resting ECG and cardiac MRI), showed no evidence for myocardial scarring or resting perfusion abnormalities. Taken together, the low cardiovascular risk profile and the absence of evidence of ischaemia, argue against the presence of a (meaningful) AMI.

Alternatively, the elevation in cTn levels may relate to the preceding exercise stimulus, such as observed in Case 1. However, the magnitude of cTn levels was substantially higher than typically reported in previous studies. Also, cTn levels remained elevated during the two days after exercise, whilst it can be expected that cTn will start to decline rapidly after exercise. Therefore, we believe it is unlikely that the elevated cTn levels were solely due to the walking exercise. Previous studies have reported that other (cardiovascular) pathologies are related to elevated cTn levels, such as pericarditis, myocarditis, pulmonary embolus, heart failure, renal failure and sepsis [26]. These conditions should be taken into consideration when evaluating the high cTn levels in this patient. Given the temporal nature of physical complaints, normal ECG pattern after admission, absence of signs of dyspnea or hypterthermia, normal leukocyte concentration and mildly elevated CRP levels, it is unlikely that these (cardiovascular) pathologies can explain the elevation in cTnI in this subject. Finally, the elevated cTn levels in Case 3 might relate to the presence of a very small AMI. This limited ischemic region could explain the (modest) elevated troponin levels, whilst the size of this AMI would be too small to detect significant scarring or changes in cardiac function. Taken together, a final diagnosis is challenging for this subject. The elevation in

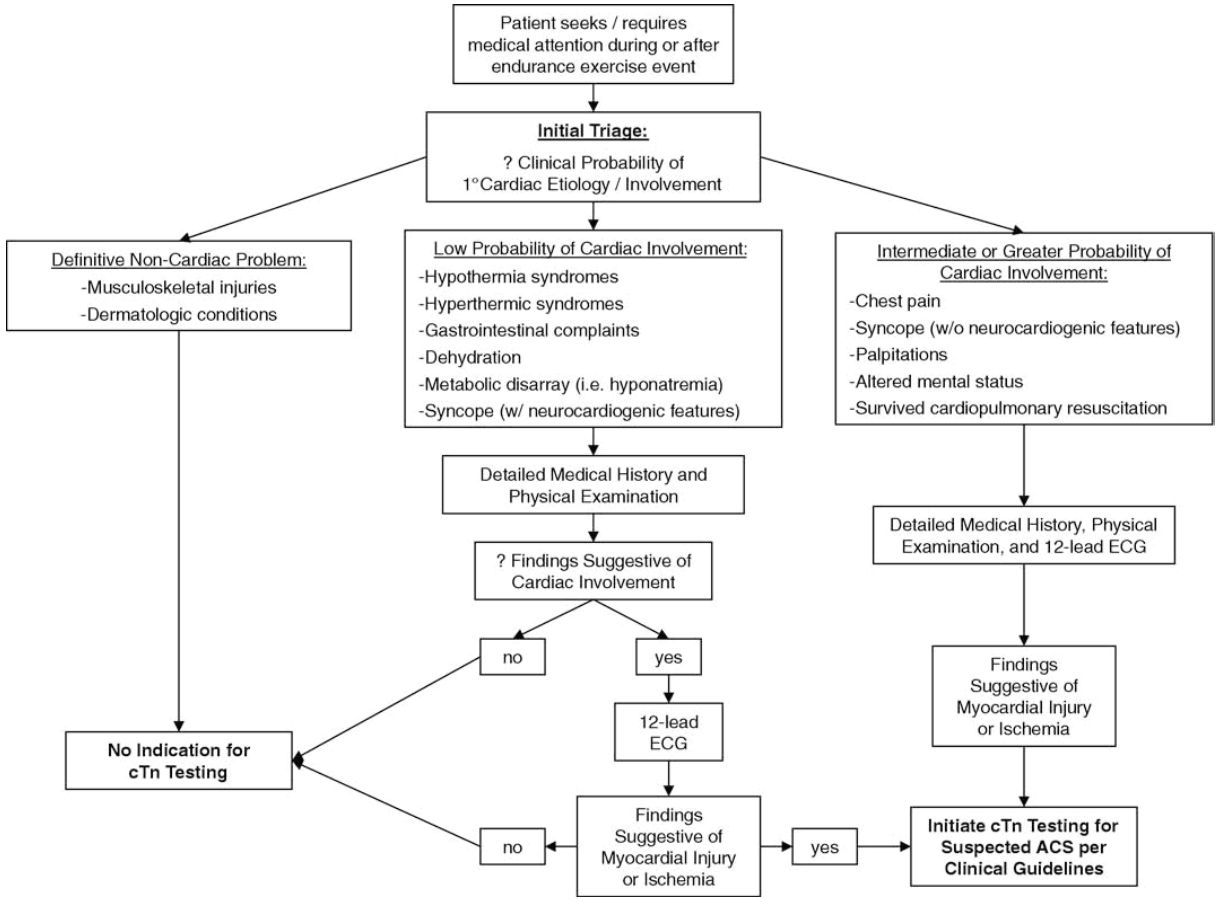

Fig. (1). Algorithm for the initiation of cardiac troponin (cTn) testing in patients after prolonged exercise, proposed as an adjunct to the standard clinical guidelines for acute coronary syndrome (ACS). ECG _ electrocardiogram. With permission from Shave *et al.* [19].

cTnI in this subject unlikely relates to the preceding exercise bout, but also does not represent the typical AMI. Thus, this case highlights the clinical confusion that can occur with troponin testing in patients that have recently participated in exercise events.

CONCLUSION

Taken together, minor elevations in cTn in individuals admitted to hospital after strenuous exercise can sometimes be difficult to interpret as the minimal increase may relate to; 1. early release from necrotic tissue, and/or 2. a physiological exercise-induced stimulus. Before making a final diagnosis based on a positive cTn, physicians should take into account the magnitude and nature (transient/delayed) of cTn release, clinical symptoms as well as the (exercise) history of the individual.

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CONFLICT OF INTEREST

None of the authors have conflict of interest.

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