The current paradigm of cardiac troponin increase among athletes

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Abstract

Although it is known that exercise improves cardiovascular health and extends life expectancy, a significant number of people may also experience an elevation in cardiac troponin levels as a result of exercise. For many years, researchers have argued whether exercise-induced cardiac troponin rises are a consequence of a physiological or pathological reaction and whether they are clinically significant. Differences in cardiac troponin elevation and cardiac remodeling can be seen between athletes participating in different types of sports. When forecasting the exercise-induced cardiac troponin rise, there are many additional parameters to consider, as there is a large amount of interindividual heterogeneity in the degree of cardiac troponin elevation. Although it was previously believed that cardiac troponin increases in athletes represented a benign phenomenon, numerous recent studies disproved this notion by demonstrating that, in specific individuals, cardiac troponin increases may have clinical and prognostic repercussions. This review aims to examine the role of cardiac troponin in athletes and its role in various sporting contexts. This review also discusses potential prognostic and clinical implications, as well as future research methods, and provides a straightforward step-by-step algorithm to help clinicians interpret cardiac troponin rise in athletes in both ischemic and non-ischemic circumstances.

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Introduction

Physical activity (PA) has been shown to reduce and modulate cardiovascular modifiable risk factors such as type 2 diabetes mellitus, hypertension, obesity, and cancer. As a result, it may be assumed that PA enhances people's quality of life and lowers morbidity and mortality [1-3]. That is why the current European Society of Cardiology (ESC) guidelines on sports cardiology and exercise in patients with cardiovascular disease (CVD) recommend at least 150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity aerobic exercise in healthy individuals [4]. On the other hand, it is known that PA can induce the elevation of cardiac biomarkers, especially cardiac troponin (cTn) levels. Two independent research groups first reported the post-exercise elevation of blood cTn levels [5,6]. Creatine kinase (CK) muscle-brain has been excluded from the studies since the high levels in athletes' serum, related to exercise training [7]. Whether cTn release after PA represents a physiological or pathological event remains debatable. Also, whether exercise-induced cTn increase represents a new cardiovascular risk factor must be argued. Therefore, this comprehensive review aims to explain the role of cTn in the general population and athletes and illustrate the influence of different sporting disciplines on exercise-induced cTn elevation and its clinical and prognostic implications in clinicians' everyday practice.

Methods

We conducted a narrative review of articles published from 1987 to 2023, searched in PubMed, PMC, and SportDiscus without language restriction. The leading search terms were exercise-induced troponin release, cTn elevation in athletes, endurance sports, myocardial injury, *etc*. We also reviewed the references of retrieved articles for additional studies. It was decided to exclude every manuscript that did not address our question. We organized the search and the description of the results in the following main sections: cTn in normal subjects and individuals practicing sports, the influence of different sporting disciplines on cTn elevation, and clinical and prognostic implications of cTn elevation in competitive athletes.

Cardiac troponin in normal subjects and individuals practicing sports

Cardiac troponin

The heterotrimeric complex of troponin, which comprises three molecules with distinct functions, is crucial for controlling the interaction of excitation and contraction in skeletal and heart muscle [8]. While troponin T promotes the binding of the group of troponins C, I, and T (TnT) to tropomyosin, troponin C attracts the Ca++ molecule, and troponin I (TnI) suppresses the ATPase enzyme of the actomyosin complex [9]. TnI and TnT, which are also expressed in skeletal and smooth muscles, are different from the cardiac ones, which are produced by the expression of specific genes and are present only in the myocardium of the adult [9-11]. These last isoforms are termed cTnI and cTnT. In some circumstances, these molecules can be released into circulation, and their levels can be measured using different laboratory assays [10,11].

There is no evidence that damage to non-cardiac tissues results in an increase in cTnI levels. On the other hand, because injured skeletal muscle generates substances that can be identified by the cTnT assay, according to some studies, the situation is more challenging for cTnT quantification [12,13]. Therefore, high sensitivity-cTn assays (hs-cTn) are recommended for routine clinical use. Assays are now classified as high sensitivity if the cTn concentration can be detected above the detection limit but below the 99th percentile in 50% of healthy individuals, and the coefficient of variation at the 99th percentile value is 10% or less [14]. It is commonly known that the detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury, and the injury is considered acute if there is a rise or fall in cTn values [15]. Moreover, the accuracy is highest with the sensitive cTnI assay [area under the receiver-operating characteristic curve (AUC), 0.96] as compared with the cTnT assay (AUC, 0.85), with clinical sensitivity of 90.7% and specificity of 90.2% [16]. Nevertheless, various myocardial ischemia or non-ischemic conditions can be linked to elevated cTn levels, and the complexity of clinical situations can occasionally make it challenging to distinguish between particular distinct processes of myocardial injury [15]. In fact, increased concentrations of cTn do not reveal the pathophysiological mechanisms behind the myocardial damage and can even develop after preload-induced mechanical strain or para-physiological stressors in healthy hearts [17,18].

Exercise-induced troponin release and predicting factors

Regular exercise is commonly known to lower the chance of developing CVD; nonetheless, multiple studies have shown post-exercise increases in cTn levels suggestive of heart damage in otherwise healthy people [19]. The invention of very sensitive cTn assays, which are highly capable of determining very low levels of myocardial injury, made possible a more precise assessment of exercise-induced cTn increase [20].

In 1987, the first study describing the immediate rise of cTn concentrations in some people after vigorous exercise was published [21]. This discovery first seemed counterintuitive because PA was typically thought to bring only benefit, and cTn levels were only thought to be indicators of myocardial damage. Several investigations have been carried out to better understand the troponin response during exercise, with contradictory findings concerning prevalence and cTn levels, most likely due to variability in trial design [19,20,22].

However, it is still debatable how this biomarker is released and if it represents a physiological or pathological activity. Elevated cTn in response to exercise can be explained by various processes. Cardiomyocyte stress brought on by exercise may change the permeability of the cell membrane, allowing passive diffusion of troponin fragments into the extracellular space and circulation [23]. Additional data sustain that this exercise-related cTn release is due to enhanced apoptosis or accelerated cardiomyocyte turnover caused by cardiac stress or transient ischemia [23]. Another explanation is that a small degree of necrosis after vigorous exercise could increase cTn levels in vulnerable people. There are also other non-cardiac explanations of cTn increase, such as exercise-induced disruptions in fluid balance and mild reduction in kidney function [19,23]. However, the relative importance of these models for exercise-induced cTn release remains unclear.

Various circumstances can influence and modulate the release of heart biomarkers, such as age, gender, hydration level, training experience, blood pressure, ambient conditions, time of cTn sampling, and type of assay utilized for its analysis, as well as exercise intensity and duration (Figure 1) [24-26]. Early research revealed that exercise duration was positively correlated with the amount of cTn released [25]. On the other hand, intensity has been consistently cited as a potential predictor of the cTn response, although not all studies have found a correlation [27]. There might be a threshold exercise intensity at which cTnI release becomes more pronounced [19]. The first-generation troponin T enzyme-linked immunoassay could yield erroneously elevated readings in individuals with significant skeletal muscle damage. This occurrence of false-positive outcomes is attributed to the non-specific attachment of skeletal muscle troponin T to the test tube's surface. Consequently, the enzyme-labeled antibody used in the first TnT assay could detect this cross-reactive binding, leading to misleading results [28]. Nonetheless, utilizing the most recent highly sensitive methods, nearly all subjects exhibit increased cTn levels after exercise. Whether cTn elevation represents true myocardial injury is still debatable. On the other hand, it is widely known that strenuous sports may be associated with myocardial damage in some circumstances.

Influence of different sporting disciplines on cardiac troponin elevation

The spectrum of physical activity components

Sports can be classified into two primary groups depending on the intensity and type of exercise: dynamic (isotonic) and static (isometric). They can be divided, considering the immediate physiological effects (heart rate and blood pressure) and the long-term effects

on cardiac output and remodeling [29]. A slight increase in blood pressure and cardiac output usually occurs with an augmented heart rate. Also, the length of the workout and the level of intensity change significantly depending on the sport and the athlete's function. Blood pressure and heart rate may increase to almost maximum levels while alternating with recovery phases [29]. The dynamic exercise entails muscle length and joint movement alternations, accompanied by rhythmic contractions that generate a relatively modest intramuscular force. In contrast, static activity generates a reasonably significant intramuscular force with minimal or no changes in muscle length or joint movement [30]. These two forms of exercise can be viewed as the extreme ends of a spectrum, as most PAs involve a combination of static and dynamic components [30]. High-intensity dynamic exercise leads to a considerable rise in heart rate and stroke volume. These effects are achieved by elevating the end-diastolic volume (using the Frank-Starling mechanism) and reducing the end-systolic volume due to an enhanced contractile state. Conversely, in high-intensity static exercise, the end-diastolic and end-systolic volumes of the LV experience minimal changes [30]. Nevertheless, arterial pressure and the contractile state of the ventricle are heightened [31]. The 2020 ESC guidelines on sports cardiology and exercise in patients with CVD categorize various sports disciplines based on their predominant component (skill, power, mixed, and endurance) and the intensity of the exercise (high, medium, low) [4]. Power sports require explosive muscle power, and an example of this type of activity is represented by weightlifting; mixed sports, such as ball and team sports (like soccer or basketball), involve alternating stages of dynamic and/or static effort and recovery, while sports that need endurance are those that require long-term, intense, high-dynamic exercise such as running [32]. Several studies analyzed changes in cTn concentrations in different types of sports. Some of them also showed a difference between young and master athletes. The correlation between cTn increase and different types of sport is shown in Figure 2.

Cardiac troponin in young and masters

Previous research was limited to master athletes and examined the interactions between acute cTnI reaction to prolonged PA and the wide range of exercise-induced hypertension. However, after endurance exercise, cTnI levels were shown to be higher in adolescents than adults, and their myocardium may be more vulnerable to cardiac damage [33-36].

Adolescents displayed considerably greater concentrations of hs-cTnT than adult runners who had received equivalent training after endurance running for 90 minutes at the same relative intensities, indicating that age may impact the degree of cTnT increase after strenuous exercise. Although age is probably a factor in the

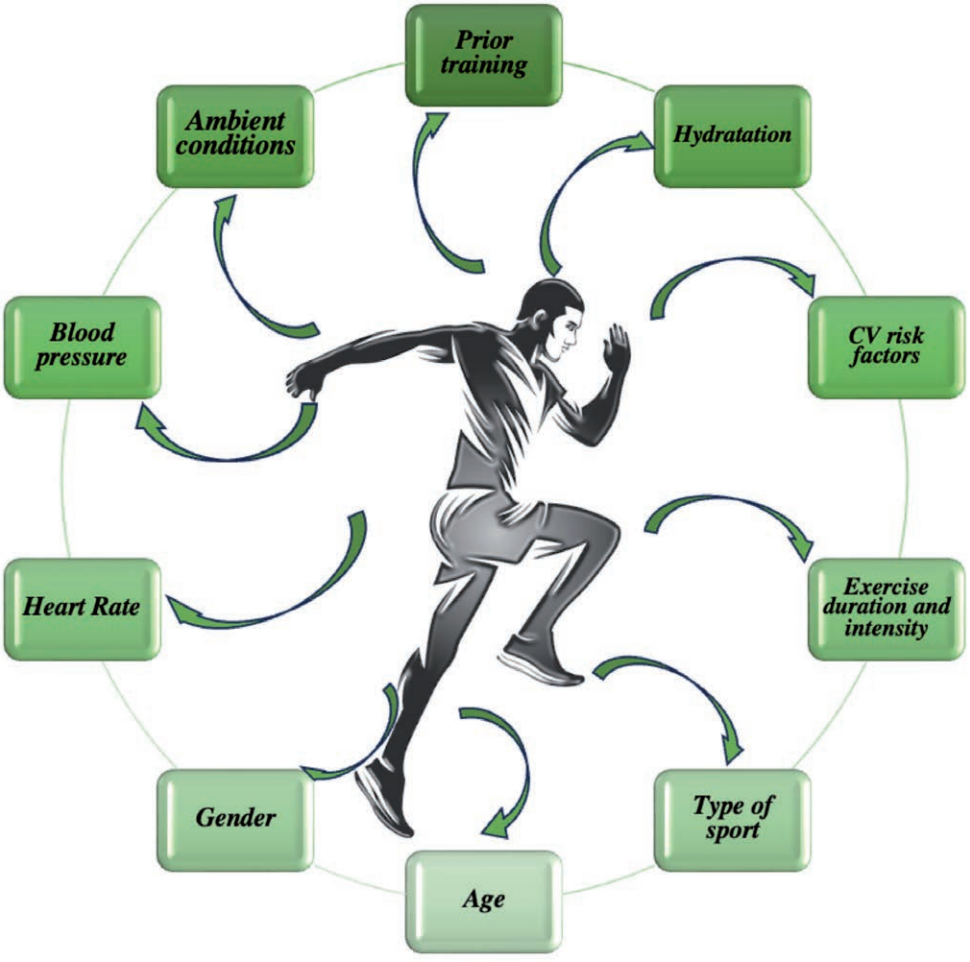

Figure 1. Factors of exercise-induced cardiac troponin levels. CV, cardiovascular.

peak hs-cTnT reaction, the release pattern of hs-cTnT after prolonged exercise occurs over a comparable time course in adult and young runners [33].

However, another study showed that adolescent athletes, such as swimmers, experience an increase in exercise-induced cTnI, but without significant differences between adolescents and adults [7]. Anyway, it has been suggested that the immaturity of adolescents' myocardium, which would undergo more significant stress in response to an increased myocardial workload, may be considered the cause for the frequently found higher exercise-induced concentration of cTn in younger [7]. Young hearts have fewer antioxidant defense mechanisms against potentially damaging chemicals than adult hearts. Therefore, oxidative stress, which can significantly rise during exercise, makes young hearts more susceptible [37]. In addition, according to Tesema *et al*., 12-week endurance training in young athletes initially increases cTnI, which is positively and significantly linked with systolic blood pressure, mean arterial pressure, and resting heart rate. This suggests that after the 12-week endurance training program, the gradual training adaptation lowers serum cTn levels and related cardiovascular parameters in young, poorly trained amateur athletes [38]. On the other hand, earlier research has connected older athletes' increased mortality and cardiovascular event rates to exercise-induced elevations of cTn [39]. In this instance, more significant elevations among older athletes may be linked to underlying, subclinical heart disease, but further research is required to confirm this latter claim.

Cardiac troponin elevation after endurance sports

Engaging in sports that involve either high dynamic demand (endurance) or high static demand (power) leads to increased cardiac mass and structural remodeling in numerous athletes [30]. Dynamic exercise primarily imposes a volume load on the LV, while static activity generates a pressure load [31]. Sports that need endurance are those that require long-term, intense, high-dynamic exercise. Athletes who undergo training in sports with a significant dynamic component exhibit a substantial increase in the absolute LV mass and chamber size (referred to as eccentric hypertrophy) [30]. Moreover, several researchers investigated the cTn release in athletes practicing prevalently dynamic sports.

Vilela *et al*. conducted a systematic review to investigate the pattern of hs-cTn release following running [29]. Of the 424 participants with a mean age of 40 years, nearly 70% exhibited post-running high-sensitivity troponin values surpassing the 99th percentile reference value. The pattern of cTn release in this context, with a relatively quick decline in plasma cTn levels after reaching peak values, suggests a reversible phenomenon, and cardiac strain could potentially account for the cTn release following running [29]. The

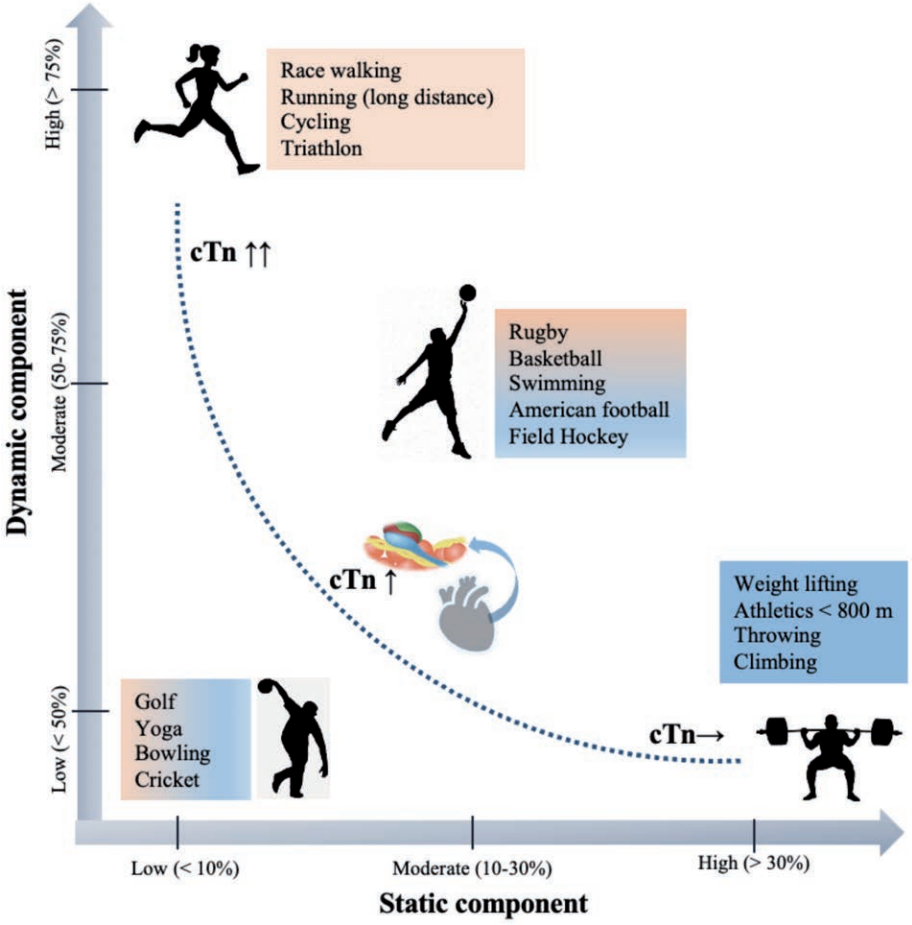

Figure 2. Classification of sports based on the prevalence of dynamic and static components and their correlation with the level of cardiac troponin increase, established by articles available in the literature. →, normal values; ↑, slightly increased; ↑↑, greatly increased; cTn, cardiac troponin.

authors concluded that using high-sensitivity assays, elevated plasma concentrations of cTn were observed in over two-thirds of the participants studied, indicating a more widespread phenomenon than previously believed [29]. Furthermore, Neumayr *et al.* conducted a study to examine the world's top ultra-endurance cyclists participating in the remarkable "Race Across the Alps" (RATA) to assess the possibility of stress-induced myocardial damage [40]. The study included 16 male volunteers out of 31 subjects participating in the inaugural RATA held on July 7, 2001. The workload of the race is distinctive, covering 509 km with a cumulative altitude difference of 12,200 meters [40]. Immediately after the competition, cTnI levels increased to the upper reference limit of 0.5 µg/L in two athletes (12.5%) and were significantly elevated in another four subjects (25%) within a range of 0.7 to 5.1 µg/L. In the athlete with the highest cTnI value (5.1 µg/L), cTnT was also elevated (0.11 ng/mL). One day after the competition, neither cTnI nor cTnT was detectable in any athlete. The increases in cTn did not correlate with the changes in CK and CK-MB [40].

Moreover, in 2008, four male cyclists with extensive training and expertise participated in cardiovascular assessments, including cTn assay, before, during, and after the "Race Across America" (RAAM) [41]. The RAAM is a competitive and continuous one-stage cycle race covering approximately 4800 km in length, with a cumulative elevation gain of about 33,000 meters. Serum samples collected before the race showed no detectable cTnI, but following day 1 of the RAAM, cTnI levels were elevated above the detection limit for all riders. Riders 1, 2, and 4 had their peak cTnI on day 1, whereas rider 3's peak cTnI exceeded the upper reference limit on day 5 [41]. In addition, extended periods of walking have been compared to extended periods of running. Eijsvogels *et al.* studied a cohort of 46 people; 23 participants engaged in a 40.6 km walk, while another group of 23 individuals ran a marathon [27]. Both activities impacted cTn levels, but the response was most pronounced in the running group. Specifically, 83% of the runners showed cTnI values above the cut-off associated with MI, compared to only 17% of the walkers [27].

Troponin elevation in athletes practicing exercise with static and mixed components

Power sports require explosive muscle power. During repeated bursts, there is a significant increase in heart rate and blood pressure. There is cardiac remodeling with a little increase in the size and function of the LV cavity and an increase in the LV wall thickness [30]. Indeed, athletes who participate in sports with a high static component also have a large LV mass but no increase in chamber size (concentric hypertrophy) [30]. Conversely, mixed sports, such as ball and team sports, involve alternating stages of dynamic and static effort and recovery, leading to mixed cardiac remodeling [29].

Several studies with variable results have been conducted on the release of cTn and mixed sports. Nie *et al.* evaluated blood levels of cTnT and cTnI in 10 adolescent male basketball players before the game and at 2, 4, and 24 hours after [42]. Four out of the 10 subjects had serum cTnT levels above the threshold of 0.01 ng/mL for myocardial injury at 4 hours after the game. Among these four subjects, two had values exceeding the cut-off of 0.05 ng/mL, which indicates the potential for acute myocardial infarction (AMI). Additionally, three of the four subjects had serum cTnI levels above the cut-off of myocardial injury. These findings suggest that the physical stress experienced during intense, intermittent-type sports may lead to the release of cTn [42]. In another research study aimed at exploring the connection between cTn release and physical exercise, a group of 23 healthy male elite floorball players with a median age of 19 years were recruited as participants [43]. At three distinct time intervals – before the game, immediately after, and 2 hours after the game – blood samples were collected to assess levels of CK-MB, myoglobin, and hs-cTnT [43]. Postgame hs-cTnT levels were significantly elevated, surpassing the cut-off for myocardial damage in the same six floorball players during two separate games. This was the first study to determine the reproducibility of cTn response to high-intensity intermittent exercise among elite-trained athletes [43].

However, in another cohort of 19 male athletes (nine rugby league players and ten soccer players participating in interuniversity games), George *et al*. demonstrated no evidence of cTn release in the blood samples taken before, immediately after, and 24 hours after the sporting activity [44]. It should be emphasized that the timing of the blood sample after exercise (within 30 minutes of exercise cessation) could be considered a potential limitation of this study [44]. Nevertheless, if there had been a pathological release of cTnT, it would likely have still been detectable 24 hours after exercise. Similarly, Rahnama *et al*. examined the influence of three bouts of 90-minute high-intensity intermittent exercise specific to soccer on the release of cTn in a cohort of twelve elite soccer players. The results of this study revealed that there was no significant distinction among the pre-exercise levels of cTnI, both after three exercise sessions and during resting states [45].

On the other hand, Stephenson *et al.* studied the effect of weightlifting on markers of myocardial damage: 17 male participants, aged between 20 and 34, participated in a 90-minute weightlifting session [46]. The workout consisted of three sets of 8-10 repetitions, with the weight used being 70% of their one-repetition maximum. There were no detectable levels of cTn in any of the blood samples collected after exercise [46]. Furthermore, Carranza-Garcia *et al*. investigated how intermittent exercise affects the release of cardiac biomarkers [47]. Experienced athletes were the subjects of the study, in which the researchers examined the impact of a heavy resistance training session on the release of cTnI, cTnT, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Blood samples were collected at different time points: at rest, immediately after exercise, and at 1-, 3-, 6-, 12-, and 24-hours post-exercise. The results demonstrated that the heavy resistance training session increased NT-proBNP levels [47]. However, there were no significant changes in cTnI levels (pre: 0.024±0.009 µg/L, peak post: 0.025±0.011 µg/L; p=0.809), and cTnT remained undetectable in all samples. These findings suggest intermittent exercise bouts lead to minor disruptions in cardiac biomarkers with scarce evidence of myocyte injury [47].

In conclusion, we can assume that sports activity can be associated with elevated cTn levels, which seems more pronounced in athletes practicing endurance activity. However, as mentioned before, increased exercise-related cTn levels are not found in all individuals, suggesting various factors can influence cTn levels after physical exercise.

Clinical and prognostic implications of cardiac troponin elevation in competitive athletes

Clinical implications of exercise-induced troponin elevation

It is now widely known that cTn levels may rise following prolonged vigorous exercise. Nearly 50% of the people in a recent

meta-analysis showed increased cTn levels following endurance exercise [48]. Since cTn increase is frequently transient, and levels commonly return to normal within 48 hours, it was believed that the kinetics of exertional cTn release do not always signify myocardial injury [39]. As a result, it was thought that the cTn increase in athletes was a benign occurrence [39]. However, the clinical significance of exercise-induced cTn elevation is still being debated, but it may have clinical implications for some individuals.

In patients with a clinical presentation of suspected unstable angina, Lanza *et al.* found that high sensitivity cTn significantly increased after exercise stress testing; however, the increase was unrelated to the presence of myocardial ischemia at stress testing or obstructive coronary artery disease (CAD) at angiography, indicating that it was primarily related to exercise in itself [49]. It is essential to highlight that throughout a follow-up period of 6 months, the modifications did not also predict the return of chest pain [48]. Although patients with stable CAD, a low ejection fraction, and little PA are more likely to experience cTnI release post-exercise, in the study of Kokowicz *et al*., it was not associated with the number of atherosclerotic coronary arteries [50].

Nevertheless, recent studies produced new information claiming that an elevation in cTn during exercise may not represent a benign reaction to exercise but rather a precursor to future CVD and mortality. Due to underlying, subclinical heart disease, higher post-exercise cTn concentrations may indicate myocardial damage [51]. Cardiovascular TnI concentrations were tested before and right after 30 to 55 km of walking in 725 subjects analyzed by Aengevaeren *et al*. [51]. They showed that during median follow-up of 43 months, people with post-exercise cTnI concentrations above the 99th percentile (>0.040 µg/L) experienced the composite endpoint of all-cause mortality and major adverse cardiovascular events [major adverse cardiovascular events (MACE), myocardial infarction, stroke, heart failure, revascularization, or sudden cardiac arrest] more frequently compared to controls with cTnI concentrations ≤0.040 µg/L (27% *vs*. 7%, log-rank p<0.001) [51]. After adjustment for age, sex, baseline troponin levels, presence of CVD, and cardiovascular factors, the hazard ratio of post-exercise cTnI>0.040 µg/L for all-cause mortality and MACE was 2.48 [51]. Therefore, elevated cTn may signify demand ischemia. Myocardial ischemia during either mental or physical stress was related to greater resting levels of hs-cTnI in patients with CAD, indicating that its increase is a sign of chronic ischemic burden experienced during daily life [52].

Therefore, some studies tried to evaluate the role of exercise-induced cTn in CAD prediction. Exercise (ESE) and dobutamine stress echocardiography (DSE) have high sensitivity and specificity to detect inducible myocardial ischemia in patients with significant CAD. However, cTn elevation among patients undergoing exercise or DSE did not appear to correlate with inducible myocardial ischemia [53]. Similarly, higher hs-cTn concentrations at rest were linked to increasing angiographic CAD severity in patients with suspected chronic coronary syndrome, whereas post-exercise hs-cTn concentrations employing stress testing with a bicycle lacked discriminatory potential for CAD [53]. However, these data are not sufficiently strong to deny the correlation between post-exercise TnI elevation and CAD. It should be taken into consideration that cTn levels did not reach a peak as blood samples were taken too early, after a short time of strenuous exercise, and exercise intensity was insufficient to produce cTn release with discriminatory power between CAD and non-ischemic patterns [54].

Indeed, the length of a raised heart rate and the duration of exercise are significant predictors of exercise-induced cTn increase, as shown by the analysis of the participants recruited from the North Sea Race Endurance Exercise Study trial. People with obstructive CAD may experience delayed cTn release due to poor blood flow [55]. Moreover, in recreational cyclists who took part in a 91-km mountain bike race, after doing vigorous exercise, cTn was elevated for a more extended period among the participants with occult obstructive CAD [56].

Troponin can often be elevated in patients with myocardial fibrosis on cardiac magnetic resonance, showing that this feature has prognostic and clinical relevance. However, the role of exercise-induced cTn elevation in this setting was unknown until Mohlenkampt *et al.* examined the coronary event rates and long-term all-cause mortality of 108 marathon runners and nearly 1000 controls [57]. They discovered that after and throughout the race, runners with late gadolinium enhancement (LGE) had greater high sensitivity TnI (hs-TnI) values than those without. However, ischemic events were associated only with the increasing coronary artery calcium scores and widespread myocardial fibrosis demonstrated by the presence of LGE, but not with increases in high-sensitivity cTnI [57]. Higher resting and post-exercise cTn concentrations are linked to cardiovascular risk factors and CVD. However, most of the population does not find a meaningful association between it and the severity of CAD or myocardial fibrosis. Even though clinical relevance is still difficult to establish, it may significantly impact clinically competitive athletes who engage in prolonged or high-intensity exercise.

Even though numerous studies have shown that endurance exercise has both short- and long-term positive effects on survival and cardiovascular prevention, it has been demonstrated that prolonged exercise can also be linked to pathological changes like increased platelet aggregation, abnormalities in the LV wall motion, and, rarely, ischemic events [58-62]. Furthermore, activity heart rate and cTn release impact diastolic function, which suggests that short bursts of vigorous activity are sufficient to cause cTn release and decrease LV diastolic performance [63]. According to some studies, acute right ventricle (RV) dysfunction can be caused by very intense endurance exercise, but not LV dysfunction [64]. Even when short-term recovery seems complete, some of the most skilled athletes may show signs of persistent structural alterations and decreased RV function. In fact, a recent study showed that an increase in exercise-induced cTn levels is associated with post-race diastolic dysfunction, increased pulmonary pressures, and right ventricular dysfunction, with this risk especially elevated among individuals with less training [26]. However, no association between cTn and change in LV ejection fraction is found. On the other hand, in athletes, cardiac function should not only be evaluated by the "classic" measurement of LV ejection fraction. Indeed, other methods like global longitudinal strain and myocardial work represent a better indicator of LV contraction in athletes [65]. Therefore, the disparity in the data reported in the literature is mainly caused by the small number of studies conducted, the cohort size, and the inadequate methodology for assessing echocardiographic performance.

Management of athletes with cardiac troponin elevation after exercise

Some have proposed that all athletes presenting with exercise-induced cTn increases should receive a thorough diagnostic examination, even though the following medical care of individuals

with post-exercise cTn elevation is still debatable [66]. Such examinations appear unnecessary for most asymptomatic healthy individuals without CVD because it is now apparent that cTn release may occur routinely after vigorous activity. However, patients who arrive at the emergency department post-exercise with elevated cTn concentrations may exhibit clinical uncertainty due to exercise-induced cTn increases. These patients should have the proper examination, including a 12-lead electrocardiogram, serial cTn tests, and some noninvasive or invasive risk stratification, depending on the overall clinical picture, if they present post-exercise with any clinical concern for acute coronary syndrome [67]. When distinguishing between cTn elevation linked to exercise and other reasons in stable individuals, using repeated samples to determine cTn kinetics can be effective. Indeed, serial testing of at least two sampling points is recommended to overcome the analytical and biological variation associated with hs-cTn assays [68,69].

When people experience post-exercise complaints like chest discomfort, palpitations, unsuitable breathing difficulty, or syncope that are not immediately attributable to volume depletion or neuro-cardiogenic mechanisms (musculoskeletal damage, dermatologic complaints, dehydration, malnutrition, thermal injury), it is essential to measure serum cTn. Additional cTnI or muscle damage indicators may be helpful in certain instances with minimal cardiac risk but surprisingly high cTn [70]. When cTn levels are found to be increased, and pre-test probabilities are moderate to high, it suggests that the increase is due to something aside from a benign exercise-induced release. Therefore, if computed tomography coronary angiography is available, it may be a quick and safe way to rule out cardiac involvement anytime a substantial cTn increase is followed by evident skeletal muscle injury, but cardiac involvement cannot be easily dismissed [71]. We propose a simple algorithm for managing post-exercise-induced cTn elevation, as shown in Figure 3.

Prognostic relevance

cTn response after exercise is considered harmless and without long-term negative effects. However, it has not been ruled out that exercise-induced, mild myocardial damage, which could become clinically meaningful if repeated over decades, is possible [57,72]. The potential benefit of including cTn testing in cardiac stress investigations, aiming to improve diagnostic accuracy, has so far been shown to be inconsistent. However, this may demand reconsideration, considering recent publications proposing additional sample possibilities and prognostic information [73].

According to earlier research, cTn levels at rest can predict future cardiovascular events, not just in the context of CAD or other diseases, but even in people who appear to be in good health [74-76]. Recent research has cast doubt on the "benign" notion by suggesting that an increase in unfavorable cardiovascular events or occult obstructive CAD may be linked to exercise-induced cTn release [51,56].

In a prior investigation using first-generation tests, Siegel *et al*. followed nine runners with a post-marathon cTn increase, showing that all of them were still asymptomatic for heart condi-

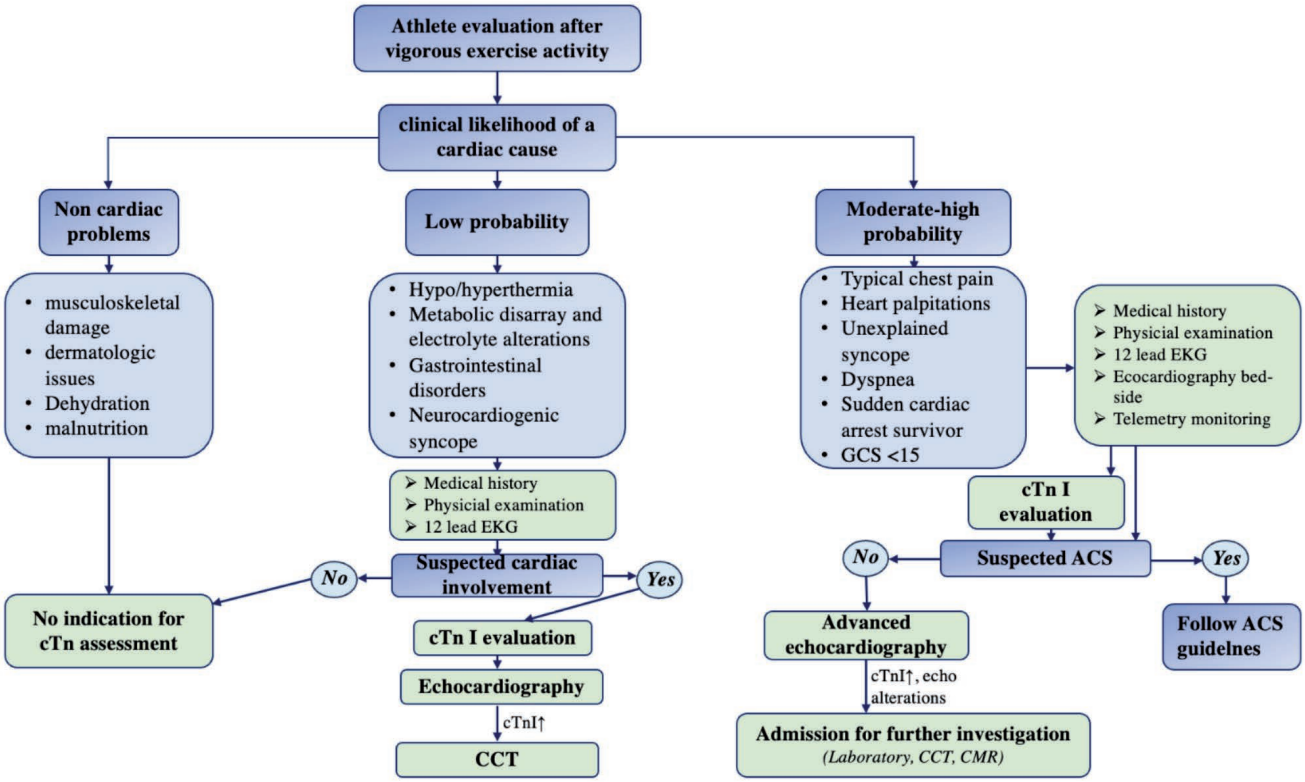

Figure 3. Algorithm delineating the proposed management of athletes after prolonged exercise activity, including troponin testing, in the setting of acute coronary syndrome suspicion and beyond. ACS, acute coronary syndromes; CCT, computed coronary tomography; CMR, cardiac magnetic resonance; cTn, cardiac troponin; GCS, Glasgow Coma Scale.

tions after a year [72]. Moreover, even though cTnI release post-exercise is more frequently noticed in patients with stable CAD who have an ejection fraction of at least 50%, engaged in minimal PA, and have a maximum systolic blood pressure equal to or greater than 160 mm Hg, it did not show prognostic significance [50]. Furthermore, marathon runners who experienced LGE in a study by Möhlenkamp *et al.* showed greater post-race hs-TnI values than those who did not [57]. However, following a 6-year follow-up period, the rates of coronary events were linked to myocardial fibrosis but not to rises in hs-TnI [57]. The trustworthiness of this study may have been hampered by the limited number of participants (74) and events documented (6), as well as the low sensitivity of the cTn test used. Additional research employing high-sensitivity tests and larger cohorts is needed to determine the prognostic significance of various cTn responses to endurance exercise. Contrary to this evidence, a recent study by Aengevaeren *et al*. on long-distance walkers with an average age of nearly 60 years found that cTnI elevations above the 99th percentile after an ultra-endurance walking event were linked to more significant mortality and cardiac events after 43 months of follow-up [51]. However, this population may not be entirely representative or comparable with most relevant studies due to its relatively high burden of cardiovascular risk factors. Since exercise-induced cTn release may be more frequently associated with reversible myocardial injury in healthy people than with irreversible myocardial injury in people with underlying CVD, mechanisms may also vary between populations. New imaging methods and innovative biomarker assays are required to investigate these possibilities. According to the research stated above, high post-exercise cTn rises might not be innocuous and could predict cardiovascular events in older people. Indeed, it has been proposed that excessive exercise-induced cTn release could serve as a brand-new indicator of cardiovascular risk [23,77]. However, more research is required to determine if a certain post-exercise time point may predict future mortality and cardiovascular outcomes.

Future directions

Further methods may resolve the current enigmas about the clinical and prognostic role of exercise-induced cTn increase. Utilizing cTn kinetics is an alternate method to enhance the clinical analysis of post-exercise cTn concentrations. According to a new study, infrared spectroscopy can be used for reliable transdermal assessments of cTnI concentrations. This cutting-edge method would make it possible to measure cTn levels more quickly, frequently, and easily, enhancing algorithms for the rule-in and rule-out of acute coronary syndrome [78].

Furthermore, looking closer into cTn structure can be a viable strategy for differentiating between exercise-related cTn increase that is normal and pathological. Separating cTn fragments by molecular size with gel filtration chromatography makes it possible to assess cTn fragments that can aid in differentiation between physiological and pathological increases [79,80]. Another intriguing approach would be *in vitro* research using cardiac organoids. Human stem cells can be used to create modified cardiac tissues that contain heart cells and that can then be subjected to simulated exercise with further cTn release examination. The extent of the damage, whether reversible or irreversible, might then be evaluated using additional methods such as specialized biochemical staining and high-resolution microscopy [81]. However, extensive prospective studies are required to determine whether cTn rises following physical stress truly increase the risk of future cardiac events and independently of established risk factors, in various active individuals. Furthermore, given previous reports of myocardial fibrosis and LGE in a small number of senior athletes, further research into the effects of a lifetime of endurance or ultra-endurance training upon the heart is recommended. Finally, more thorough reporting of exercise-related cardiac problems and using clinically recommended cTn assessment in this situation is required.

Conclusions

High-sensitivity immunoassays designed to identify cardiac forms without cross-reacting with skeletal forms can be used to detect the release of troponins. Their release is primarily a result of ischemia or non-ischemic mechanisms, but elevated cTn concentrations can still be seen in healthy people. Athletes provide a challenging group since exercise-induced cTn increase is frequent, and the concentration of cTn released after vigorous sports can vary. According to several studies, young athletes have greater post-exercise levels than master athletes, probably due to the immaturity of adolescents' myocardium. However, several anatomical, demographic, cardiovascular, and technical factors affect the release of heart biomarkers. Additionally, varying amounts of cTn rise may be experienced depending on whether an athlete performs a dynamic, static, or mixed workout. Troponin rise is not always benign, but it may have clinical and prognostic implications in some people, making it difficult for athletes who are having symptoms of heart disease to evaluate the findings of cTn testing. Thus, using a simple step-by-step algorithm, physicians may decide whether to apply cTn measurement and when to use further diagnostic techniques in symptomatic athletes following vigorous exercise. Further investigation, using large cohorts, multidisciplinary methodology, and innovative research designs, is required to better differentiate between physiological and pathological cTn elevations, to elucidate the underlying mechanisms of exercise-induced cTn release, and to ascertain if exercise-related cTn values can be used as an innovative cardiovascular risk factor.

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