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STATE-OF-THE-ART PAPER

Exercise-Induced Cardiac Troponin Elevation

Evidence, Mechanisms, and Implications

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Regular physical exercise is recommended for the primary prevention of cardiovascular disease. Although the high prevalence of physical inactivity remains a formidable public health issue, participation in exercise programs and recreational sporting events, such as marathons and triathlons, is on the rise. Although regular exercise training reduces cardiovascular disease risk, recent studies have documented elevations in cardiac troponin (cTn) consistent with cardiac damage after bouts of exercise in apparently healthy individuals. At present, the prevalence, mechanism(s), and clinical significance of exercise-induced cTn release remains incompletely understood. This paper will review the biochemistry, prevalence, potential mechanisms, and management of patients with exercise-induced cTn elevations. (J Am Coll Cardiol 2010;56:169–76) © 2010 by the American College of Cardiology Foundation

The role of exercise in the prevention, management, and treatment of cardiovascular disease has been well-described (1). Although regular exercise training reduces cardiovascular disease risk, recent studies have documented elevations in biomarkers consistent with cardiac damage (i.e., cardiac troponin [cTn]) after bouts of prolonged exercise in apparently healthy individuals (2–5).

cTns are highly specific markers of myocardial cell damage (6) and are central to the diagnosis of acute coronary syndromes (ACS) (7). cTn elevation is also apparent in conditions that result in significant cardiac stress in the absence of obstructive coronary disease (8). Even minor elevations in cTn confer worse prognosis in patients across a wide spectrum of disease processes (9–11). Accordingly, increased cTn levels after exercise can generate clinical concern and subject athletes to unnecessary hospital admissions and invasive procedures (12). Although numerous studies have reported the release of cTn after exercise, there is no consensus regarding the prevalence, mechanisms, and clinical management of exercise-induced cTn release. This review will address cTn biochemistry and present potential mechanisms for exercise-induced cTn release. In addition, we will summarize the available data characterizing exercise-induced cTn release and provide suggestions on the management of patients with cTn elevation after exercise.

Troponin Biochemistry and Routine Clinical Use

Structure and function. The myocardial sarcomeric unit consists of 7 actin monomers, double-stranded tropomyosin, and a troponin complex (6). The troponin complex is tadpole-shaped (Fig. 1) and is composed of 3 subunits: troponin T (TnT) (37 kDa), which anchors the complex to the tropomyosin strand of the thin filament; troponin C (TnC) (18 kDa), which binds calcium ions released from the sacroplasmic reticulum; and troponin I (TnI) (22.5 kDa), which inhibits the enzymatic hydrolysis of adenosine triphosphate that powers muscle contraction. The globular head of the troponin complex comprises TnC, TnI, and the C-terminal portion of TnT, whereas the tail comprises the N-terminal portion of TnT. Most (>90%) cTn is bound to tropomyosin on the thin filament of the myofibril, with the remainder accounted for by a small unbound cytosolic pool (13). Currently, the function of this pool is not known but might serve as a reservoir for repair/regeneration of tropomyosin-bound troponin.

Ontogeny and cardiospecificity. Cardiac and skeletal muscle share a common developmental pathway but originate from different embryonic precursors (14). Consequently, different forms of TnT and TnI are found in cardiac and skeletal muscle with cardiac (c) and skeletal (s) isoforms of TnT (cTnT, sTnT) and TnI (cTnI, sTnI) each encoded by separate genes. The cTnT and cTnI follow distinct pathways during fetal development. During fetal

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Abbreviations and Acronyms

ACS = acute coronary syndrome

CK-MB = creatine kinase-myocardial band

cTn = cardiac troponin

cTnI = cardiac troponin I

cTnT = cardiac troponin T

muscle development, 3 distinct TnT protein isoforms (cardiac, fast twitch skeletal, and slow twitch skeletal) are expressed simultaneously. A fourth isoform, fetal cTnT, is transiently expressed (15) but is ultimately absent in adults (16). Studies have reported that the cTnT gene is expressed in low concentrations in cardiac and skeletal muscle until mid-fetal development, at which point the cTnT gene is upregulated in cardiac myocytes and suppressed in skeletal myocytes (17). Conversely, cTnI is not expressed in the myocardium during fetal development and is only detectable in adult cardiac tissue (18). In the absence of cTnI, slow twitch sTnI dominates during fetal cardiac development until ultimately replaced by cTnI during the first 9 months of life (19).

Although skeletal and cTn proteins demonstrate a significant degree of amino acid sequence homology, more than 100 differences exist between the 2 tissue-specific isoforms. With the unique amino acid sequences, monoclonal antibodies have been produced against human cTnT and cTnI, respectively. These antibodies form the basis of the highly cardiac-specific immunoassay methods available to detect cTn. The progressive increase in specificity for both cTnT and cTnI assays has been reviewed previously (6).

Release kinetics and routine clinical use. In ACS, cTn is released from the myocardium into the circulation during the first few hours after the onset of ischemia in a biphasic manner. A small initial release of cTn is followed by a larger sustained release with a peak in serum concentration at 12 to 24 h. The initial rise in serum cTn seems to originate from the cytosolic pool with the later rise attributable to release of bound cTn (20). Although debated, the initial release of cytosolic cTn with ischemia might be due to changes in myocardial membrane permeability, whereas the release of bound cTn requires proteolytic degradation and cellular necrosis (21). The half-life of cTnT in the circulation is 120 min (22); the half-life of cTnI is presently not known.

Troponin testing is an invaluable tool for evaluating patients with ischemic chest pain or other clinical syndromes. The sensitivity and specificity of cTnT and cTnI for the detection of myocardial injury is superior to older biomarkers, including lactate dehyrdogenase, creatine kinase, creatine kinase-myocardial band (CK-MB), and myoglobin. The cTn measurement is a component of the universal definition of acute myocardial infarction (7). The release of cTn due to pathologic myocardial damage can be divided into 3 mechanistic categories (23). Primary ischemic cardiac injury describes cTn release from injury caused by a ruptured coronary arterial plaque and coronary occlusion. Secondary ischemic cardiac injury describes myocardial ischemia with myocyte injury in the absence of atherosclerotic plaque rupture and due to increased myocardial oxygen demand that outstrips myocardial oxygen supply. Nonischemic cardiac injury describes cTn release caused by direct damage to the myocardium, including blunt trauma (24), penetrating trauma (25), myocarditis (26), or drug and toxin-induced cardiotoxicity (27). At the present time, the release of cTn by healthy individuals after exercise cannot be explained by any of these pathophysiologic scenarios.

Biomarkers of Myocardial Injury in Exercise

Historical perspective. Early reports of post-exercise elevations in serum concentrations of the myocardial band isoform of creatine kinase (CK-MB) (28) after the completion of endurance events led to concern that such activities could result in cardiac injury. However, elevations in serum CK-MB after prolonged exercise lack specificity for the detection of cardiomyocyte damage (29). The CK-MB is increased in the skeletal muscle of distance runners (30) perhaps because of increases in satellite cells, which repair injured skeletal muscle (31). Therefore, it is likely that individuals with significant exercise training exposure have relatively high skeletal muscle concentrations of CK-MB, which is released during subsequent exercise-induced muscle damage. Thus, in the investigation of exercise-induced cardiac injury, attention shifted from CK-MB to cTn, a highly specific marker of cardiac muscle damage, even in the presence of significant skeletal muscle breakdown (32).

Early generation cTn assays: skeletal protein cross-reactivity. Immunoassays for the quantification of serum cTn isoforms (both T and I) were developed in the late 1980s and became commercially available in the U.S. and Europe in the mid to late 1990s. The first-generation cTnT immunoassay used bovine cTnT as the reference material and cross-reacted with human sTnT (33). Therefore, these

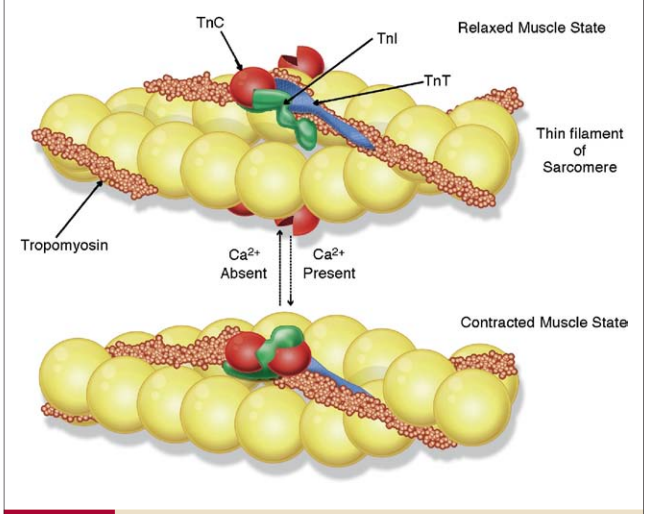

Figure 1 Schematic of Cardiac Muscle

Schematic of cardiac muscle showing location of cardiac troponin I (TnI), cardiac troponin T (TnT), and troponin C (TnC) in relation to actin and tropomyosin. Figure illustration by Craig Skaggs.

early assays could not reliably differentiate TnT of myocardial from skeletal muscle origin, and these early exercise data should be viewed with caution (34). The development of second- and third-generation cTnT assays, with recombinant human cTnT as the reference, eliminated this problem. More recently, ultra-high-sensitive assays have been developed and are undergoing clinical evaluation (35).

cTn elevation after exercise. Multiple studies have examined the cTn response to physical exertion, most from competitive athletic events that require a participant to maintain an elevated cardiac output, heart rate, and systolic blood pressure for several hours. This sustained increase in cardiac work stresses the myocardium, which in conjunction with the physiologic milieu of prolonged exercise (e.g., elevations in reactive oxygen species, altered ph, and increased core temperature) could hypothetically damage cardiomyocytes. Troponin levels from participants in marathon-distance (4,36–38) and ultra-distance foot races (39,40), triathlons (sequential swimming, cycling, and running) (3,41), and dedicated cycling events (42,43) have each been studied.

Several studies have reported no significant post-exercise cTn elevations (29,44,45), but the majority of data document statistically significant cTn increases after exercise (37–39,46,47). Consequently, there is increasing recognition that mild increases in serum cTn often follow prolonged endurance exercise, but for unclear reasons the prevalence and absolute serum concentrations of the cTn increases vary considerably. Possible explanations include differences in the fitness levels of participants, the type or duration of exercise, the timing of the post-exercise sample, the troponin assay used, and the detection limit used to define a "positive" cTn. A recent meta-analysis (47) examined data from 26 studies and found that post-exercise cTn concentrations exceeded the assay's lower limit (i.e., were measurable) in approximately one-half of participants (Fig. 2). There was a higher incidence of cTnT elevation after running events than after cycling or a triathlon. Interestingly, cTn detection was increasingly common as duration shortened; specifically, there was a higher incidence of post-exercise cTn in marathon-type events in contrast to ultra-marathon competitions. This inverse relationship between event duration and troponin elevation might be because shorter races are generally performed at higher exercise intensities. More recent studies have provided important information (Table 1) (48–53), including the observation that cTn is increased after prolonged walking in a nonathletic population and that the magnitude of increase is related to exercise intensity and cardiovascular pathology (48).

Studies examining serum cTn during controlled laboratory-based exercise testing are sparse. Recently, 9 highly trained male triathletes were studied during participation in a simulated half-ironman event (1.9-km pool swim, 90-km cycle ergometry, 21.1-km treadmill run), and cTnT increases were observed in 4 of the athletes (54). Middleton et al. (2) also reported increases in serum cTnT in all of 9 well-trained men completing a treadmill marathon (Fig. 3). Data from this report demonstrate that moderate release of cTn (range 0.02 to 0.04 μg/l) begins as early as 30 min into

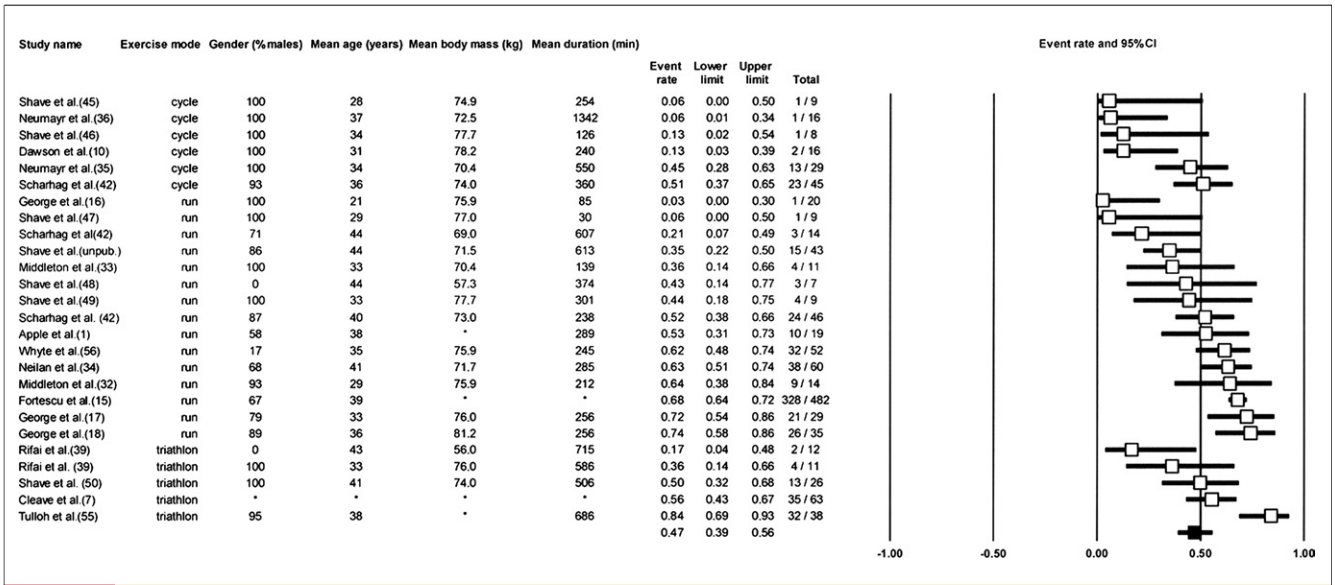

Figure 2 **Forest Plot Showing Event Rate, Sample Size, and 95% CI for Each Study**

Forest plot showing event rate (number of participants showing a positive cardiac troponin T after exercise), sample size (total), and 95% confidence interval (CI) for each study. Studies are ranked in ascending magnitude of event rate within in each subgroup of studies (cycling, running, triathlon). The overall random-effects event rate and associated 95% CI for the 1,120 research participants are shown in the bottom row of the plot. *Data that were unavailable. Sex is quantified according to the proportion (%) of men in the study sample. Please note: the reference numbers in the figure relate to the original article this figure was reprinted from. Reprinted with permission from Shave et al. (47).

Table 1 Recent Studies Examining Post-Exercise cTn Levels

Activity First Author (Ref. #)	Distance	Number of Participants	Troponin Isoform Measured	cTn Diagnostic Threshold	Prevalence of Positive cTn Observed
Walking					
Eijsvogels et al. (48)	30–50 km (4 consecutive days)	103	cTnI	>0.01 ug/ml >0.2 ug/ml	18% 6%
Running					
Lippi et al. (45)	HM	17	cTnT	0.03 ng/ml	0%
Jassal et al. (49)	HM FM	61 (HM) 68 (FM)	cTnT	"Detectable"	HM: 30.6% immediately after race; 45.9% at 1 h after FM: 35.7% immediately after race; 52.8% at 1 h after
Mingels et al. (36)	FM	85	hs-cTnT cTnI	>99th percentile >99th percentile	86% 45%
Fortescue et al. (37)	FM	482	cTnT	>0.01 ng/ml	68%
Mousavi et al. (38)	FM	14	cTnT	>0.01 ng/ml	100%
Middleton et al. (2)	FM	9	cTnT	>0.01 ug/ml	100%
Scott et al. (50)	160 km	25	cTnT	>0.01 ug/ml	20%
Giannitsis et al. (51)	216 km	10	hs-cTnT	>99th percentile	50%
Cycling					
Serrano-Ostariz et al. (52)	206 km	91	cTnI	>0.04	43%
Triathlon					
La Gerche et al. (53)	IM	26	cTnI	>0.16 ng/ml	58%

Studies after 2006.

cTn = cardiac troponin; cTnI = cardiac troponin I; cTnT = cardiac troponin T; FM = full marathon (26.2 miles/42.2 km); HM = half marathon (13.1 miles/21.2 km); hs-cTnT = highly sensitive pre-commercial assay from Roche Diagnostics (Basel, Switzerland); IM = ironman distance (swim = 2.2 miles/3.8 km, cycle = 112 miles/180 km, run = 26.2 miles/42.2 km).

sustained endurance exercise and might represent a normal or "physiologic" response to exercise. This study used repeated blood draws and was the first to demonstrate cTn release in all participants and suggests that the disparate cTn prevalence in previous studies might reflect differences in study design such as the timing of post-exercise blood draws. More recently, cTnT concentrations have been compared in 13 adolescent male runners (age 14.8 ± 1.6 years) after 4 constant load treadmill runs of varying duration (45 or 90 min) and intensity (80% or 100% ventilatory threshold) (55). Of note, the highest median cTnT concentration (0.06 μg/l, range <0.01 to 0.417 μg/l) was observed after the longest exercise duration (90 min) and highest exercise intensity (100% ventilatory threshold).

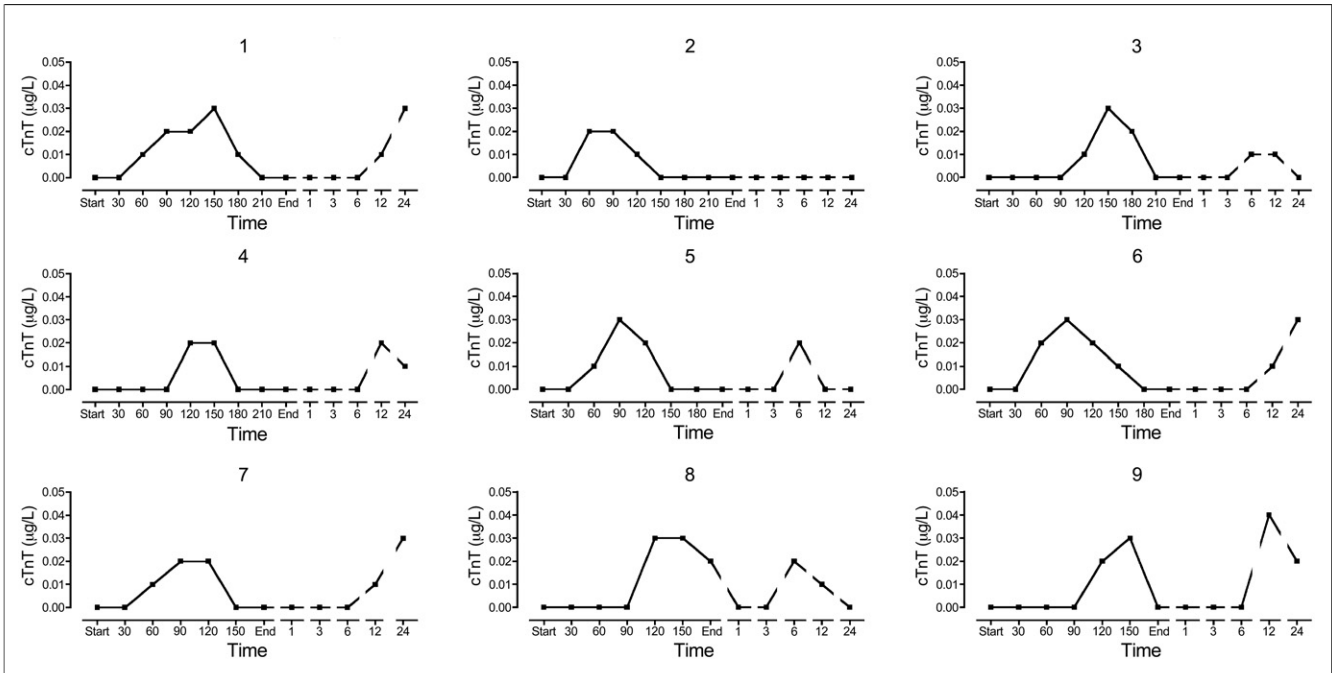

Figure 3 Individual cTnT Release During and After Completion of a Marathon

Individual cardiac troponin T (cTnT) release during (min) and after (h, after exercise) completion of a marathon. Reprinted with permission from Middleton et al. (2).

Although these previous findings strongly suggest that exercise intensity and duration are important determinants of circulating post-exercise cTn, further laboratory-based assessments are needed to clarify this issue.

cTn elevation and myocardial function. A number of investigators have coupled cTn testing with noninvasive assessment of cardiac function after endurance events. Competitors have been examined minutes to hours after race completion (38,56) and in the ensuing weeks (56) to months (57). Results from such efforts have been inconsistent. For example, Neilan et al. (4) measured cTnT and performed echocardiography 20 min after the race in nonelite participants completing the Boston Marathon, a 42-km footrace, in an average time of approximately 4 h. These authors reported that 63% of participants had a serum cTnT >0.01 μg/l, 45% had a serum cTnT ≥0.03 μg/l (the upper limit of normal), and 13% had cTnT levels in excess of 0.10 μg/l. Increases in cTnT were associated with reductions in right ventricular contractility, measured by strain echocardiography. However, although concomitant changes in cardiac function and cTn release have been shown after prolonged exercise, correlation analysis does not prove cause and effect. Furthermore, George et al. (40) observed no correlation between post-race troponin elevations and echocardiographic parameters of left ventricular function in a small cohort of athletes completing the Comrades Marathon, an 89-km footrace.

Elevations in cTn and possible impaired myocardial function raise the question of whether prolonged endurance exercise could produce persistent myocardial damage and dysfunction. Mousavi et al. (38) reported elevated cTnT in 14 marathon finishers with concomitant echocardiographic evidence of transient right ventricular systolic and biventricular diastolic dysfunction. Contrast-enhanced magnetic resonance imaging 1 week after the marathon did not show any evidence of persistent myocardial dysfunction or myocardial fibrosis. The majority of noninvasive imaging data argue against an association between post-exercise cTn elevations and permanent myocardial injury (34,58), but a case report of myocardial fibrosis in a veteran endurance athlete (59) and a study finding increased late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in master's (age 50 to 72 years) marathoners (60) underscore the need for further work.

Potential Mechanisms of Exercise-Induced cTn Release

Several theories, each presently lacking sufficient confirmatory data for full acceptance, have been proposed to explain cTn elevations after prolonged or strenuous exercise.

Increased membrane permeability. Exercise-induced increases in myocardial sarcolemmal permeability might facilitate the release of cytosolic cTn. Thus, it is possible that post-exercise cTn is due to passive diffusion of cTn from the intra- to extra-cellular compartment. Such an increase in membrane permeability might be due to increased mechanical stress on the cardiomyocytes (61), increased production of oxidative radicals (62), or altered acid base balance (63). These physiologic processes have been documented in skeletal muscle exposed to exercise and seem to play an important role in adaptive skeletal muscle hypertrophy (61,64). Mechanical stimuli might produce transient disruptions of the myocardial plasma membrane, termed "cell wounds" (65), making it possible that exercise-induced cTn release reflects the activation of cellular cascades that result in cardiac hypertrophy (58).

An alternative mechanism for exercise-induced cTn release is the stimulation of integrins by myocardial stretch (66). Integrins act as bidirectional signaling molecules and are involved in cardiac re-modeling with pressure overload or after myocardial infarction (67). Stimulating stretch-responsive integrins mediates the transport of intact cTn molecules out of viable cardiomyocytes (68). This release differs from the discharge of cTnI from necrotic cardiac myocytes, which is associated with extensive cTnI degradation.

After ACS, both intact cTn and degradation products of cTn are present in the serum (69). Eleven modified cTnI products have been identified, and the number and extent of modified proteins change with time after the acute event (70). A number of cTnT fragments have also been detected (70). It is possible that the release of cTn after exercise reflects the release of degraded cTn products rather than intact troponin. Recently, Feng et al. (71) have shown in a rat model the degradation of cTnI with increasing preload, in the absence of ischemia, suggesting that myocardial stretch per se can degrade cTn. Although prolonged exercise results in sustained periods of myocardial stretch, no study has yet examined cTn degradation products after exercise.

Myocardial cell necrosis. Myocardial cell necrosis might also be responsible for post-exercise cTn elevations. It is possible that some individuals with detectable post-exercise serum cTn will have sustained a myocardial injury with cell death. This explanation for post-exercise cTn elevation is not presently supported by convincing data. In addition, the relatively small elevations in cTn that have been observed after exercise and the kinetics recently described (2) do not seem to support irreversible cell death. As discussed previously, cTn release during ACS follows a biphasic pattern with an initial release approximately 2 h after the event followed by a later release due to degradation of the contractile apparatus. If exercise-induced cTn release were due to cell death of even a small number of cardiomyocytes, a similar sustained release of cTn would be anticipated, and there are no data to support this theory. Consequently, it remains unclear what underlies the presence of cTn after exercise; however, the data that are available support a mechanism of release that is unrelated to frank myocardial injury.

Clinical Approach to Patients With Post-Exercise cTn Elevation

cTn measurement has a firmly established role in the assessment and management of patients with cardiovas-

cular disease. Serum cTn elevation is central to the diagnosis of ACS, and thus clinicians need to be aware of alternative conditions that might cause cTn elevations. The data summarized in this review indicate that participation in endurance-based athletic events can lead to mild cTn elevation in the absence of ACS. Although the subsequent management of patients with post-exercise cTn elevation remains controversial, some have suggested that all athletes presenting with exercise-induced cTn elevations should undergo comprehensive diagnostic evaluation (72). Because it is now clear that cTn release might occur routinely after prolonged or strenuous endurance exercise in healthy individuals without cardiovascular disease, such investigations seem to be unwarranted in the majority of cases.

In our opinion, routine cTn testing is not indicated for the evaluation of individuals who present for medical attention after participation in athletic events or substantial exercise sessions, unless there are specific clinical data suggesting cardiac involvement. Patients encountered in the post-exercise setting should undergo a comprehensive medical history and physical examination with attention directed to the presence of cardiovascular signs/symptoms and risk factors for atherosclerostic disease. Twelve-lead electrocardiography should be considered as an option in this routine assessment. Patients found to have common post-participation ailments (i.e., musculoskeletal injury, dermatologic complaints, dehydration, malnutrition, thermal injury) and no evidence of cardiopulmonary involvement do not require an assessment of serum cTn concentration. In contrast, it is valuable to measure serum cTn in individuals who present with post-exercise complaints that might be explained or mediated by myocardial ischemia such as chest pain, palpitations, unusual/inappropriate dyspnea, or syncope not clearly attributable to volume depletion or neurocardiogenic mechanism. In these circumstances, the finding of an elevated cTn coupled with the moderate to high pre-test probability that cTn elevation reflects more than benign exercise-induced release, is sufficient to mandate adherence to published guidelines for the management of ACS. Such patients require hospital admission for observation, serial cTn measurement, risk-stratification, and/or definitive intervention. An algorithm delineating this proposed approach has been provided (Fig. 4).

Future Studies

Although the mechanisms responsible for the release of cTn after exercise remain uncertain, a number of plausible,

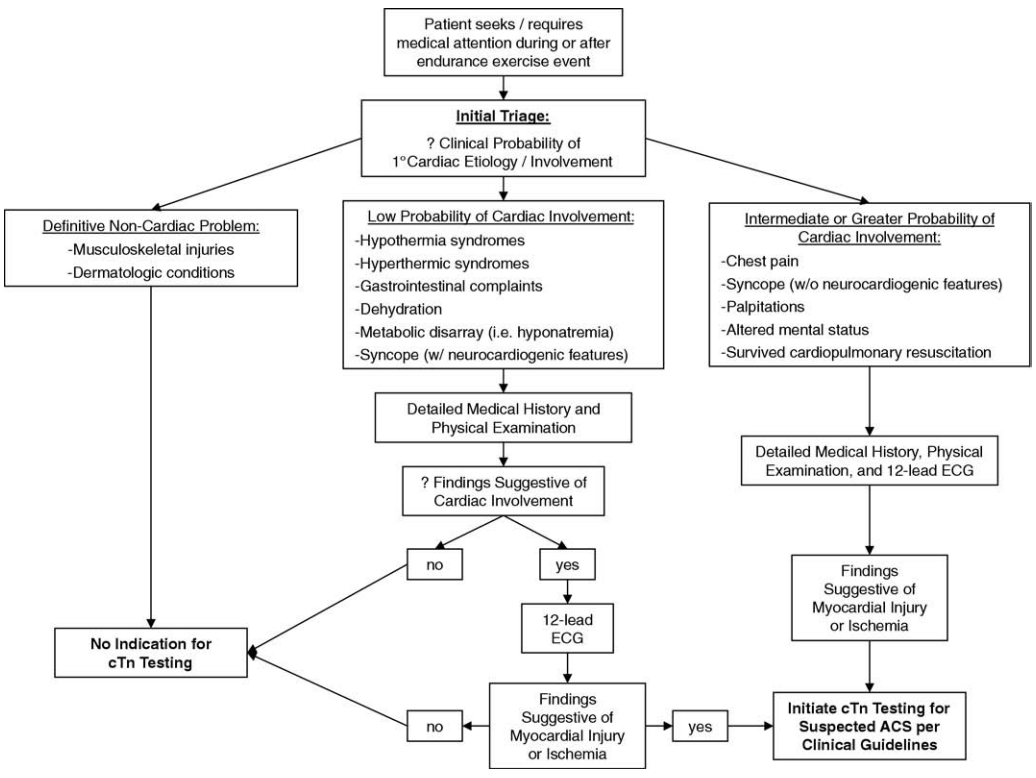

Figure 4 **Algorithm Outlining Proposed Management of Patients With Suspected ACS After Prolonged Exercise**

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.

perhaps complementary suggestions have been proposed and warrant further investigation. The influence of exercise on cardiac sarcolemmal permeability and integrins both deserve attention. Furthermore, the study of circulating cTn fragments after exercise might provide additional insight into the mechanisms of release and might also assist in the differentiation of exercise-induced cTn release from pathological release. Continued study of the influence of a lifetime of endurance or ultra-endurance exercise upon the heart is also prudent, given the case reports of myocardial fibrosis and late gadolinium enhancement in a small number of veteran athletes. Finally, more comprehensive reporting of exercise-related cardiac complications and the role of clinically indicated cTn measurement in this setting are needed.

Conclusions

cTn testing is an invaluable tool for the assessment of patients with suspected or confirmed myocardial ischemia/infarction. The development of highly specific cTn assays coupled with theoretical concern about the cardiovascular safety of prolonged or strenuous exercise has led to numerous studies documenting cTn elevation after exercise. Because most of these data involve healthy individuals with no underlying cardiovascular disease, it seems likely that exercise-induced cTn release is a benign process. Widespread recognition that exercise stimulates release of cTn will help physicians to make informed clinical decisions about how to use cTn testing appropriately in patients who present after exercise.

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