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Physical activity, exercise and cardiac troponins: Clinical implications☆

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ABSTRACT

Cardiac troponins constitute essential components of the cardiac contractile apparatus and are released into the bloodstream following cardiomyocyte injury. Because of their cardiac specificity, cardiac troponin I or T are the recommended biomarkers for diagnosing acute myocardial infarction. However, cardiac troponin concentrations also frequently increase acutely after strenuous prolonged exercise, making the interpretation of cardiac troponin test results in patients presenting with acute chest pain challenging. This acute troponin response following exercise is commonly considered to be physiological and without adverse long-term consequences, but the possibility of exercise-induced, minor myocardial injury that may become clinically relevant if repeated over decades, has not been ruled out. Attempts to biochemically differentiate between physiological cardiac troponin release versus release after acute ischemic myocardial injury has so far proved largely unsuccessful, but future measurement of specific troponin fragments could be promising. Cardiac troponins also provide strong prognostic information across the spectrum of cardiovascular (CV) disease (CVD). In the chronic setting, low-level elevation of cardiac troponins has been associated with adverse outcome, and concentrations even within the normal range provide independent information concerning risk of developing heart failure (HF) and CVD death. Exercise exerts many beneficial effects on the CV system, and longitudinal observational data from epidemiological studies suggest that higher physical activity (PA) is associated with lower concentrations of cardiac troponins. Conversely, a sedentary life-style has been associated with higher cardiac troponin concentrations and a parallel increase in the risk of HF. Serial measurement of cardiac troponins using high sensitivity assays for monitoring the effect of life-style intervention, including PA appears promising.

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Abbreviations and acronyms: AMI, acute myocardial infarction; CAD, coronary artery disease; CCTA, coronary computer tomography angiography; CMR, cardiac magnetic resonance; CRF, cardiorespiratory fitness; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; METs, metabolic equivalents of task; PA, physical activity; RCTs, randomized controlled trials.

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Physical fitness and cardiovascular (CV) health are closely linked. Data from large population-based, prospective observational studies has shown that maintaining or improving fitness is associated with lower CV disease (CVD) risk.[1] Conversely, low cardiorespiratory fitness (CRF) has been linked to increased risk of heart failure (HF) and HF related deaths.[2–4] Even though multiple studies have shown CV benefits related to physical activity (PA), controversy still remains concerning the optimal PA level for CV maintaining health, and a potential U-shaped relation between the life-long PA exposure and CVD events has been suggested[5,6] (Fig. 1). For instance, chronic structural myocardial disease, such as myocardial fibrosis or atrial fibrillation may be more frequent in long-practicing endurance athletes,[7–10] suggesting that long-term, repetitive strenuous PA may be harmful for the myocardium in some individuals. Other studies have shown a dose-dependent relation between life-long exposure to PA and the burden of coronary atherosclerotic plaques.[11,12] These findings are, however, nuanced in a very recent publication. A large population study followed 21,178 healthy men for ten years, demonstrating that the HRs for CV death and all-cause mortality were lowest at the highest PA level (>3000 metabolic equivalents of task (METs) minutes pr. week).[13,14] This was in spite of a slight increase in the observed plaque burden in the high PA group.

CV biomarkers are essential tools for diagnostic and prognostic assessment of patients with suspected or established CVD. In contemporary cardiology, cardiac troponins, the prototypical biomarkers of myocardial injury, are routinely used for confirming or excluding a diagnosis of acute myocardial infarction (AMI). During the past decade, there have been notable improvements in troponin assay sensitivity and precision. In contrast to earlier generation assays, which did not detect measurable concentrations in healthy subjects or patients with stable coronary artery disease (CAD), the high sensitivity assays that are currently used in clinical practice can reliably measure circulating cardiac troponin concentrations in the majority of an adult general population. In other words, from previously being a largely quantitative test ("troponin positive or negative"), current high sensitivity assay are capable of accurately measuring very low circulating concentrations of cardiac troponin T and cardiac troponin I. This means that not only major myocardial necrosis, but also minor myocardial injury can be detected by serial measurements.

Exercise can elicit an acute release of cardiac troponins. Traditionally, this has been interpreted as a physiological response. However, the magnitude of the troponin response depends on the intensity and duration of PA, and the long-term prognostic significance of repetitive, exercise-induced, troponin release is not known. Conversely, chronically increased circulating concentrations of cardiac troponins are related to a poor prognosis.[15–18] If changes in PA level can modulate troponin concentrations, serial troponin measurements may serve as an index of change in CVD risk.

In this review, we will provide an overview of the acute effect of exercise and the chronic effects of PA on the cardiac troponins and discuss the potential clinical implications of these biomarkers responses.

Cardiac troponins, biomarkers of acute myocardial injury

Troponins are protein complexes attached to tropomyosin that are present in all skeletal and cardiac muscle cells. Tropomyosin covers the actin-myosin binding sites on the actin filaments and blocks muscle contraction. During calcium influx into the muscle cell, calcium binds to the troponin complex initiating a conformational change leading to exposure of the binding sites with actin-myosin binding and muscle

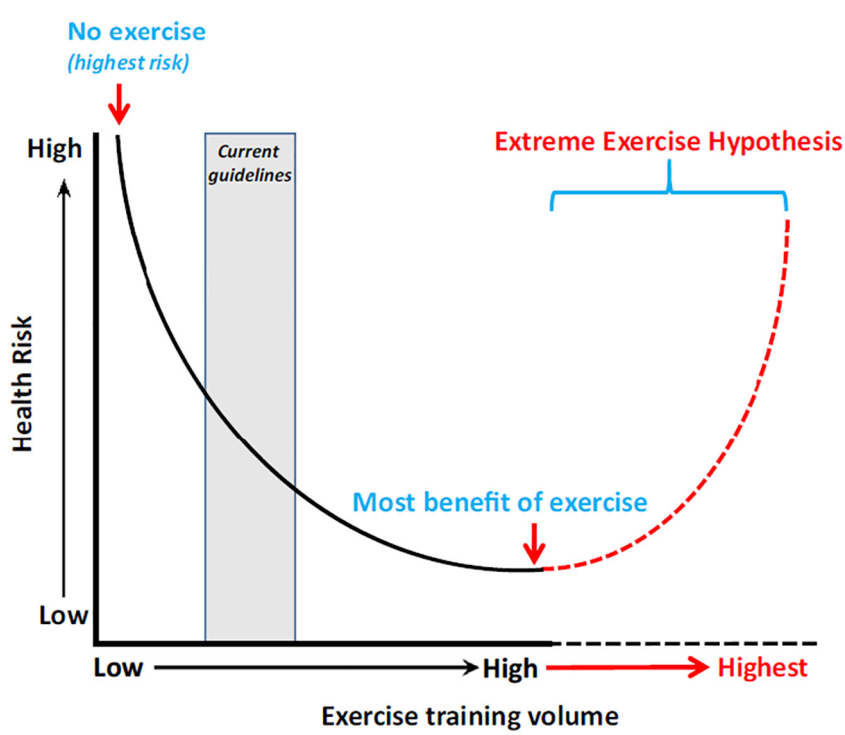


Fig. 1. Relation between exposure for exercise and health risk. Reprinted with permission (Eijsvogels TMH, et al. Curr Treat Options Cardiovasc Med 2018;20:84).

contraction as a result. Troponin has three different subunits (troponin T, troponin I and troponin C), of which two exist in cardiac specific forms; cardiac troponin T and cardiac troponin I. Detection of acutely increasing concentrations of cardiac troponins in the circulation is a sign of acute myocardial injury, but provides no etiologic information as to the underling condition or disease causing the release. Accordingly, although cardiac troponins are most commonly used to detect acute ischemic injury, a variety of other primary cardiac (e.g. myocarditis, cardiac arrhythmias) and non-cardiac (e.g. sepsis, burns, exercise) conditions may be associated with acutely increased circulating concentrations of cardiac troponins.

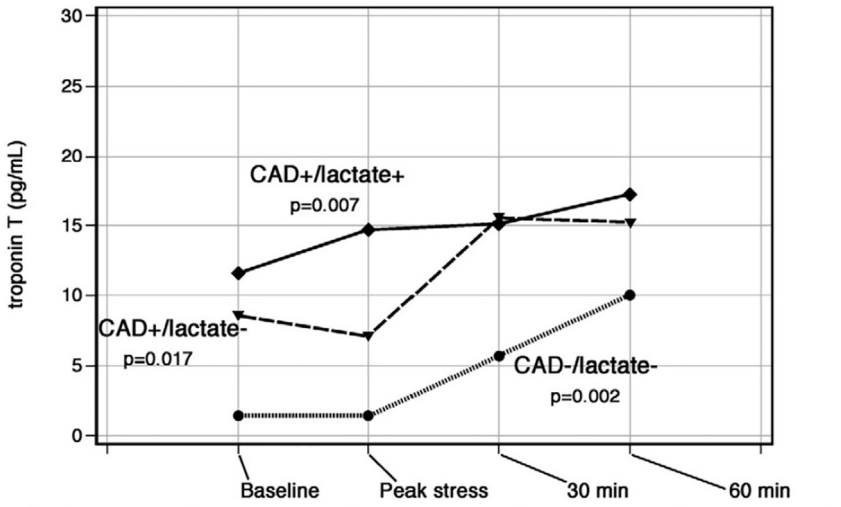
Exercise-induced troponin response

Exercise is commonly associated with an acute increase in circulating concentrations of cardiac troponins. The first article describing acute elevation of troponin concentrations in some individuals following strenuous physical exercise was published in 1987.[19] As PA was generally believed to be healthy and cardiac troponins were interpreted as biomarkers of cardiomyocyte necrosis only, this observation initially seemed paradoxical. If a physiological troponin response exists, this has the potential to confound the association between cardiac troponin elevation and the presence of myocardial ischemia or injury used in the emergency room to diagnose AMI or identify patients with a poor prognosis. More than a hundred studies have been performed to further elucidate the troponin response during exercise, showing conflicting data regarding prevalence and expected concentrations, most likely due to heterogeneity in study design (e.g. different intensity and duration of exercise, differences in age, training experience and risk factors of participants, different timing of the samples and different assays used).[20,21]

Several important observations were made during this initial phase to characterize exercise-induced troponin release. In a landmark study, Turer et al. showed that following rapid pacing troponin concentrations in the coronary sinus increased to a similar extent in patients with and without significant CAD and regardless of pacing-induced lactate production (i.e. interpreted as a sign of ischemia)[22] (Fig. 2). Healthy individuals had lower baseline cardiac troponin values than patients with CAD, but appeared to have an increase of similar magnitude following pacing. Other studies of patients with suspected CAD undergoing myocardial perfusion imaging examining the association between baseline and exercise-induced troponin levels and the presence and magnitude of reversible perfusion defects have shown diverging results.[23,24] Although patients with reversible ischemia have higher baseline troponin levels, in most studies the exercise-induced increase is not consistently higher in patients with ischemia. In 2008 Middelton et al. conducted a small but important study including nine well-trained men who were sampled every 30 min during and up to 24 h after, a marathon run. Troponin elevation was evident in all participants, even though a contemporary, and not a high-sensitivity troponin T assay was used[25] (Fig. 3). Subsequent studies using high sensitivity assays have confirmed this finding.[26] Taken together, these findings suggest that physiological factors e.g. increased heart rate in patients without CAD, can cause acute release of cardiac troponins into the blood stream regardless of the presence or absence of myocardial ischemia. However, it also raises the question how to define and establish the presence or absence of minimal myocardial necrosis. Current imaging modalities lack the sensitivity required to detect necrosis that can be detected by a minor, transient increase in cardiac troponin concentrations. Accordingly, it is not surprising that imaging studies, including cardiac magnetic resonance (CMR) studies, have been unable to confirm development of myocardial necrosis after endurance exercise. For instance, in 17 runners no evidence of myocardial inflammation or other indices of necrosis was evident after a marathon.[27] On the other hand, transient post-exercise ventricular dysfunction has been shown to correlate with troponin increase after intense endurance exercise.[28,29] It is conceivable that regular repetition of strenuous activities far beyond regular intensity over several decades eventually may lead to permanent myocardial dysfunction.

Troponin profiles as a tool to differentiate between causes of release

Troponin profiles may differ according to the underlying mechanism leading to the release. Thus, after transmural AMI the troponin



CAD+/ lactate+	11.6 (6.4, 34.3)*	14.7 (5.6, 26.0)*	15.1 (8.0, 18.2)	17.2 (9.8, 24.7)
CAD+/ lactate-	8.5 (3.5, 14.3)#	7.1 (5.1, 20.9)	15.5 (7.3, 26.9)	15.1 (7.2, 37.6)
CAD-/ lactate-	1.5 (1.5, 1.5)	1.5 (1.5, 4.6)	5.7 (5.3, 15.6)	10.1 (6.9, 20.4)

Fig. 2. Time-dependent increases in troponin concentrations were measured in the coronary sinus during atrial pacing. Similar increase was observed in patients with and without ischemia (defined as lactate production) and in the presence and absence of coronary artery disease. Figure 1. Relation between exposure for exercise and health risk. Reprinted with permission (Turer AT et al. J Am Coll Cardiol 2011;57:2398-405).

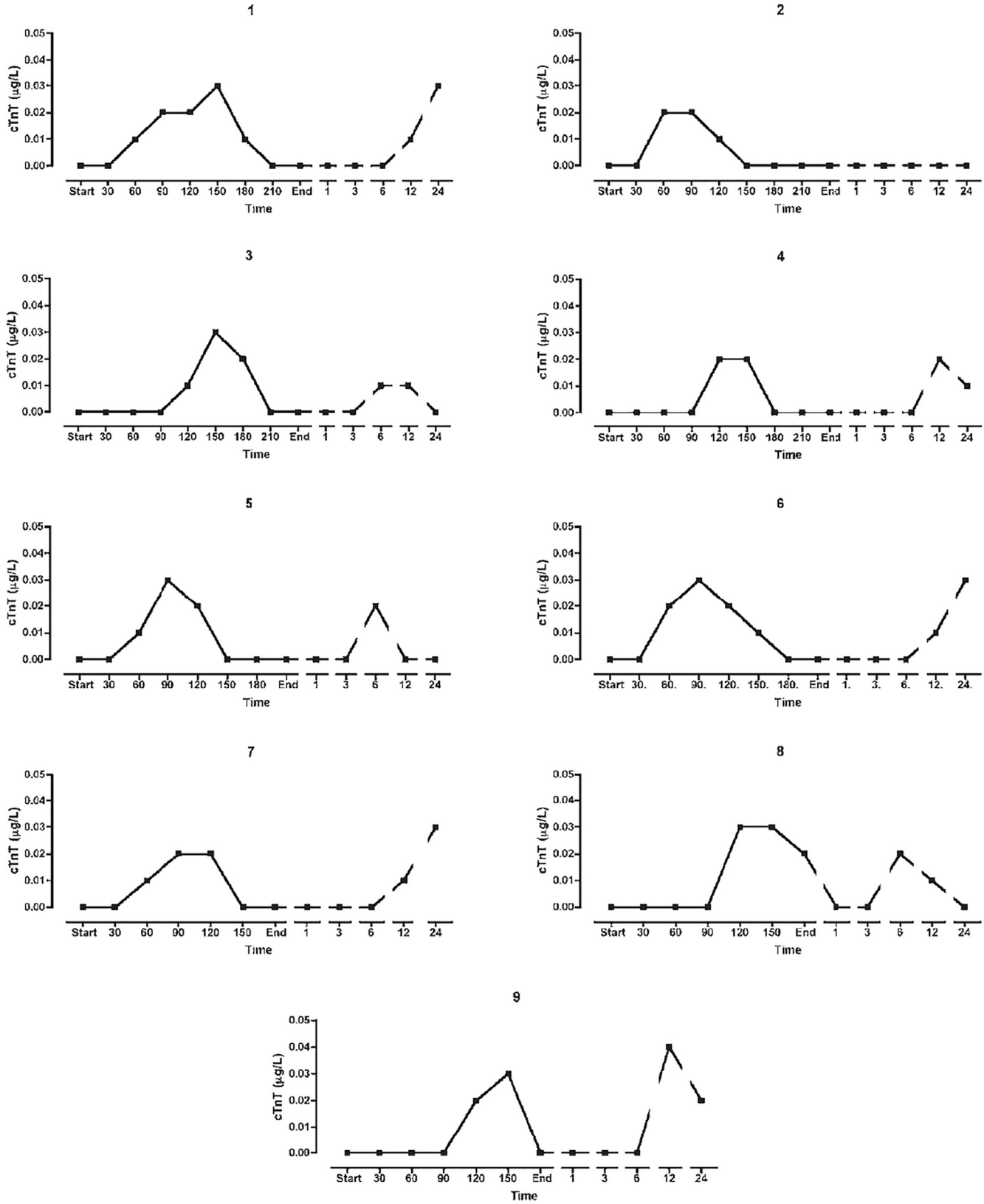


Fig. 3. Troponin response in 9 runners measured before, during and after a marathon run. Reprinted with permission (Middleton N et al. J Am Coll Cardiol 2008;52:1813-4).

release pattern is characterized by a prolonged phase (>48 h) of elevated troponin concentrations, compatible with ongoing cell fragmentation and necrosis.[30] In contrast, after exercise troponin concentrations typically peak within a few hours and normalize within 1–2 days.[20,31,32] Indeed, a recent study, showed that a marked and prolonged (>24 h) troponin elevation after endurance exercise is associated with obstructive CAD on coronary CT angiography while troponin levels obtained immediately after exercise show no such association.[33] Data from animal studies indicate that the troponin washout in minor type 2 AMI is much faster compared to what is

expected after transmural AMI[34] and similar dynamics could be expected in patients with a minor type 2 AMI and in healthy recreational athletes. Another interesting observation is that the ratio between troponin I and troponin T seems to be higher in patients with transmural AMI than after endurance exercise.[35] However, the clinical implications still remain unclear.[36]

Determinants of exercise-induced troponin release

Identifying potential determinants of troponin elevation after exercise may provide clues as to whether the release is physiological or not. Although results are not entirely consistent, the majority of studies links greater troponin increases to higher exercise intensity rather than exercise duration.[20] Accordingly, even short term exercise, such as during exercise stress testing, is associated with significant increase in troponin concentrations, although levels typically are lower than after long-term strenuous exercise, such as bike races or marathon runs.[20,23,24,26,37] Concerning prior CRF, the preponderance of data seem to suggest that a low CRF is associated with a greater response compared to those with high CRF and extensive prior training experience.[29,38] A weaker troponin response associated with higher CRF may be interpreted as a possible adaptive process to repetitive reversible injury.[39] Concerning the impact of age on the magnitude of the troponin response, data are conflicting.[20]

Mechanisms of exercise-induced troponin response

Currently, three different main mechanisms for troponin release have been proposed: through injured cell membranes from viable cells, or as a result of apoptosis or necrosis[40] (Fig. 4). The relative importance of these models for exercise-induced troponin release remains unclear. Traditionally, the dominating hypothesis has been that a small pool of free troponin T and troponin I circulates in the cytoplasm and may readily exit a viable cell through cell wounds, membranous blebs or microparticles following reversible cell injury. The remaining troponin content (>90%) within the cardiomyocyte is bound to tropomyosin as troponin T-troponin I-troponin C complexes that are only released after cell necrosis and subsequent degradation of structural protein.[41] A more recent version of this hypothesis proposes that cardiac troponins do not actually circulate in the cytosol, but that a pool of troponin molecules displays a weaker affinity binding to the myofilaments.[40] Cardiomyocyte stress due to contraction, stretching, beta-adrenergic stimulation or limited ischemia may activate proteolytic enzymes (e.g. calpain or caspase) or induce pH changes within the cell leading to a release of the loosely bound troponin molecules from the myofilaments and subsequent release through an injured cell membrane.[40] The second possible mechanisms for exercise induced troponin response proposes an initiation of a cell death program leading to cardiomyocyte apoptosis.[42–44] Apoptosis has been demonstrated in patients with heart failure and is likely to occur after AMI.[42] The increased cardiac preload and subsequent stretching of the cardiomyocytes that occur during exercise has been suggested to be a trigger for apoptosis. According to a strict definition apoptosis should not lead to intracellular content being released into circulation, however, cardiomyocytes have been suggested to represent an exception from this rule. According to current theory, apoptotic bodies from cardiomyocytes or the entire cell break and release their content into circulation, instead of being engulfed by the surrounding cells.[42] The third model for troponin release during exercise is cardiomyocyte necrosis and subsequent inflammation. Necrosis occurs in a situation with disrupted cell membrane, large Ca^{2+} influx and ATP depletion. The biochemical hallmark of necrosis is an immediate and substantial troponin increase followed by a prolonged (>24 h) less prominent troponin release due to slow washout of troponin molecules bound to degrading myofibrils from necrotic

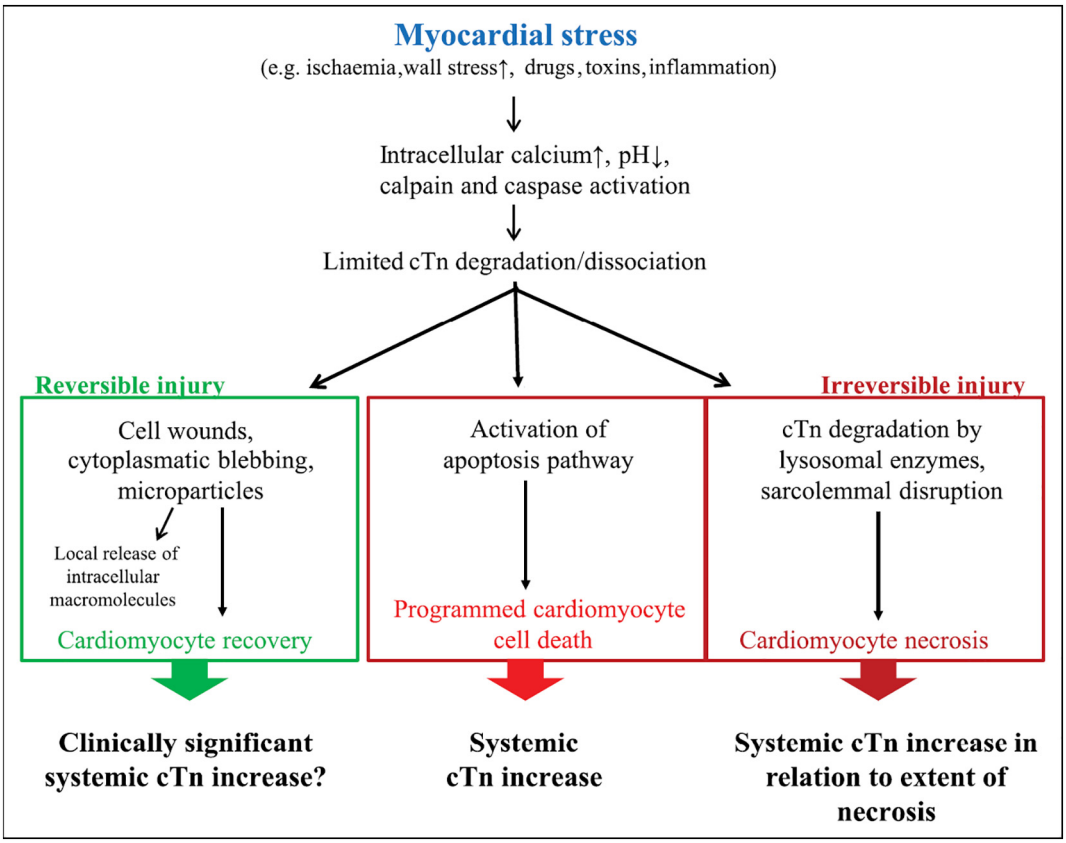


Fig. 4. The model shows the three different release pathways currently suggested for cardiac troponins. Reprinted with permission (Mair J et al. Eur Heart J Acute Cardiovasc Care 2018;7:553-60).

cells. This washout is flow-dependent and fluctuations in concentrations can therefore sometimes be observed.[45] The observation that the troponin concentration usually normalizes within 24 h after exercise speaks against major necrosis as an important factor in exercise-induced troponin release but the resemblance with profiles observed after minor AMI means that minor necrosis cannot be totally excluded as a contributing mechanism.

Assays measuring exercise-induced troponin fragments

Troponin molecules in the circulation may be modified depending on the mechanism causing the release. A recent publication has shown that circulating intact troponin T is detectable in only a few patients with AMI. After AMI, troponin T is degraded in a time-dependent manner and two different main troponin fragments of 29 kDa and 14–18 kDa, respectively, have been detected.[46] Extensive and time dependent fragmentation after AMI has also been demonstrated for troponin I.[47] Mingels and colleagues further investigated circulating troponin molecules after endurance exercise and identified circulating troponin fragments of 14–18 kDa only.[48] A similar pattern has been seen in patients with chronic kidney disease.[49] The technology measuring these fragments has certain limitations, e.g. the lower limit for analytical sensitivity is as high as 70 ng/L,[48] but future development of troponin assays identifying troponin fragments derived from reversible myocardial injury, apoptosis or cardiomyocyte necrosis would be most useful to distinguish between physiological and pathophysiological troponin release.

Is exercise-induced troponin response linked to long-term health outcomes?

In the clinical interpretation of the troponin response following endurance exercise, the long-term prognosis associated with different response patterns is obviously a key question. Data relating troponin levels before or during PA to long-term clinical outcomes are unfortunately scarce, but in a recent study of 108 recreational marathon runners coronary plaque burden (measured using coronary computer tomography angiography (CCTA)) and myocardial fibrosis (measured using CMR with late gadolinium enhancement, but not the magnitude of the troponin I increase after the run, were associated with future CVD events.[50] However, this was a relatively small study and the troponin I assay used was not a high sensitivity assay (TnI-Ultra, ADVIA Centaur XP analyser, Siemens Healthcare Diagnostics). Clearly, further studies in larger cohorts using high sensitivity assays are required to establish the prognostic value of different troponin responses after endurance exercise.

Exercise intolerance is a cardinal feature of HF with preserved ejection fraction (HFpEF). Several randomized controlled trials (RCTs) performed in older patients with HF have demonstrated that regular exercise increases the peak oxygen uptake in patients with HFpEF and improves myocardial strain.[51–54] In a recently published study, troponin concentrations were >2-fold higher in subjects with HFpEF, both at rest and during exercise, than in control subjects. Furthermore, troponin T elevations during exercise correlated inversely with aerobic capacity[55] (Fig. 5). These observations indicate that aerobic capacity may influence the post-exercise troponin response, raising the question whether the troponin response during activity may be used as indication of treatment effect in HFpEF.

Cardiac troponins as measures of chronic myocardial injury and prognosis

After the introduction of cardiac troponins as diagnostic tool in clinical practice, it was observed that some patients, e.g. with chronic kidney disease or chronic HF, had stable, low-level elevations in troponins.[56,57] Moreover, chronic elevation in cardiac troponins was

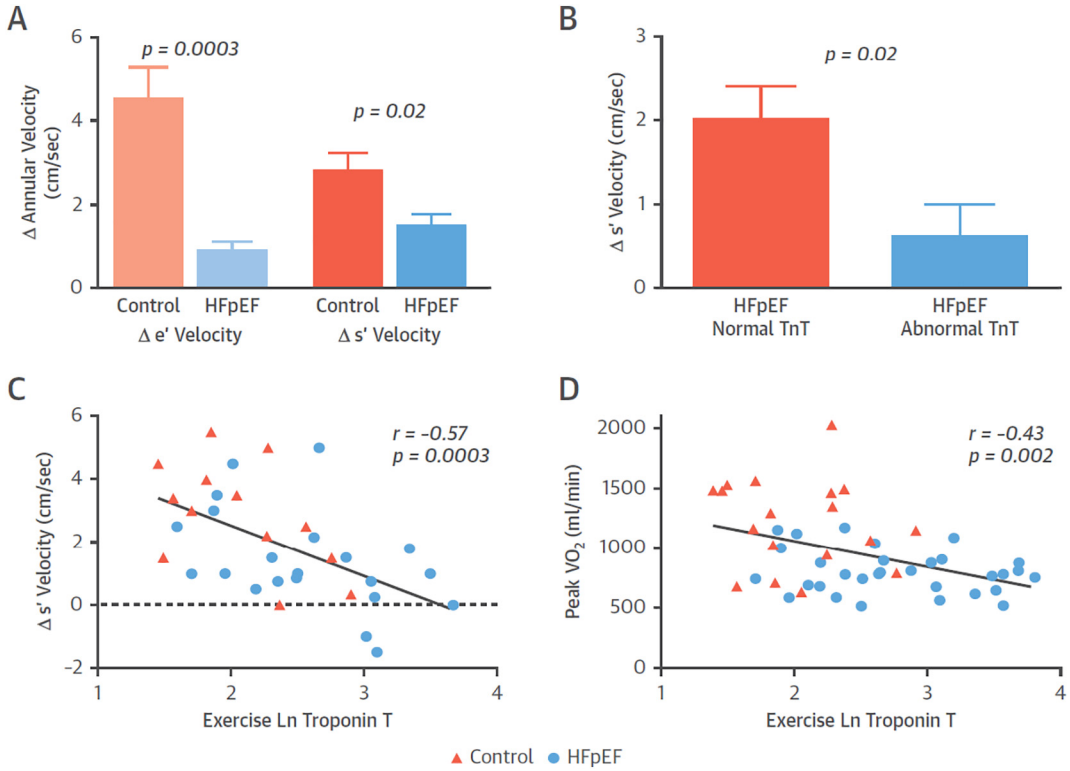


Fig. 5. Relation between troponin concentration, ventricular reserve, and exercise capacity. Panel A: Compared with control subjects (n = 20), subjects with HFpEF (n = 38) displayed less increase in LV diastolic (e') and systolic (s') mitral annular tissue velocities during peak exercise. Panel B: Compared with subjects with HFpEF with normal troponin T at rest, those with elevated troponin T displayed impaired systolic reserve during peak exercise. Panel C: Elevated peak exercise troponin T was associated with impaired LV systolic reserve with exercise. Panel D: Exercise troponin T concentrations were inversely correlated with peak oxygen consumption (VO2). Reprinted with permission (Obokata M et al. J Am Coll Cardiol 2018;72:29-40).

associated with a high risk for CVD events and imminent death. With the introduction of high sensitivity assays it became clear that even cardiac troponin levels below the measurable range of prior assays provided strong and graded prognostic information.[15,16,58] Accordingly, even in patient groups that previously rarely had detectable levels of cardiac troponins, such as patients with stable coronary artery disease, patients without heart failure and subjects from the general population, high-sensitivity cardiac troponins were closely associated with CVD risk, independently of traditional CVD risk factors and markers.[15–18] Interestingly, the association between cardiac troponins and CVD risk is particularly strong for the incidence of HF, and less strong for atherothrombotic events.[15,59] In recent cardiac magnetic resonance studies, cardiac troponins correlate closely with the presence of non-ischemic, but not ischemic myocardial scars.[60] Accordingly, in this context circulating cardiac troponins should be regarded as indices of subclinical myocardial injury rather than as an index of the severity of CAD per se.

Are the beneficial effects of physical activity associated with changes in resting troponin concentrations?

Complex interactions may influence the association between PA and cardiac troponin concentrations. In large-scale epidemiological studies of elderly subjects from the general population self-reported PA has been inversely associated with troponin levels.[61] Moreover, in middle-aged subjects sedentary behaviour measured by an accelerometer (i.e. sedentary time was defined as <100 cpm using an Actical (Phillps Respironics) activity wrist monitor) has been associated with higher troponin T concentrations.[62] Circulating cardiac troponin concentrations increase with age,[16,63] and in the elderly temporal changes in physical activity are related to changes in troponin concentrations in that higher PA seems to attenuate the age-dependent increase in cardiac troponins.[61] So far, data from RCTs are sparse. However, one recent RCT has confirmed these observational data showing that moderate exercise intervention in older sedentary adults slows down the age-expected increase in troponin T concentrations evident in control subjects.[64] These findings suggest that resting troponin concentrations are modifiable by regular exercise programs, and future work should investigate whether reductions in cardiac troponins are linked to a favourable long-term prognosis. Such data would be of particular interest in vulnerable patient cohorts with few treatment options, like patients with HFpEF.

Conclusions

Cardiac troponins are released into circulation as a result of reversible cardiomyocyte cell membrane injury, apoptosis or necrosis. Exercise may induce acute troponin release in the absence of manifest cardiac pathology. The mechanisms responsible for exercise-induced troponin release are not fully known, but clinical and experimental data suggest acute necrosis as an unlikely underlying cause in most cases. The possibility of measuring troponin molecules that are specific for ischemia-induced necrosis would simplify diagnosis of acute coronary syndromes. Stable elevation of cardiac troponin suggests chronic myocardial injury, and has been linked to sedentary life style, low physical fitness, and increased risk of CVD in general, and HF in particular. Regular physical exercise leads to improvement in CRF, and even though limited randomized data exists, observational studies indicate that increased PA leads to reduced resting troponin concentrations and possibly also a reduction in the exercise-induced troponin response. The clinical utility of cardiac troponin measurements for monitoring the treatment effect of exercise programs should be investigated in future studies.

Acknowledgement

None.

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