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Physical activity and troponin elevation

PERSPECTIVES

ERLE EDVARDSSON

ev.edvardsson@gmail.com
Erle Edvardsson, medical student at the University of Oslo
The author has completed the ICMJE form and declares no conflicts of interest.

TORBJØRN OMLAND

Torbjørn Omland PhD, MD, professor at the K.G. Jebsen Center for Cardiac Biomarkers, Institute of Clinical Medicine, University of Oslo, and senior consultant at the Department of Cardiology, Akershus University Hospital
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Physical activity is associated with troponin elevation. What do we know about exercise-induced troponin elevation?

Most doctors associate the cardiac muscle proteins troponin T and I with a blood test used to detect acute myocardial infarction. An increase and/or decrease in troponin concentration, with at least one value above the 99th percentile, is an absolute criterion for diagnosing acute myocardial infarction (1). However, with the introduction of high-sensitivity assay methods, it has become evident that low concentrations of troponin T and I can be detected in the blood of healthy individuals, and that troponin levels are also elevated in a variety of other acute and chronic medical conditions. Observing a mildly to moderately elevated troponin concentration alone therefore provides limited

insight into the underlying cause of cardiac injury, whereas very high levels are typically indicative of ischemic injury due to acute coronary artery occlusion (1).

It appears that, regardless of the underlying cause, elevated blood concentrations of troponin are associated with a higher risk of cardiovascular disease and premature death (2, 3). One possible exception to this is troponin elevation during and after physical activity. Several studies have found troponin levels above the reference range following both prolonged and short-duration physical activity (4). The fact that exercise can induce troponin concentrations that meet the biochemical criteria for acute myocardial infarction has sparked debate. Is the elevation physiological and unrelated to cardiovascular disease, or could repeated episodes of troponin elevation be a sign of myocardial injury? What do we know about the mechanisms behind exercise-induced troponin elevation, and what is the clinical significance?

What are troponins?

Troponins are intracellular protein complexes involved in the contraction of striated muscle (4). Three types of troponin have been identified: troponin T, C and I. Troponin T facilitates the binding of tropomyosin to thin filaments. Troponin C binds calcium, leading to a conformational change. Troponin I inhibits actomyosin ATPase activity (4). Cardiac troponin T and I are often referred to as cardiac-specific because their isoforms are immunologically distinct from the isoforms in skeletal muscle (4). Troponin T and I can therefore be used as cardiac-specific clinical biomarkers for myocardial injury and as a key criterion in the diagnosis of acute myocardial infarction. Troponin C cannot, however, be used for this purpose (1).

Mechanisms of troponin release

Cardiomyocyte necrosis due to ischemia has traditionally been regarded as the mechanism behind troponin elevation in acute myocardial infarction (4). Because cardiomyocytes have limited regenerative capacity, injury caused by this mechanism is irreversible and can lead to fibrosis and reduced cardiac function. The mechanism by which physical activity triggers the release of troponins into the bloodstream is not yet fully understood. Transient, reversible injury or apoptosis of cardiomyocytes have been proposed as possible mechanisms (4). Another possible mechanism is increased membrane permeability, which allows passive diffusion of smaller troponin fragments into the bloodstream (4, 5). The formation of membrane blebs is another theory that has been proposed. Temporary hypoxia contributes to the formation of cytoplasm-containing blebs, which are released into the bloodstream without membrane rupture (6). While the mechanisms behind exercise-induced troponin elevation remain unclear, the process is generally thought to be physiological (6).

Exercise-induced troponin elevation

Troponin elevation due to physical activity is best documented for exercise involving prolonged exertion, such as marathon running and other long-distance events (7). Perhaps more surprisingly, shorter training sessions can also induce troponin concentrations that exceed the upper reference limit (7, 8). Sixty minutes of running, cycling or swimming may be sufficient to induce elevation, and the observed increase in troponin has been shown to be independent of exercise mode (8).

To better understand exercise-induced troponin elevation, several explanatory variables have been investigated. Intensity level is a key contributing factor as several studies have demonstrated a positive correlation between intensity and troponin concentration (4, 7). One study observed that moderate and high-intensity exercise led to a significant increase in troponin, but low-intensity exercise did not have the same effect (5). Although the moderate-intensity exercise lasted longer, the troponin increase was still greatest after the high-intensity exercise (5). This illustrates how intensity may play a more significant role than exercise duration in the troponin response.

Exercise-induced troponin increases are typically transient and characterised by a rapid rise in concentration, followed by a relatively quick decline (6). As a result, troponin concentrations normalise within 24–72 hours after physical activity (9). In comparison, troponin levels can remain elevated for 4–12 days following a myocardial infarction (4). The prolonged half-life of troponin after a myocardial infarction is likely due to its simultaneous release from the necrotic cells as it breaks down. Since these processes occur concurrently, estimating the half-life of circulating troponins has been challenging. A recent Danish study has shown that the half-life is shorter than previously thought (10). In the study, plasma exchange was performed in patients with acute myocardial infarction during the acute phase, followed by autologous transfusion three weeks later and serial blood tests. This approach allowed for the differentiation of troponin elimination from ongoing troponin release (10).

Association with cardiovascular risk?

Regular exercise is widely accepted to have beneficial effects on cardiovascular health. Higher levels of physical activity over time are associated with a reduced age-related increase in circulating troponin levels (11). Combined with the absence of cardiovascular symptoms or pathological findings during physical exertion, this has been key to shaping our current understanding of exercise-induced troponin elevation as a benign physiological phenomenon. However, long-term follow-up with post-exercise troponin measurements in a sufficiently large cohort is needed to evaluate its relationship with cardiovascular risk. The first study to demonstrate an association between troponin concentrations and cardiovascular events included 725 middle-aged participants in a walking event

with a median duration of eight hours (3). The association with increased risk was independent of baseline troponin I concentrations and conventional risk factors. One possible interpretation of these findings is that the walking event functioned as a stress test, and that a greater increase in troponin was associated with subclinical atherosclerotic disease, which in turn is associated with future events. It is important to emphasise that these results cannot be extrapolated to a younger population, for whom subclinical coronary artery disease is considerably less prevalent.

«Elevated heart rate alone may impact on troponin levels»

When troponin concentrations in individuals with chronic coronary artery disease are compared with the general population, baseline levels are found to be higher in those with confirmed coronary disease, and even values within the normal range are associated with a poorer prognosis (2, 12). It is therefore plausible that myocardial ischemia during physical exertion is linked to a greater increase in troponin levels. However, most studies have not found such a connection (13). In a study where participants' heart rates were raised to 160 beats per minute using a temporary pacemaker, patients with coronary artery disease and elevated lactate levels in the coronary sinus did not exhibit a significantly greater increase in troponin T concentration compared to healthy controls (12). This suggests that elevated heart rate alone may impact on troponin levels.

«Physical activity can induce a troponin increase that meets the current biochemical criteria for acute myocardial infarction»

Sudden cardiac death associated with prolonged and intense physical activity is rare and difficult to predict. The question of whether troponin measurements during physical activity can serve as a predictive test has therefore been raised (14). However, troponin concentrations measured during and up to two hours after exercise do not differ significantly between athletes with and without atherosclerotic disease (15). Neither has any correlation been observed between the severity of atherosclerosis and the troponin increase following physical activity (16). Conversely, troponin concentrations 24 hours after exercise have been shown to be significantly higher in athletes with atherosclerosis (17). The reason the troponin response appears to last longer in individuals with atherosclerotic disease is unclear, but prolonged release from the ischemic area may be a contributing factor.

Physical activity can induce a troponin increase that meets the current biochemical criteria for acute myocardial infarction. It is important to be aware that recent physical activity can significantly affect the troponin response in both healthy individuals and hospital in-patients. When evaluating patients with atypical infarction symptoms, additional information about their activity level during the preceding 24 hours will be relevant for assessing the clinical significance of the observed troponin elevation. In individuals with subclinical or confirmed coronary artery disease, a prolonged troponin increase following physical activity may indicate ischemic myocardial injury and be associated

with an increased risk of cardiovascular events. More knowledge is needed about exercise-induced troponin elevation in order to help distinguish between physiological exercise-induced troponin elevation and troponin elevation secondary to more serious underlying pathology.

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