Exercise-Induced Cardiac Troponin Release: Irreversible or Reversible Myocardial Cell Damage?

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Siriraj Med J 2012;64:131-135
E-journal: http://www.sirirajmedj.com

Performing regular exercise of mild to moderate intensity has been proven to be beneficial for general health and represents an effective tool in the prevention and management of cardiovascular disease. Nonetheless, it has been repeatedly reported in recent years that strenuous endurance exercise such as marathon running, alpine bicycling and triathlon are associated with significant release of the cardiac specific markers troponins into the circulation, reflecting myocardial cell damage. The questions thus arise, as to whether exercise-induced cardiac troponin release indicates irreversible or reversible myocyte damage, and whether the elevated troponins found have prognostic significance. These represent topics of great interest and are of public health concern, as reflected by an article in the January 2007 issue of The Times as well as by another in the September 2009 issue of The New York Times, entitled "Ironman athletes put hearts at risk of fatal damage, experts warn" and "How do marathons affect your heart?", respectively. The questions also have global health relevance since millions of people worldwide are actively engaged in endurance exercise events.

Definition of irreversible cell damage

The European Society of Cardiology (ESC) and American College of Cardiology Foundation (ACCF) in collaboration with the American Heart Association (AHA) and World Health Federation (WHF) jointly released guidelines in 2007, stating that cardiac biomarkers, especially cardiac troponin T (cTnT) and troponin I (cTnI), play a central role in the diagnosis of acute myocardial infarction (AMI), and their measurements provide useful prognostic information in acute coronary syndrome (ACS) patients.[1,2] According to the new guidelines, any detectable rise of cardiac troponins above the 99th percentile cut-off concentrations, determined in a reference population, and subsequent fall reflect acute irreversible myocyte damage and necrosis. The irreversible cell injury can occur spontaneously after atherosclerotic plaque rupture with subsequent thrombotic occlusion, or as a result of the mismatch between blood oxygen supply and demand (vasospasm, anemia, arrhythmias, hypotension, etc.), as well as after interventional revascularization procedures (e.g. percutaneous or surgical coronary intervention).[3]

Models of reversible cell damage

Elevated troponin levels above the 99th percentile decision limit have been demonstrated in various clinical conditions other than ACS, including acute and chronic heart failure, pulmonary embolism, myopericarditis, sepsis and septic shock, as well as acute neurologic diseases (ischemic stroke, subarachnoid hemorrhage, epileptic seizure).[4-6] Significant elevations of cardiac troponins have also been reported in acute physical or psychological stress.[7,8] Due to the absence of obstructive coronary arteries in most of these conditions, a non-ischemic cause of troponin increases has been postulated. In this context, results from recent studies have indicated the possibility that in many of these clinical entities the troponins are released into the circulation from viable and not necrotic myocytes, reflecting reversible cell injury. One of the models that has been intensively used for this study purpose is strenous endurance exercise.

Models of exercise-induced troponin release

In the past decades, several studies on the effect of exercise on cardiac marker releases using currently available troponin assays have been performed both in animal and human models of exercise-induced cardiac injury.[8-10] Most of these trials reported transient minimal increases in cardiac troponin concentrations during prolonged endurance exercise in a significant number of study subjects.[11,12] However, since most of the current assays showed high analytical imprecision at the low-range concentrations which did not fulfill the recommended guidelines of the international cardiology societies mentioned above, so they do not

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Received 25 January 2012
Revised 5 July 2012
Accepted 6 July 2012

provide reliable methods for cardiac troponin measurements and for interpretation of cardiac marker test results. Another limitation of the conventional assays lies in their inability to provide a sensitive measurement of cardiac troponin concentrations which distinguish reversible from irreversible injury. Thus, the concept of exercise-induced reversible cell damage has remained for several decades a controversial issue.[13,14]

Developments of sophisticated immunoassay systems in recent years have led to cardiac marker tests with improved analytical sensitivity and precision, and measurements by these ultrasensitive assays have been shown to produce reliable test results.[15,16] Up to date, at least 4 studies utilizing the new assays have provided data indicating that troponin releases after endurance exercise may reflect reversible myocyte damage.

In a study on 15 male non elite runners participating in the London Marathon (42.2 km) in 2007, Dawson et al.,[17] reported increases in post-race high-sensitivity cardiac troponin I (hs-cTnI, Siemens Medical Solutions Diagnostics) above the detection limit of the assay (0.006 ng/ml) and clinical cut-off level for AMI (0.05 ng/ml) in 92% and 69% of the runners, respectively. The high prevalence of post race elevations of cardiac troponins was also demonstrated in a study on 10 participants in the Badwater Ultramarathon (216 km), with a mean finishing time of 51.2 hours.[18] During the race, there was a transient minimal increase from detectable baseline high-sensitivity cardiac troponin T (hs-cTnT, Roche Diagnostics) concentrations in most of the runners, with an early peak and a subsequent fall in some runners indicating minor myocardial cell damage.

Recently, Mingels et al.,[19] reported on patterns with cardiac troponin release observed during the Mass Marathon (42.2 km) in the Netherlands using the hs-cTnT compared with the conventional troponin T (cTnT, both Roche Diagnostics), and the hs-cTnI (Abbott Diagnostics). All of the pre-ace cTnT were below the limit of detection (LoD) of the assay, whereas both high-sensitivity troponin assays were able to measure pre-race troponin concentrations in most of the runners. Immediately after the marathon, there was an approximately 8 to 10 fold increase from detectable baseline concentrations in both of the ultrasensitive troponins and the levels returned to normal (hs-cTnT) or near-normal range (hs-cTnI) 24 hours after the race, which is in contrast to the prolonged elevations of more than 1 week observed in irreversible cell damage or necrosis. The transient minimal increases in cardiac troponin T levels have also been demonstrated in a more recent study on marathon runners using the same high-sensitivity immunoassay.[20]

Role of non-invasive imaging techniques

Over the past decades, sophisticated imaging techniques including dobutamine echocardiography, positon-emission tomography (PET), single-photon-emission computed tomography (SPECT) and magnetic resonance imaging (MRI) have become sensitive tools for detection of myocardial ischemia and assessment of the viability of cardiomyocytes.[21,22] The new techniques have also been performed in combination with cardiac troponin tests to detect cardiac pathology in healthy individuals undergoing endurance exercise. However, there are contradictory results about the concept of exercise-induced reversible cell damage.

By using SPECT as an indicator of reversible myocardial ischemia, Kurz et al.,[23] reported no increase in hs-cTnT (Roche Diagnostics) levels either after brief exercise or pharmacologic stress testing. In contrast, Sabatine et al.,[24] were able to demonstrate a quantifiable rise in circulating hs-cTnI (Singulex, Inc.) levels in response to stress testing, and the magnitude of the rise was proportional to the degree of ischemia on perfusion imaging (Table 1). The positive result in the latter study may be related to the higher analytical sensitivity of cTnI assay used, as compared to cTnT assay, with the limit of detection of 0.0002 ng/ml and 0.002 ng/ml, respectively.

Cardiac MRI, particular when enhanced with gadolinium-based contrast agents, is a powerful clinical tool for characterizing myocardial abnormalities, especially in patients presenting with chest pain but "normal" coronary arteries.[25] The MRI in combination with cardiac marker tests are also capable of providing clinically useful information in condition such as strenuous exercise. The presence of a delayed myocardial hyperenhancement on MRI reflects irreversible injured myocardium or replacement fibrosis,[26] whereas the absence of such enhancement corresponds to areas of viable myocardium.[21]

TABLE 1. Clinical trials on non-invasive imaging in association with exercise-induced myocardial cell damage.

Author (year)	Exercise event	Troponin	Imaging technique	Imaging result
Kurz et al. (2008)	Bicycling	hs-cTnT	SPECT	Hs-cTnT did not increase after reversible myocardial ischemia
Sabatine et al. (2009)	Exercise stress testing	hs-cTnI	SPECT	Myocardial ischemia was associated with a quantifiable increase in circulating troponin levels
Breuckmann et al. (2009)	Marathon	-	MRI	Twelve percent of study subjects showed delayed hyperenhancement
Scharhag et al. (2006)	Running or bicycling	cTnI, cTnT	Echocardio-graphy, MRI	No pathologies were demonstrated by echocardiography or delayed enhancement MRI
Mousavi et al. (2009)	Marathon	cTnT	MRI	No delayed hyperenhancement
Trivax et al. (2010)	Marathon	cTnI	MRI	No evidence of ischemic injury to any chamber by late gadolinium enhancement.
Hanssen et al. (2011)	Marathon	cTnT	MRI	A transient increase in cTnT was not associated with detectable myocardial necrosis as evidenced by MRI imaging.

In a study on 102 nonprofessional male marathon runners, Breuckmann et al.,[27] have demonstrated both coronary artery disease (CAD) and non-CAD patterns on left ventricular late gadolinium enhancement in 12% compared with 4% of age-matched control subjects (Table 1). Unfortunately, measurement of cardiac troponin was not performed in this trial. By contrast, a previous study on 20 male athletes who had completed a 1-hour and a 3-hour stress testreported a marginal increase in cTnI (Beckman Coulter) after both exercise trials. However, no pathologies could be demonstrated either by echocardiography or delayed-enhancement MRI.[28] Results from this study was later confirmed by Mousavi et al.,[29] who found no evidence of delayed enhancement of the left ventricular myocardium in the presence of increased cTnT (Roche Diagnostics) concentrations in 14 runners participating in the 2008 Manitoba Marathon (Table 1). It was concluded in both studies that exercise-induced increases in cardiac troponin may represent a physiological reaction under special conditions, indicating the cytosolic release of the biomarkers and not the true breakdown of the myocytes. A similar conclusion was drawn by Trivax et al.,[30] who reported that increased cTnI levels post a marathon run are not associated with imaging evidence of ischemic injury to any chamber by late gadolinium enhancement (Table 1). The authors postulated that increased wall tension and dilatation of the right sided chambers might account for the elevation in cardiac troponins associated with prolonged endurance running, rather than of ischemic damage or infarction. Results from these trials were later confirmed by a recent study by Hanssen et al.,[31] were performed on 28 healthy male marathon runners. They found that, although marathon running leads to a transient increase in cTnT levels, no detectable myocardial necrosis was observed as assessed by late gadolinium enhancement MRI.

In summary, existing data has demonstrated a release pattern of cardiac troponin after endurance exercise which resembles many features of reversible cell damage. These include egress of the troponins from the cytosolic pool which constitutes around 3-7% of the total troponin content of cardiomyoytes indicating minimal myocardial injury, an early peak and a rapid fall to the normal range within one to two days after exercise events. In addition, several studies reported no delayed hyperenhancement on MRI in the presence of increased cardiac troponins, which reflects troponin release from viable and not necrotic cardiomyocytes.

Molecular mechanism of exercise-induced troponin release

The different pattern of cardiac troponin increase after endurance exercise compared with that of myocardial ischemia in the setting of ACS mentioned above have led to the assumption that cardiac troponins can be released from viable myocytes. Experimental evidence for this hypothesis was provided some decades previously by Piper et al.,[32] who demonstrated reversible bleb formation on membranes of rat myocytes after limited periods of hypoxia, with subsequent release of cardiac enzymes into cell supernatant. The process can occur without rupture of the plasma membrane.[33] In this context, it has been shown that a brief (15 minutes) period of mild ischemia, an interval too short for inducing cell death, was able to cause cTnI release.[34]

Several molecular mechanisms of exercise-induced myocardial cell damage have been postulated. One potential mechanism is the oxidative stress-induced generation of free radicals[35] causing increased membrane permeability and release of the cytosolic troponins.[36] Prolonged aerobic exercise has also been shown to produce a significant decrease in the overall antioxidant capacity of rat hearts.[37] In addition, exercise-induced myocardial ischemia caused by catecholamine-mediated coronary vasospasm as well as catecholamine-induced endothelial dysfunction and calcium overload are being discussed as the underlying causes.[8] As shown in Table 2, endurance exercise seem to represent the only physiological condition that is associated with this type of myocardial injury. Recently, Hessel et al.,[38] demonstrated that viable cardiomyocytes release cTnI by a stretch-related mechanism mediated by integrins which are transmembrane glycoprotein receptors which link the extracellular matrix to the intercellular cytoskeleton. The authors hypothesized that these mechanically induced alterations in cardiomyocyte's sarcolemmal permeability are involved in the release of cTnI from the cytosolic pool in the absence of necrotic cell death.

Prognostic relevance

Although a large body of evidence points to the existence of a transient reversible myocardial damage following endurance exercise, a public health concern remains since, as has been demonstrated by Breuckmann et al.,[27] a significant number of healthy athletes showed delayed hyperenhancement on MRI indicating irreversible damage. In addition, there is post-mortem evidence of the existence of myocardial fibrosis in animals and athletes.

In one study on racehorses that died suddenly, autopsy findings revealed foci of fibrosis in the right atrium, interatrial and interventricular septum, as well as in the conduction system.[39] In a rat model of long-term intensive exercise training, Benito et al., have documented the presence of cardiac fibrosis in association with changes in ventricular function and increased arrhythmia inducibility.[40] Rowe[41] described a case of the Burmese marathon runner, Sy Mah, who set a world record of 524 marathons, in whom stress testing showed a probable exercise-induced coronary vasospasm with circadian variation several months before death from lymphoma at the age of 62 years. A necropsy revealed focal fibrosis of the papillary muscles in the absence of coronary atherosclerosis. It was postulated that the finding was related to exercise-induced high concentrations of catecholamines. Whyte et al.,[42] reported on the presence of idiopathic interstitial myocardial fibrosis and left ventricular hypertrophy in the heart of an athlete that died suddenly during a marathon race. The authors postulated that fibrosis might create a potential substrate for arrhythmia causing sudden cardiac death. Similarly, Claessen et al.,[43] have demonstrated a significant associa-

TABLE 2. Physiological and pathological conditions associated with catecholamine-mediated myocardial cell injury.

Physiological condition
Strenous endurance exercise: marathon running, alpine bicycling, triathlon
Pathological condition
Phaeochromocytoma
Acute and chronic heart failure
Stress-induced (Tako-tsubo) cardiomyopathy
Acute neurologic diseases: stroke, subarachnoid hemorrhage, epileptic seizure
Cocaine and amphetamine abuse

tion between long-term endurance sports (cycling, running, swimming) and the development of lone atrial flutter. They and others have suggested that chronic ultra-endurance exercise may provide arrhythmogenic substrates and increase the vulnerability to tachyarrhythmias in endurance athletes. In this context, it is of interest to note that Heidbuchel et al.,[44] reported sudden death in 20% of endurance athletes with ventricular arrhythmias during a median follow-up of 4.7 years.

Since there are, to our knowledge, thus far no other reports on the long-term follow-up of endurance athletes in the literature, more information from prospective studies on a large number of subjects are required to answer the question, as to whether frequent participations in prolonged arduous exercise events are associated with future cardiovascular morbidity and mortality.

CONCLUSION

Endurance exercise is in most cases associated with reversible myocardial cell damage, as reflected by a transient minimal increase in cardiac troponins and the absence of a delayed hyperenhancement on MRI. However, the long-term cardiovascular consequences of strenuous exercise are at present largely unknown and remain to be determined in future investigations. In addition, since strenuous physical activity has been shown to unmask concealed, potentially lethal cardiac anomalies including hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy/dysplasia by triggering life-threatening arrhythmias,[45] individuals with a family history of cardiac disease or premature cardiac death, as well as older people should undergo pre-participation screening procedures including physical examination, and ECG and probably cardiac troponin testing for sports eligibility.[46] This screening system has been shown to be able to detect apparently healthy subjects who are carriers of concealed cardiac defects which may cause sudden cardiac death during sporting events. Therefore these high-risk subjects should be excluded from athletic and vigorous exercise participation.

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