Pattern and Molecular Mechanisms of Cardiac Troponin Release in Conditions Other than Acute Coronary Syndromes

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Measurements of cardiac troponin concentrations are at present universally accepted and recommended as the gold standard biochemical methods for diagnosis of acute myocardial infarction (AMI) in patients presenting with chest pain. In addition, levels of cardiac troponin T (cTnT) and troponin I (cTnI) provide useful prognostic information and can help to guide the management of acute coronary syndrome (ACS) patients.[1] Nonetheless, although the currently available troponins have a nearly absolute cardiac specificity, they are not disease specific and cannot be used to distinguish reversible from irreversible myocardial cell injury.

According to the new criteria of international cardiology societies,[1,2] the definitive diagnosis of AMI can be made in the presence of a rise and/or fall of cardiac troponins (or CK-MB mass when the troponins are not available) together with ischemic symptoms, electrocardiographic changes indicative of new ischemia, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Thus, the presence of significant changes in troponin levels is essential for the diagnosis of myocardial cell necrosis. There is, however, thus far no consensus about the extent of these changes should be. Some experts have suggested a troponin change of 20% or more,[3,4] but as has recently been reported, the intra-individual biological variability of troponin concentrations in healthy persons can be higher than 50% and thus, should be considered in the interpretation of tests results.[5,6] Another biochemical characteristic of myocardial cell necrosis due to obstructive coronary artery disease is the prolonged elevation of cardiac troponins beyond 1 week. This pattern of cardiac troponin release can be explained by the initial egress of the free (unbound) troponins from the cytosolic pool (3-7% of the total troponin content), followed by detachment of the bound form of troponins from the myofilament and subsequent release into the circulation.[7] Accordingly, the serum or plasma troponin concentrations found in patients with AMI are distinctively high, with peak levels usually in the range of 10 to more than 100 folds of the upper limit of reference range.

Based on the guidelines of the international cardiology societies mentioned above, the pattern of cardiac troponin elevations may represent AMI type 1 (spontaneous MI) which is due to a primary coronary event such as plaque erosion and/or rupture with subsequent thrombotic occlusion of coronary arteries, or AMI type 2 which is secondary to ischemia due either to increased oxygen demand or decreased supply (e.g. coronary spasm, anemia, hyper- or hypotension). In addition, AMI may lead to sudden cardiac death (AMI type 3) or can occur following coronary revascularization procedures such as percutaneous coronary intervention as well as coronary artery bypass grafting (AMI type 4 and 5, respectively).

Several conditions other than ACS have been reported to be associated with increased cardiac troponin concentrations indicating myocardial damage. These can be divided into 2 groups of cardiac and non-cardiac causes with myocardial involvement (Table 1). As compared with patients with AMI, different patterns of troponin increases have been reported in these patients and can be described as follows:

1. A constant release of cardiac troponins without a significant rise and/or fall of cardiac marker levels, the difference of which in most cases does not exceed 50%, is usually found in congestive heart failure, myopericarditis, sepsis and septic shock, and drug toxicity.

2. The small troponin increases observed in several cases of thermal burns and extreme exertion return to the reference limit within a few days, reflecting a transient reversible injury.

3. A certain number of patients with stress cardiomyopathy, acute neurologic diseases, phaeochromocytoma and drug abuse exhibit a troponin release profile which mimics AMI.

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TABLE 1. Elevations of cardiac troponin in conditions other than acute coronary syndromes.

Cardiac causes
• Cardiac trauma (contusion, ablation, pacing, etc.)
• Acute and chronic congestive heart failure
• Stress cardiomyopathy (Tako-tsubo cardiomyopathy)
• Hypertrophic cardiomyopathy
• Tachy- or bradyarrhythmias
• Myocarditis, pericarditis
Non-cardiac causes
• Acute neurologic diseases (stroke, subarachnoid hemorrhage, epilepsy)
• Pulmonary embolism, severe pulmonary hypertension
• Sepsis and septic shock
• Amyloidosis, scleroderma, sarcoidosis
• Renal failure
• Thermal burns
• Phaeochromocytoma
• Drug toxicity (adriamycin, herceptin, etc.)
• Drug abuse (cocaine, amphetamine)
• Extreme exertion

Modified from Wu, et al. (reference 7).

4. Troponin concentrations are in the majority of these cases less than 10 fold the upper reference limit which indicates minor myocardial injury.

Based on these observations, it can be summarized that most types of troponin elevations may be characterized as persistent low level increase or a rapid decline of cardiac markers, and are believed to occur as a result of the sole leakage of the free (unbound) troponins from the cytosolic pool of the viable (not necrotic) cardiomyocytes.

The molecular mechanisms underlying cardiac troponin release in patients with conditions other than ACS are at present speculative, but emerging evidence points to multiple mechanisms that are potentially operative in these patients. Several of these conditions have been reported to be associated with neurohormonal activation, releases of pro-inflammatory cytokines, oxidative stress and/or alterations in Ca^{++}-handling. As shown in Table 2, neurohormonal activation of the sympathetic nervous system with catecholamine-mediated cardiomyocyte damage possibly represents the principal cause of troponin increases in patients with congestive heart failure,[8,9] stress cardiomyopathy,[10,11] acute neurologic diseases,[12,13] phaeochromocytoma,[14,15] drug abuse[16-19] and extreme exertion.[20-22] In an experimental model of cardiac injury, norepinephrine treatment of cardiac myocyte cultures resulted in a significant release of cardiac enzyme creatine kinase into the medium.[23] In another animal model, the isoprenaline-induced cardiac damage with elevations of cTnT and cTnI has been reported to be related to the severity of histologic changes.[24] It has been postulated that the sympathetic overactivity encountered in the conditions mentioned above may lead to myocardial stunning that results from a combination of myocardial ischemia related to diffuse microvascular dysfunction and multivessel epicardial spasm.[25-27] In addition, catecholamine may induce endothelial dysfunction, with a decrease in nitric oxide production.[22] Furthermore, the excess of sympathetic activity may potentiate oxidative stress, increase cytokine production and alter Ca^{++}-handling of cardiomyocytes.[28]

Another mechanism other than overt myocardial ischemia is the presence of pro-inflammatory cytokines generated during the course of disorders such as myopericarditis,[29,30] sepsis and septic shock,[31,32] thermal burns[33,34] and drug-induced cardiotoxicity.[35-37] Excessive production of interleukins (ILs) and tumor necrosis factor-α (TNF-α) has been demonstrated to be associated with cardiac cell damage, and inhibition of TNF has been shown to prevent myocardial dysfunction during burn shock.[31,34,38] In this context, it has been reported by Altmann et al.,[31] that elevations of cTnI concentrations occurred in 22 out of 38 patients (58%) with sepsis and septic shock, with a median level of around 3 fold the upper limit of the reference limit. Since significant coronary artery disease has been ruled out by dobutamine stress echocardiography or by autopsy in the majority (64%) of troponin-positive patients, and the presence of microvascular flow disturbance provoked by a hypercoagulable state has not been found, the authors suggested that a pathophysiological mechanism other than thrombus-associated myocardial damage might play a major role, including reversible myocardial membrane leakage and/or cytokine mediated apoptosis of cardiomyocytes. In an animal model reported by Oppeltz et al.,[33] mice which received a scald burn showed increased cTnI concentrations at 3 hours after injury. At 24 hours after the burn, the cTnI levels began to normalize and did not differ from those of the uninjured animals. These results, again, point to the reversibility concept of cytokine-mediated cardiac cell damage, with increases in the permeability of sarcolemmic membranes of cardiomyocytes.

Cardiotoxicity is a common complication of several antitumoral agents such as anthracyclines and trastuzumab. Numerous studies have demonstrated that measurements of cardiac specific biomarkers such as troponins can be a valid diagnostic tool for early identification, risk assessment, and monitoring of cardiac toxicity.[35] It has been reported that

TABLE 2. Mechanisms of cardiac troponin release in certain conditions without overt myocardial ischemia.

	Neurohormonal activation	Pro-inflammatory cytokines	Oxidative Stress	Altered Ca^{++}-handling
Congestive heart failure	+ +	+ +	+ +	+ +
Stress cardiomyopathy	+ +	+	+	+ +
Myocarditis, pericarditis	+	+ +	+	+
Acute neurologic diseases	+ +	+	+	+
Sepsis, septic shock	+	+ +	+ +	+
Thermal burns	+	+ +	+	+
Phaeochromocytoma	+ +	+	+	+
Drug toxicity	+	+ +	+ +	+ +
Drug abuse	+ +	+	+	+
Extreme exertion	+ +	+	+ +	+

+ + = key mechanism, + = co-mechanism.

patients without cTnI elevation after chemotherapy showed no significant reduction in left ventricular ejection fraction (LVEF) and had a good prognosis, whereas cTnI-positive patients and those with the persistence of cTnI elevation in particular exhibited greater cardiac impairment and a higher incidence of adverse cardiac events at long-term follow-up.[36] Multiple mechanisms of anthracycline-induced myocardial cell injury have been proposed. These include oxidative stress and the formation of reactive oxygen species (ROS: superoxide anion, hydrogen peroxide, hydroxyl radical). Anthracyclines induce membrane damage through ROS via lipid peroxidation and, in severe cases, may cause myocyte cell death by both apoptosis and necrosis. In addition, these antitumoral agents may induce changes in adrenergic function as well as abnormalities in Ca^{++}-handling.[37,39] In a recent experimental study on rats undergoing 3 hours bout of swimming with 5% body weight attached to their tails, small but significant increases in cTnT levels were observed 2 hours after completion of physical exertion.[40] The exercise-related elevations of cTnT disappeared by 24 hours post-exercise. In addition, it was found that the time course of troponin elevations was temporally associated with decreases in the specific antioxidant glutathione (GSH) and increases in malondialdehyde (MDA, a marker of lipid peroxidation) myocardial levels, reflecting the presence of oxidative stress during the endurance exercise event. In this context, it is of interest to note the findings of Wagner et al.,[41] who reported that there is no persistent oxidative stress in response to an Ironman triathlon in trained athletes despite an initial increase in oxidative stress marker MDA and conjugated dienes (CD). The authors hypothesized that the results are mainly due to an appropriate antioxidant intake and point to the importance of an adequate intake of nutritive antioxidants to preserve antioxidant responses to ultra-endurance exercise.

In conclusion, the mechanisms of cardiac troponin release in several conditions without overt myocardial ischemia differ significantly from those with obstructive coronary artery disease. These lead to different patterns of troponin increases that can be characterized as a persistence of small elevations or transient minimal increases of cardiac troponin concentrations. Nevertheless, since a certain number of patients with conditions other than ACS display a significant rise and/or fall of cardiac markers mimicking myocardial infarction, the results of cardiac troponin testing in these patients should be interpreted in the context of the presence of CAD risk factors, clinical signs and symptoms, and electrocardiographic findings, as well as, when indicated, angiographic or imaging results.

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