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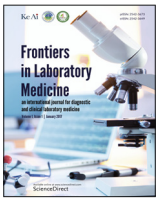

Release of cardiac troponin from healthy and damaged myocardium

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ABSTRACT

Cardiac troponins T and I are proteins released into serum after cardiac injury, and are the standard biomarkers for patients presenting to the emergency department with a suspicion of acute myocardial infarction (AMI). Cardiac troponin that appears in blood within a few hours is due to release from the cytosolic pool. A sustained irreversible release over the ensuing days is due to the degradation of the myofibrils, although recent data have challenged this concept. The analytical sensitivity for troponin assays have significantly improved since the initial release of commercial troponin assays over 20years ago. As a result, the specificity of troponin for AMI has steadily declined, with abnormal concentrations seen in many non-cardiac diseases such as renal failure, sepsis, pulmonary embolism, and cardiac injury after chemotherapy such as with trastuzumab and doxorubicin. There are many theories as to how troponin is released into blood from patients with reversible myocardial ischemia and from patients with cardiac damage that is not related to ischemia. These theories include release of free subunit release through bleb formation, transient imbalance of oxygen supply and demand such as what occurs with acute vasospasm of coronary vessels, pulmonary embolism with right heart damage, apoptosis, acute cardiac stress leading to release of catecholamines and integrins, myocardial stretching, inflammation, and release of degraded troponin peptides. The mechanisms for these etiologies are reviewed.

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Introduction

Troponin is a complex of three regulatory proteins that is bound to tropomyosin and actin, the thin filament of striated muscle. Troponin C binds to calcium, troponin I inhibits actin-activated myosin Mg^{+2}ATPase, and troponin T is the tropomyosin binding protein.[1] Cardiac troponin C has complete amino acid homology with skeletal muscle troponin C and is therefore not used as a cardiac biomarker. Both troponin T and I exist in low concentrations within the cytoplasm.

The Task Force for Universal Definition of Myocardial Infarction has defined several types of myocardial infarction based on the underlying etiology.[2] Under this designation, Type I AMI is characterized by the rupture of a coronary artery plaque with the resultant formation of a thrombus. Type II AMI is characterized by vasospasm or endothelial dysfunction, fixed atherosclerosis with a supply versus demand imbalance, or a supply versus demand imbalance alone. International cardiology and laboratory medicine guidelines have recommended the use of cardiac troponin (cTnT or cTnI) as the standard biomarker for diagnosis of acute myocardial infarction.[2,3] Currently, these markers cannot be used to classify the type of AMI present.

Biomarker release after myocardial injury

Prolonged myocardial ischemia leads to an oxygen deficit and irreversible myocardial necrosis. A deficit in the delivery of blood to myocardial tissues, either due to increased demand or the presence of a ruptured coronary artery plaque causes myocardial ischemia which initiates a cascade of molecular and cellular events.[4] Early oxygen deficits lead to a transition from aerobic metabolism as a source of ATP production, to the less efficient anaerobic pathway. In order to reduce ATP utilization, the myocyte shuts down the ATP-dependent sodiumpotassium membrane pump. The reduced or lack of coronary artery blood flow lead to the accumulation of metabolites such as lactate. These low molecular weight substances are able to pass through the interstitial space directly into the vascular space. The reduced or lack of coronary artery blood flow also leads to the accumulation of metabolites such as lactate and phosphate. By bypassing the interstitium, these ions and metabolies appear in blood with the first few minutes after reversible ischemia. It has been long thought that proteins are not released into the circulation until there is permanent damage to the myocytes. Given the compensatory mechanisms to preserve vital myocardial functions, irreversible injury does not occur for an hour or more. Once released from the cells, macromolecules initially inter the lymphatic system and gradual passage to the circulation, unless there is restoration of coronary artery blood flow through reperfusion, in which case there may be more direct access.

The smaller the protein the earlier that they appear in blood. Thus the order of appearance of cytoplasmic proteins used as cardiac biomarkers are: myoglobin, troponin, creatine kinase, and lactate dehydrogenase. The proteins that are entirely cytosolic in origin, exhibit a mono-phasic release pattern. Proteins such as myosin light chains are found exclusively in the thin or thick filament of muscle have a delayed release due to the gradual breakdown of the sarcomere. Troponin has both cytosolic and structural distributions, therefore following injury, the appearance in blood exhibits a biphasic release pattern. Since the clearance of free troponin once in blood is only 2h,[3] the prolonged appearance of troponin of 57days.

Evidence for reversible myocardial ischemia

The release of cardiac troponin into the circulation does not always follow the classic biphasic pattern as described above. In cases where the initial appearance of troponin is followed by a rapid decline back to baseline concentrations with 24h suggest the absence of permanent myofibril damage. When early generations of troponin assays were used, it could be argued that the analytical sensitivity was insufficient to track the steady decline of troponin following minor myocardial injury (Fig. 1A). With the release of highly sensitive troponin assays, it can be confirmed that the rapid clearance is not the result of assay insensitivity. Therefore, for patients who exhibit a rapid appearance and decline in cardiac troponin, e.g., over 24h, is evidence of reversible myocardial ischemia (i.e., no evidence of structural damage as it would be indicated with the release of intact troponin complexes, Fig. 1B). Permanent irreversible damage would show the biphasic release

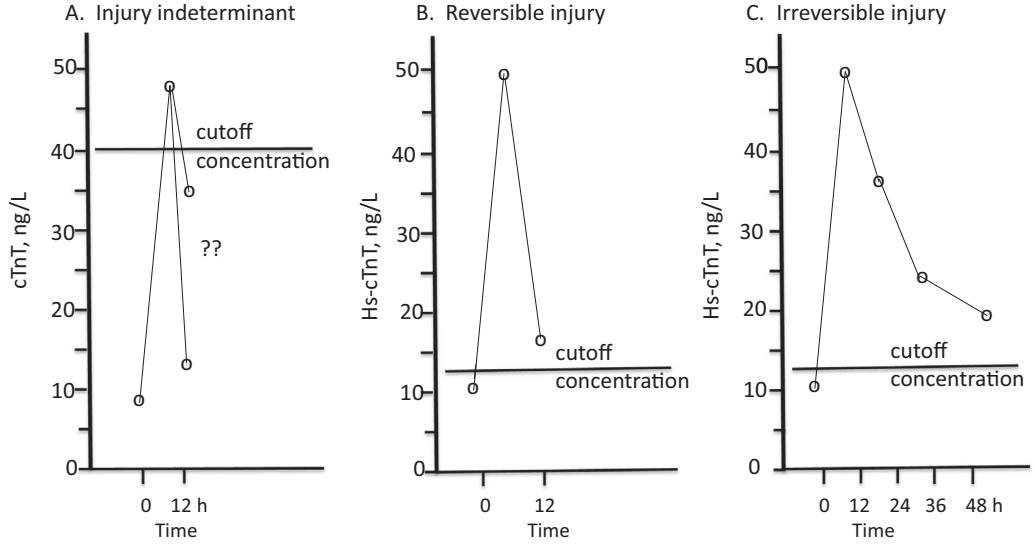

Fig. 1. Transient increase in cardiac troponin in a patient who presents with chest pain. A. Injury indeterminate. Use of a conventional troponin assay with a cutoff of 40ng/L. A peak positive result occurs on the second sample. The subsequent sample 4h later is below the cutoff, i.e., the actual result cannot be accurately measured. B. Reversible injury. The third sample is near the cutoff concentration. C. Irreversible injury. Use of a high-sensitive troponin assay with a cutoff of 13ng/L on the same patient. The third and subsequent samples are above the cutoff concentration.

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