Troponin as a Biomarker for Cardiac Injury

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Introduction

Troponin is the preferred biomarker for detecting cardiac injury and has been used successfully for decades[1,2]. During the 1950s, researchers discovered that human transaminase activity increases following cardiac injury[3,4] and by 1963, Professor Setsuro Ebashi first characterized a new factor[5], together with actin and myosin, that confers Ca^{2+} sensitivity to actomyosin. This new factor was later revealed to exist as a complex between tropomyosin and a novel family of proteins named troponins[5]. After demonstrating that the troponin complex is the Ca^{2+} binding site[6], Ebashi et al characterized the molecular mechanisms of both myocyte contraction and relaxation[7]. Without Ca^{2+}, the contractile interplay between actin and myosin is suppressed by the troponin-tropomyosin complex. However, with increasing Ca^{2+}, this suppression is relieved when Ca^{2+} binds to the troponin complex which in turn initiates contraction[8].

Troponin exists as a complex of three subunits referred to as the I, T, and C tissue-specific isoforms [1,9]. After the amino acid sequence of troponin was determined[10], the troponin complex structure was solved[11] and further explored using X-ray crystallography, NMR, and fluorescence resonance energy transfer[12]. The gene families that encode the troponin subunits are named TnI, TnC, and TnT[13]. Gene expression studies reveal a fast skeletal and a slow-skeletal cardiac isoform of TnC[14,15], and also a fast skeletal, a slow skeletal, and also a cardiac isoform of both TnT and TnI[14,16]. The cardiac isoforms of TnT and TnI are referred to as cTnT and cTnI, respectively, and the concentrations of these proteins serve as biomarkers indicative of cardiac injury[17].

Evidence Supporting the Use of Troponin

Since the early 2000s, cTn has been considered the preferred biomarker for both cardiac injury and cardiotoxicity because it has both a high sensitivity and “nearly absolute specificity”[1]. cTn elevation is correlated with both the disease severity and the patient’s life expectancy[18].

Troponin is considered the “gold standard”[19,20] biomarker for cardiac injuries for not only humans, but all mammals. Several other biomarkers were considered for detecting cardiac injury before troponins were discovered. These included lactate dehydrogenase, creatine kinase, and fatty acid binding protein 3 (FABP3), among others[21–24]. Unfortunately, these alternative biomarkers lack both tissue specificity

and sensitivity[19] and therefore represent less useful biomarkers for cardiac injuries when compared to troponin.

Biomarker Precision

First-generation troponin assays are useful for both prognostic and diagnostic purposes when assessing acute coronary syndrome patients. These troponin assay results can be used to inform triage decisions and to help patients select their preferred treatment option[25,26].

High-sensitivity troponin assays are now available[27–29] to detect the concentrations of the same cTnT and cTnI proteins as the first-generation troponin assays, except these high-sensitivity assays are capable of also detecting cardiac myocyte necrosis[27,28]. Two separate, large studies in emergency departments reveals that these high-sensitivity troponin assays are significantly more accurate than previously-developed assays at detecting acute myocardial infarction[30,31].

This new generation of troponin assays are called “high-sensitivity” if the coefficient of variance (CV) is less than 10% at the 99th percentile of the population being considered[28]. Concentrations below the 99th percentile should be detectable above the assay’s detection limit for greater than 50% of healthy patients in the population being considered.

How this example corresponds with the biomarker ontology and data model

Table 1: *LOINC codes and related lab test information for troponin biomarkers in the Biomarkers project data model*

LOINC Code	Lab Name, Details	Protein
6598-7	Troponin T, Serum/Plasma	Troponin T
10839-9	Troponin; Troponin I; Troponin I, Serum/Plasma Random	Troponin
16255-2	Troponin I Cardiac Units/volume Serum or Plasma	Troponin I
42757-5	Troponin I Cardiac Quantitative Blood	Troponin I
49563-0	Troponin I Cardiac Quantitative Serum or Plasma Detection Limit <= 0.01 ng/mL	Troponin I

10839-9	Troponin; Troponin I; Troponin I, Serum/Plasma Random	Troponin I

How additional illumination could improve their clinical value

With the introduction of high-sensitivity troponin assays[27] comes the challenge of properly understanding the significance of extremely low troponin concentration increases. Specifically, new thresholds likely need to be established for these high-sensitivity troponin assays[32], especially relating to the detection (and possible quantification) of cardiac myocyte necrosis. Additional illumination of clinically meaningful troponin biomarkers could reveal patterns or associations between high-sensitivity troponin concentration measurements and specific cardiac disease states or injuries. Multi-biomarker panel troponin assays could be developed in the future[31] which builds upon the success of the cTn assay.

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