Troponin as a Biomarker for Cardiac Injury

Case Study for the CFDE BiomarkerKB Project

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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.

Exploring Cardiac Injury DO identifiers

Question: which types of cardiac injury to consider? What about cardiac myocyte necrosis (is this considered a cardiac "injury" in the literature?)

Note from Jeremy: we may want to later add UMLS CUIs, or other IDs (e.g. ICD10). DO is not included by UMLS, but the DO team provides a mapping.

Cardiac troponin tests detect a wide array of conditions leading to heart muscle injury, not just myocardial infarction (heart attack). These include conditions like:

- acute coronary syndrome (ACS)
- myocarditis
- Sepsis
- heart failure
- pulmonary embolism
- renal failure
- myocardial contusion

The conditions detected via troponin testing are associated with different Disease Ontology (DO) IDs; however, identifying a single DOID for all cardiac injuries detectable by troponin testing is not possible because there are many distinct conditions.

Conditions associated with elevated cardiac troponin levels:

Cardiac Inflammatory and infiltrative Diseases

- Myocarditis [**DOID: 0014664**]

Ischemic Heart Disease:

Acute Coronary Syndrome (ACS), which includes unstable angina and myocardial infarction.

- Myocardial Infarction (type I and Type 2), Type 1 is an ACS; Type 2 is an imbalance due to conditions like tachycardia, hypotension, or severe blood loss. [**Acute Myocardial Infarction DOID:0060001]**
- Unstable angina, insufficient oxygen supply to the myocardium. Best to use the DO entry for coronary artery disease **[DOID:3393]**

Aortic dissection - inner layer of main artery (aorta) tears. [**DOID 10729**]

Non-Coronary Conditions:

- Heart failure [**DOID:0060122, also DOID 2914**]
- Pulmonary Embolism [**DOID:13284**]
- Sepsis [**DOID:0004058**]
- Renal Failure (Kidney Failure) - elevated troponin levels are common in patients with kidney failure, making it the preferred biomarker. [**Chronic kidney disease DOID:8996**]
- Takotsubo cardiomyopathy - broken heart syndrome, excessive release of stress hormones, or catecholamines, is believed to damage heart muscle. [**DOID: 4336**]
- Cardiac contusion, damage to the heart muscle from blunt chest trauma [**DOID:365**]
- Pericarditis, inflammation of the thin, sac-like tissue surrounding the heart [**DOID:821**]

For Troponin I: The primary UniProt ID for human Cardiac Troponin I is **P19429** (for the TNNI3 gene), but other UniProt IDs exist for different Troponin I isoforms and species, such as P19237 for slow skeletal muscle troponin I and P48788 for fast skeletal muscle troponin I.

For Troponin T: The main UniProt ID for human Troponin T, cardiac muscle, is **P45379**. This entry, designated as TNNT2_HUMAN, corresponds to Troponin T Type 2, a component of the cardiac muscle troponin complex involved in muscle contraction.

Below are the most-common Troponin T and Troponin I LOINC Codes:

Troponin T LOINC Codes

LOINC 6598-7:

Troponin T.cardiac [Mass/volume] in Serum or Plasma.

LOINC 89576-3:

Troponin T.cardiac panel - Serum or Plasma by High sensitivity method.

LOINC 89575-5:

Troponin T.cardiac [Interpretation] in Serum or Plasma Qualitative by High sensitivity method.

Troponin I LOINC Codes

LOINC 10839-9:

Troponin I.cardiac [Mass/volume] in Serum or Plasma.

LOINC 89577-1:

Troponin I.cardiac panel - Serum or Plasma by High sensitivity method.

LOINC 89578-9:

Troponin I.cardiac [Interpretation] in Serum or Plasma Qualitative by High sensitivity method.

Table 1: Diseases and their associated LOINC codes and Troponin Uniprot IDs

Disease Name	DOID	LOINC Code(s)	Troponin(s) T, I, or Both	Uniprot ID(s)
Acute Myocardial Infarction	DOID:0060001	LOINC LA24436-0	T or I or Both	P19429, P45379
Unstable angina	DOID:3393	High Sensitivity Troponin T: 89576-3, 89575-5 High Sensitivity Troponin I: 89577-1, 89578-9	T or I or Both	P19429, P45379
Aortic dissection *Note: not for diagnosis*	DOID 10729	Any of the 6 Troponin LOINC codes.	T or I or Both	P19429, P45379
Heart failure	DOID:0060122, also DOID:2914	Any of the 6 Troponin LOINC codes.	T or I or Both	P19429, P45379
Pulmonary Embolism	DOID:13284	High-sensitivity Tropon I or Troponin T preferred, so 89576-3, 89575-5, 89577-1 and 89578-9	T or I or Both	P19429, P45379

Sepsis	DOID:0004058		T or I or Both	P19429, P45379
Chronic Kidney disease	DOID:8996		T or I or Both	P19429, P45379
Takotsubo cardiomyopathy	DOID:4336		T or I or Both	P19429, P45379
Cardiac contusion	DOID:365		T or I or Both	P19429, P45379
Pericarditis	DOID:821		T or I or Both	P19429, P45379

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