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Review Article

Cardiac troponins: Current status

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ABSTRACT

The use of biomarkers in a variety of conditions is aimed at rapid and precise diagnosis leading to timely treatment. The evolution of cardiac troponins and more recently high sensitive troponin assays allows both prompt identification of ACS and earlier discharge of nonischemic chest pain patients. Moreover, there is increasing evidence of prognostic importance of troponins in nonischemic cardiac conditions such as heart failure and AF as in noncardiac conditions such as sepsis and COPD and more recently in the general healthy population. With the increasing scientific data backing troponins, it is the best contemporary available assay closest to " the ideal biomarker ".

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1. Introduction

10–15% of ED patients or approximately 10 million patients in the United States annually present with chest pain or other signs suggestive of myocardial ischemia, but a final diagnosis of ACS can only be made in 15–25% of them, which overall represents the 2–5% of all incomers.[1] Since ACS is a potentially fatal condition with outcome tightly coupled to time to revascularization, a delayed or wrong diagnosis can significantly alter prognosis. Wildi et al. demonstrated that a significant increase in morbidity and mortality may be caused by withholding evidence based therapy including antiplatelet therapy, rhythm monitoring for 48 h and early revascularization.[2] Herein comes the role of a biomarker which is defined as any measurable, surrogate characteristic, which reflects either the presence or the absence of a disease state. The role of a biomarker in such patients is to assist in the early diagnosis and risk stratification of patients presenting with symptoms suggestive of ACS. In this article, we shall discuss the current role of cardiac troponins.

The ideal biomarker of MI should provide early detection of myocardial injury, provide rapid, sensitive and specific diagnosis for an AMI with determination of timing of infarction and infarct size and serve as a risk stratification tool in acute coronary syndromes (ACS). In addition, it should assess the success of reperfusion after thrombolytic therapy, detect reocclusion and reinfarction t determine the timing of an infarction and infarct size and detect procedural-related perioperative MI during cardiac or noncardiac surgery. Till date, no such ideal biomarker exists but the quest starting from 1955 has brought us progressively closer to this goal. In 1955, Karmen et al. first reported elevated AST from necrotic cardiac tissue but it was found to have low specificity.[3] Subsequently, discovery of other nonspecific markers namely LDH and CK followed by relatively specific CKMB led to the 1979 WHO definition of MI including rise and fall of biomarkers (AST, LDH and CKMB) as one of the three criteria.[4]

The history of troponins dates to its discovery by Professor Ebashi in 1963.[5] In 1971, Greaser and Gergely demonstrated that the troponin complex consisted of 3 components. The next 10 years witnessed extensive research including amino acid sequencing

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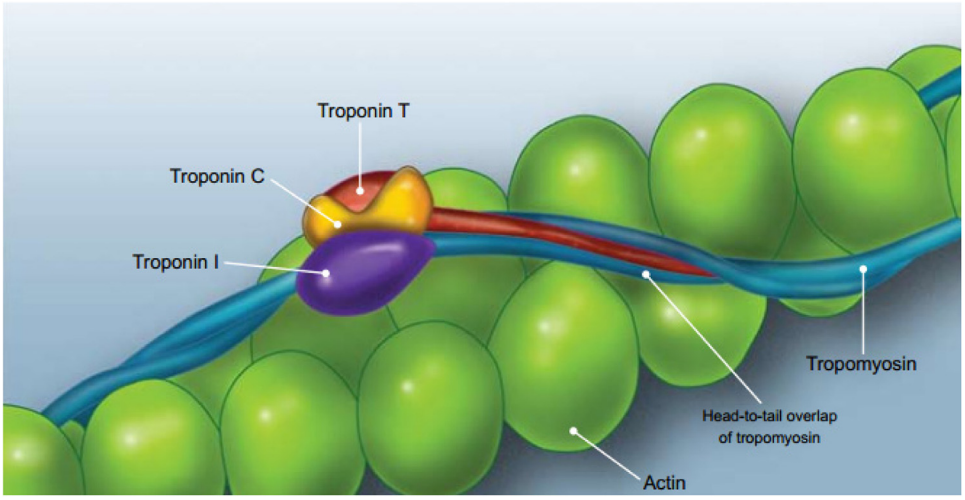

Fig. 1. Schematic Figure.

followed by nuclear MR and X-ray diffraction to elucidate the complete structure of troponin. The revelation of multiple distinct isoforms of troponin in different tissues promoted interest in their role as cardiac biomarkers. In 1987, Cummins developed the first RIA for detection of cTnl in serum. 3 years later, monoclonal antibodies against cardiac troponin was developed which is the basic principle behind all current assays. The first commercial cTnl assay for the Stratus I analyzer (Dade Behring) appeared in 1996. In parallel, the first cTnT immunoassay based on an ELISA with 2 antibodies was developed by Katus and colleagues in 1989. Studies have shown that both cTn T and Tnl are equally efficacious in detecting myocardial injury.[6] With its high specificity, cardiac troponins became the only accepted biomarkers for Ml and in 2000, the 3rd universal definition of Ml necessitated the detection of a characteristic rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia, ECG changes or imaging evidence of new loss of viable myocardium or intracoronary thrombus.[7]

The cardiac troponin complex is a tadpole shaped group of 3 proteins that regulate interaction between actin and myosin, the cardiac contractile proteins. (Fig. 1) Trop T binds to tropomyosin which keeps actin in an inactive state. Trop I is the inhibitory component binding to actin and prevents actin-myosin coupling. When Ca2+ enters the cell/Trap C binds to Caz+ and causes a conformational change allowing actin-myosin interaction. Two pools of troponin exist – a small cytosolic PQQJ (5%) that is released upon initial myocardial injury and a second pool bound to myofilaments that offers sustained release only on irreversible cell death. Trop C found in type 2 skeletal muscle and cardiac muscle is identical and hence not used as a cardiac marker.

Over time, the troponin assays underwent progressive technical modifications through 4 generations to become increasingly sensitive (Table 1). Also, the incidence of false positive reports due to improper calibration, heterophile antibodies and endogenous interfering substances (such as bilirubin and haemoglobin) has been significantly reduced. The hs cardiac Trop T assay is a fifth generation test implemented in 2010 that is able to accurately measure 10- fold lower concentrations of cardiac troponin than contemporary assays (threshold of 3 ng/l).Assays are defined as high sensitivity if they fulfil the following two conditions: 1) a coefficient of variance less than 10% at the 99th percentile value of the reference healthy population and 2) concentrations above the assay's limit of detection are measurable in greater than 50% of healthy individuals (as opposed to conventional cardiac troponin assays that detect cardiac troponin in less than 35% of a normal population).[8] High sensitive cardiac troponins not only have increased sensitivity and specificity but also have faster result times. A study comparing hs cTn and conventional troponin assay by Ru-Yi Xu et al. showed that these theoretical advantages may translate into difference between life and death in patients presenting early after onset of chest pain.[9] While cardiac Trop T (both conventional and hs assay) is under patent of a single manufacturer, Trop I assays are provided by numerous manufacturers with different antibodies and hence not standardized. Therefore, the ESC guidelines necessitate the determination of thresh old, reference and change values for each assay.[7] Newer ultra-sensitive assays that measure cardiac troponin at levels below the minimum detectable levels in healthy persons are being tested in post chemotherapy and exercise stress testing situations.

The 2015 European Society of Cardiology(ESC) guidelines provide a class I recommendation for both a 0-h/1-h rapid-rule out and rule-in protocol and a0-h/3-h rapid rule-out sampling protocol (Fig. 2). Serial measurement of troponins categorises patients into rule out, rule in and observational groups. The observational group has to be evaluated depending on clinical suspicion as there is a prevalence of 8-16% of Ml in this group. The

Table 1
Main features of the diagnostic assays for cardiac Trop I from the origin to the present.

Generation	Availability	Limit of detection (ng/L)	Detection in a 'normal' population (%)	Recommended time to testing after T0 (hours)
First	Late 80s'	500	0	12–24
Second	Late 90s'	100	0	12
Third ('contemporary' sensitive)	2000–2007	20–50	0–35	3–6
Fourth (high sensitive)	2012	1–3	>50	1–3
Fifth (ultra-high sensitive)	Research	0.2	>95	NA

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