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Review

Increasing specificity of high-sensitivity troponin: New approaches and perspectives in the diagnosis of acute coronary syndromes

Maria Giulia Marini (MD), Maria Teresa Cardillo (MD), Annalisa Caroli (MD), Chiara Sonnino (MD), Luigi M. Biasucci (MD)*

Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy

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ABSTRACT

In the past years, new generations of assays to detect cardiac troponin (cTn), called sensitive or high sensitivity troponin (hs-Tn), have been introduced. Progressive improvement in the analytical sensitivity of cTn assays has led to a more rapid diagnosis of acute myocardial infarction (AMI) and improved risk stratification in patients with non ST-elevation acute coronary syndromes (NSTE-ACS) but, at the same time, has introduced the problem of a lower diagnostic specificity. As a matter of fact, hs-Tn assays are able to detect very small increases in the biomarker concentration and therefore result "positive" in a wide range of non-ischemic clinical conditions, acute and chronic, cardiac and extra-cardiac. The reduced specificity of hs-Tn versus the previous generation cTn assays may, therefore, lead to an increased number of inappropriate hospitalizations, i.e. patients with high cTn due to no-ACS conditions, and requires a more careful evaluation, not only on the clinical side, but also on the information that hs-Tn assessment may provide. Several approaches to increase this specificity have been used, but the most promising appear to be the "delta approach", which tries to quantify the relative or absolute change in cTn concentration, and the "age approach", which highlights the need for a different cutoff with a better diagnostic efficiency in the elderly population, often affected by other conditions, different from ACS, that can cause an increased level of cTn.

Contents

Introduction

Cardiac troponins (cTn) are regulatory proteins that play a pivotal role in the process of interaction between actin and myosin, controlling contraction and relaxation of skeletal and cardiac muscle. This complex is formed by three different proteins, bound to the thin filaments of the muscle: troponin C (cTnC), which binds calcium; troponin I (cTnI), which inhibits actin–myosin interactions; troponin T (cTnT), which binds the troponin complex to tropomyosin and facilitates contraction. cTnC is expressed by cells in both cardiac and skeletal muscle, in contrast cTnI and cTnT are unique to cardiac muscle, therefore they can be used as specific biomarkers for myocardial damage. CTn are released into the blood

* Corresponding author at: Istituto di Cardiologia – Policlinico A Gemelli, L.go Gemelli, 8, 00168 Roma, Italy. Tel.: +39 0630154187; fax: +39 063055535.
E-mail address: lmbiasucci@virgilio.it (L.M. Biasucci).

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stream after myocardial damage, first from an "early appearing" myocyte pool and subsequently from a structural pool [1]. In the past 10 years cTn have been identified as the preferred marker for acute myocardial infarction (AMI) [2,3] because of their specificity for cardiac muscle and sensitivity. The third universal definition of MI [4], in fact, establishes that the diagnosis of AMI is based on a rising and/or falling pattern of cTn serum concentrations with, at least, one value above the 99th percentile limit of the reference value distribution. However, an increased level of cTn is necessary, but not sufficient, for the diagnosis of AMI, that also requires clinical features of myocardial ischemia, indicated by symptoms of ischemia, electrocardiographic changes indicative of new ischemia, development of pathological Q-waves, or imaging evidence of the new loss of viable myocardium or new regional wall motion abnormalities [4].

The first assays for measurement of cTn appeared in 1991 [5] and since then a number of assays have been studied and introduced in clinical practice. However, the earlier assays were characterized by an insufficient precision at very low levels of cTn concentration [expressed as coefficient of variation (CV) > 20% at the 99th percentile]. Over time cTn assays have had a significant evolution, leading to more and more sensitive assays, with the aim of allowing a faster and more reliable diagnosis of AMI [6–8].

Characteristics and advantages of new high sensitivity assays

New generations of assays to detect cTn have been called sensitive or high sensitivity troponin (hs-Tn) and are able to measure cTn concentrations approximately 10- to 100-fold lower than conventional assays, allowing a more accurate measurement in particular at very low concentrations. To be defined as hs-Tn, an assay should meet two criteria: first, the imprecision (CV) at the 99th percentile value should be ≤10% ("guideline acceptable"), although assays with an imprecision >10% and ≤20% are still "clinically usable" [7]. Second, the assay should be able to measure cTn concentrations below the 99th percentile in ≥95% of normal individuals [7].

Only six new hs-Tn assays potentially meet these criteria: five hs-TnI assays (Abbott ARCHITECT, Beckman Access, Nanosphere MTP, Singulex Erenna, Siemens Vista) and the Roche hs-TnT assay, that is commercially available worldwide, except in the USA [7,8].

The introduction of hs-Tn has led to an earlier and more accurate diagnosis of non ST-elevation acute coronary syndromes (NSTE-ACS), reducing the risk of missing subjects with ACS and improving the rule out. Previous guidelines for the diagnosis of NSTE-ACS recommended a second sampling at 6 h to confirm or exclude such a condition [9], on the contrary, several studies have supported a reduction of the sampling interval from 6 to 3 h with hs-Tn, allowing a comparable efficacy and a reduction in unnecessary hospitalizations and of observation time [8–12]. As a consequence, current European Society of Cardiology guidelines on management of NSTE-ACS recommend to reduce the minimal time between two consecutive blood samples from 6 h to 3 h [13,14].

More sensitivity, less specificity: the need to evaluate other causes of cardiac troponin elevations

Progressive improvement in the analytical sensitivity (SE) of cTn assays has led to a more rapid diagnosis of AMI [11,12] and improved risk stratification in patients with NSTE-ACS [15,16], but, at the same time, has introduced the problem of a lower diagnostic specificity (SP). It is of remarkable importance to consider that the specificity of cTn as marker of AMI, caused by myocardial ischemia, is different from the specificity as a marker of myocardial damage that could be due to other mechanisms. As a matter of fact, hs-Tn assays are able to detect very small increases in the biomarker concentration and therefore result "positive" in a wide range of non-ischemic clinical conditions, acute and chronic, cardiac and extra-cardiac, such as pericarditis, myocarditis, Tako-tsubo syndrome, tachyarrhythmias, heart failure, pulmonary embolism, stroke and sepsis [17,18] (Table 1), thus current guidelines recommend that, to make a diagnosis of ACS, it is necessary to observe a rise and fall in hs-Tn. However, this pattern could also be found in acute conditions other than ischemic heart disease; the most common causes of acute elevations of cTn are acute pericarditis and myocarditis, tachyarrhythmias and acute pulmonary embolism (Table 1). Persistent, but without a rise and fall pattern, elevation of hs-Tn can be found in patients with stable coronary artery disease (CAD), chronic renal failure, chronic heart failure (CHF) and severe left ventricular hypertrophy: these conditions must be differentiated from ACS [19] (Table 1). The need for differentiation of true "thrombotic" MI from other causes of myocardial damage has been emphasized, with some excess, also in the recent "third definition of MI" [4].

The reduced specificity of hs-Tn versus the previous generation assays may, therefore, lead to an increased number of inappropriate hospitalizations, i.e. patients with high cTn due to non-ACS conditions, and requires a more careful evaluation, not only on the clinical side, but also of the information that hs-Tn assessment may provide.

Reducing uncertainty in ACS diagnosis: the "delta approach"

The most frequently used approach for a correct evaluation of hs-Tn is the "delta approach" that tries to quantify the magnitude of concentration changes (δ) in cTn values, obtained by serial measurement and calculated with the following equation: $\delta = C_{max} - C_{baseline}$.

Table 1
Causes of cardiac troponin elevation other than ACS.

Damage related to supply/demand imbalance of myocardial ischemia
√Tachy- or bradyarrhythmias
√Aortic dissection and severe aortic valve disease
√Cardiogenic, hypovolemic or septic shock
√Hypertrophic cardiomyopathy
√Severe respiratory failure
√Severe anemia
√Hypertension with or without LVH
√Coronary embolism or vasculitis, e.g. systemic lupus erythematosus, Kawasaki syndrome
√Coronary spasm
√Coronary endothelial dysfunction without significant CAD, e.g. cocaine abuse
Damage not due to myocardial ischemia
√Cardiac contusion
√Cardiac incisions with surgery
√Radiofrequency or cryoablation therapy
√Pacing or defibrillator shocks
√Rhabdomyolysis with cardiac involvement
√Myocarditis
√Cardiotoxic agents, e.g. anthracyclines, herceptin, carbon monoxide poisoning
Multifactorial causes of myocardial damage
√Heart failure
√Takotsubo cardiomyopathy
√Severe pulmonary embolism or pulmonary hypertension
√Renal failure
√Severe acute neurological diseases, e.g. stroke, trauma
√Infiltrative diseases, e.g. amyloidosis, sarcoidosis
√Extreme exertion
√Sepsis

ACS, acute coronary syndrome; LVH, left ventricular hypertrophy; CAD, coronary artery disease.