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The Role of High Sensitivity Troponin: More Acute Coronary Syndromes or More False Positive Results?

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ABSTRACT

Cardiac troponins (cTn) are the most sensitive and specific biomarkers of myocardial damage. Troponin has both diagnostic and prognostic significance for acute coronary syndrome (ACS). The joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation task force recommendations for a universal definition of acute myocardial infarction (AMI) in 2007 are based on detection of cTn and associated clinical evidence. Although the clinical introduction of new generation high sensitivity cTnT and cTnI assays is certainly valuable in the appropriate setting, its widespread use in a variety of clinical situations may lead to the detection of cTn elevation in absence of thrombotic ACS. Until now there is no clarity between "sensitive" and "high sensitive" cTn assays something that raises concerns regarding the interpretation of the latest clinical studies. The increased analytical sensitivity against compromised specifity may increase "false positive" results in patients with cardiovascular disease or apparently healthy subjects with previously undetected cTn levels. A cTn rise in the absence of ACS should prompt for an assessment for a different, non-ischemic mechanism of troponin elevation and direct management at the primary cause. The role of the clinician is to apply clinical doubts where abnormal cTn levels are not due to myocardial injury. The current strategy of management of such patients is based on established algorithms and clinical knowledge.

KEY WORDS: *high sensitivity troponin assays; acute coronary syndrome; myocardial infarction; differential diagnosis*

Abbreviations
ACS = acute coronary syndromes
AMI = acute myocardial infarction
cTn = cardiac troponin
CV = coefficient of variation
ECG = electrocardiogram
ESC = European Society of Cardiology
hs-cTn = high sensitivity cardiac troponin
URL = upper reference limit

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Cardiac troponins I (cTnI) and T (cTnT) have been documented as the preferred biomarkers for the recognition of myocardial damage, in the diagnosis of myocardial infarction and risk stratification of patients presenting with symptoms of acute coronary syndrome (ACS).[1] The recently released guidelines from the European Society of Cardiology (ESC) emphasized again the use of the 99th-percentile value derived from a reference population as the clinical-decision threshold, using an assay with an imprecision (coefficient of variation, CV) of ≤10% at the upper reference limit (URL).[2] Thus, only one in a hundred healthy people will have a result above this and even then it will not be more than a few units higher. Until recently however, there was no clinically available assay capable of consistently achieving this recommended precision. Additionally, since the troponin concentration cut off is influenced by the analytic precision and sensitivity of the assay and diverse troponin assays have diverse

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performance features, interpretation of troponin results often varies among institutions.[3,4]

The continuously improved analytic performance of troponin tests has led to the advent of "sensitive" and "high sensitive" troponin assays. Although there is no consensus regarding the definition of an hs-cTn assay it has two differentiating features from contemporary cTn assays: 1) detection of cTn in healthy persons and 2) a precise definition of what is "normal" (= the 99th percentile).[5] Its unique ability is to measure troponin concentrations in populations with previously undetectable levels. For example, the 99th percentile value for the first-generation troponin T assay was 0.06 μg/L, which was reduced to 0.01 μg/L by the fourth-generation assays.[6] Now the fifth generation high sensitivity troponin assay can measure troponin concentrations approximately 10-fold lower than conventional assays, and as a result, the 99th percentile concentration continues to decrease.[7] Although criteria are not established at this time, some suggested characteristics might be:

1. Capability to generate credible measurements for most samples (>80%) of a normal reference population.
2. The required cTn quantity relevant to a CV of the total error of <10% is significantly lower than the 99th percentile of the normal reference population.[8]

A classification based on the analytical imprecision at the 99th and the % of reference subjects showing detectable values has been proposed. This schema suggests that immunoassays should be classified as guideline acceptable if inaccuracy is <10%, clinically usable if it is between 10%-20% and non-acceptable if >20%. Depending on their analytical sensitivity and imprecision characteristics, contemporary and high-sensitivity cardiac troponin assays are classified into one of 4 categories: <50%, 50%-75%, 75%-95%, and >95%.[9] At the present time, there are 23 cardiac troponin assays available (21 for cTnI, 2 for cTnT) from 14 manufacturers.[10] According to the above mentioned characteristics, none of the current cTn methods could be denominated as high-sensitive.[9] This raises some serious concerns since a clinical study that uses cardiac troponin cannot be comprehended from a reader in terms of content, value, impact and generalizability, without identifying the exact cardiac troponin immunoassay used and its performance characteristics.[10] Additionally the implementation of a credible meta-analysis for the assessment of cardiac troponin utilization cannot be conducted if the particular troponin assay used in each study included is unknown. This is an acceptable method to ensure that only data from equivalent troponin assays are shared.

A recently published study determined that lowering the diagnostic threshold of cTn for diagnosis of acute myocardial infarction (AMI) could reduce morbidity and mortality. However, the biggest challenge of lowering the diagnostic threshold of cTn for AMI would be a greater number of patients with elevated cTn, including those due to non-ACS thrombotic causes.[11] A range of sometimes unknown mechanisms can cause non-thrombotic myocardial tissue injury and a rise of cardiac troponin and an excess of non-coronary situations can also lead to troponin elevation, but they usually do not follow the characteristic escalation pattern of an AMI and the accompanying clinical, ECG and imaging standards.[12] In other words, increased cTnI or cTnT values alone are unable to indicate the pathophysiological mechanism underlying the detected myocardial damage, which may be unrelated to ischemia. Therefore, an increased marker value, without clinical indication of myocardial ischemia, should prompt for a search for other causes of cardiac damage (Table 1).

Amongst others, the anticipated causes for non-ACS cTn elevation comprise autonomic nervous system disorders, with subsequent excess of sympathetic activity and increased catecholamine effect on myocardial cells;[13] straight myocardial-cell damage by traumatic or inflammatory development; volume and pressure overload, causing an extreme intensification in wall tension with secondary myofibrillary damage;[14] and reduced renal excretion.[15] Occasionally the result of inflammatory cytokines or oxidative stress, myocardial hibernation, or apoptosis might be elevated cTn. Another important issue is assay interference with heterophilic antibodies which through hemolysis can lead to false- positive troponin elevations.[12] It is estimated that heterophilic antibodies cause about one false result in every 2000 investigations with modern immunoassays.[16] To minimize the occurrence of false-positive troponins, non-specific blocking antibodies have been added to modern assays to reduce interference with the results.

Recently, Eggers et al reported a ~7% of misclassified with AMI diagnosis (i.e., false positivity rate) troponin-positive patients with preexisting ST-T segment abnormalities, admitted for non-ACS chest pain or other symptoms indicative of myocardial ischemia.[17] Accordingly, several studies have validated that hs-cTn assays increased the number and promptness of ACS diagnosis, but also increased the amount of false positives, that is, non-ACS-related origin.[18,19] Hence, with hs-cTn assays, even the healthiest of people will demonstrate measurable troponin concentrations, and this has a direct effect on the application and interpretation of the 99th percentile as a cutoff. Although studies using this cutoff for myocardial infarction with hs-cTn have demonstrated excellent sensitivity compared with conventional cTn assays, the diagnostic specificity for AMI[20] has decreased, with the prevalence of positive results nearly doubled in the emergency room setting. For instance, Kavsak et al have indicated that it is unclear, when using hs-cTn assays, whether the 99th percentile cut-off derived from a younger/healthy population is appropriate for the stated use according to the universal definition of AMI, or an aged matched population would be the most appropriate.[21] Similarly Potter et al have found a transient troponin rise in apparently healthy young children assessed on 3 separate occasions with hs-TnT assays more due to an infective etiology

TABLE 1. Acute Troponin Elevation in Non-Thrombotic Situations

Trauma (including contusion, ablation, pacing, implantable defibrillator firings, cardioversion, cardiac biopsy, cardiac surgery)
Acute and chronic congestive heart failure
Aortic valve disease, hypertrophic, obstructive cardiomyopathy with left ventricular hypertrophy
Hypertension- Hypotension with arrhythmias
Tachyarrhythmias
Postoperative non-cardiac surgery
Renal failure
Critical illness – especially diabetes, respiratory failure, GI bleeding, sepsis
Drug toxicity (adriamycin, 5-Fluorouracil, herceptin, snake envenomation, carbon monoxide poisoning)
Hypothyroidism
Abnormalities in coronary vasomotion – including coronary vasospasm
Apical ballooning
Inflammatory disease – myocarditis, parvovirus B19, Kawasaki Disease, sarcoid, myocardial involvement in bacterial endocarditis
Uncomplicated percutaneous coronary intervention (PCI)
Pulmonary embolism, pulmonary hypertension
Sepsis
Burns – particularly when surface area >30%
Infiltrative disease affecting myocardium – amyloidosis, hemochromatosis, sarcoid, scleroderma
Acute neurological disease – e.g. stroke, subarachnoid hemorrhage
Rhabdomyolysis with cardiac injury
Transplant vasculopathy
Vital exhaustion

TABLE 2. Recommended Protocol for Troponin Testing Using High Sensitivity Assays in "Ruling-Out" Acute Coronary Syndrome (ACS)

All patients with a suspected ACS should undergo troponin testing on arrival at ED to 'rule in' ACS within the differential diagnosis
For a patient with a positive troponin result or a change in troponin levels over time, neither ACS nor other significant pathology (e.g. pulmonary embolus, aortic dissection, and sepsis) can be excluded. These patients are at higher risk of subsequent events. A positive result should be considered within the entire clinical context (history, examination, ECG findings and other investigations). Further investigations directed at all plausible clinical diagnoses should be considered and, if ACS is thought to be the likely cause, these patients may require cardiology assessment.
All patients with a negative result should undergo repeat testing 3–4 hours later.
The testing interval to 'rule out' MI may be reduced to 3 hours, provided that one sample is taken at least 6 hours after symptom onset.
Patients with a negative result at 3 hours after presentation and at least 6 hours after the onset of pain should be considered for early assessment by non-invasive anatomic or functional testing, as determined by local availability.
For patients presenting more than 6 hours after pain onset, a single high sensitivity troponin assay is sufficient to rule out myocardial infarction in the absence of on-going chest pain.

ECG = electrocardiogram; ED = emergency department; MI = myocardial infarction

than of cardiac origin.[22]

The utilization in clinical practice of the new highly sensitive troponin assays is a trade-off and, it is unclear if they will lead to increased clarity or more confusion for most physicians.[23] Existing data clearly suggest that they will allow earlier diagnosis of AMI (within 1–2 hours after thoracic pain onset), as well as recognition of very small (focal) areas of myocardial necrosis, without avoiding also the detection of non-ischemic causes of cardiomyocyte necrosis related to various diseases, which challenges the clinician to differentiate them (Table 2).[4] It is stated that the larger the rise in high-sensitivity cTn within the first few hours in the emergency department, the higher the probability that it is AMI.[5]

Serial changes documented by a second sample earlier than previously recommended, e.g. after 2 hours rather than after 6 hours, accelerate the diagnostic process and help to differentiate acute cardiac disorders (showing a rise and/or fall) from chronic cardiac disease which usually exhibit constant cTn levels.[25] It is a matter of debate whether absolute or relative changes best separate acute from chronic cTn elevations, as well as AMI from other causes of cTn elevation even if preliminary data suggest that an absolute change in hs-cTn level appears to improve diagnostic performance.[25] For emergency room physicians faced with disposition decisions, the question is not so much about whether the patient experienced an acute myocardial infarction but rather what their risk of a pending cardiovascular episode is. Earlier decision making should result in earlier treatment or to earlier triage to an invasive strategy, whereas a repeated normal level at an earlier time point than currently recommended may lead to

earlier discharge of patients with the consequent improvement of health outcomes and profound cost savings on the care of suspected ACS patients.

In conclusion, there is evidence that it is problematic to reliably diagnose ACS in patients with suspicious chest pain syndrome based only on one sample measurement of cTnI or cTnT due to the relatively low specificity of existing cardiac troponin assays for ischemic myocardial injury.[26] Clinical judgment and ECG findings integrated into algorithms with the inclusion of hs-cTn have been proposed to be useful tools for the management of patients admitted to an emergency department with suspected ACS.[12] The new generation of high sensitivity troponin assays can better define the true normal levels and the 99th URL, facilitating better risk stratification of patients who do not have increased troponin by current assays and may allow risk stratification of patients with chronic stable angina and patients with heart failure.[28] Research progress and development has led to the advent of a multimarker approach for the diagnosis of ACS based on the combination of selected biomarkers which seems to add incremental predictive value to further risk stratification in an otherwise seemingly homogeneous non-ST elevation ACS population.[29] All these data pave the way for adaptation of treatment options that can offer benefit to patients recognized to be at increased risk, which will eventually improve patient outcome.

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