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EDITORIAL

High Sensitivity Cardiac Troponins: a Curse or a Blessing?

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ABSTRACT

The use of cardiac troponins (cTn) in lieu of creatine kinase to diagnose myocardial infarction (MI) has allowed us to detect even the smallest myocardial damage. Recently the use of high-sensitivity assays to measure even the tiniest myocardial injuries has led to a substantial increase in the diagnosis of MI. However, the specificity of such tests has been compromised and false positive results are rising. Clinicians should be aware that elevated cTn may be encountered in a variety of conditions of non-thrombotic cardiac damage, but also in a plethora of non-coronary diseases and laboratory interferences. These caveats are herein overviewed and an algorithm is proposed of a step-wise approach to using cTn measurement to triage and manage patients with suspected acute coronary syndromes.

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KEY WORDS: *acute coronary syndrome; cardiac troponin; high-sensitivity troponin assay; myocardial infarction; chest pain syndromes*

LIST OF ABBREVIATIONS:
ACS = acute coronary syndrome(s)
BNP = brain natriuretic peptide
CABG = coronary artery bypass grafting
CK = creatine kinase
cTn = cardiac troponin
ECG = electrocardiogram
LBBB = left bundle branch block
MI = myocardial infarction
NSTEMI = non-ST-elevation myocardial infarction
PCI = percutaneous coronary intervention
URL = upper reference limit

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Triage of patients with chest pain in the emergency departments in a timely fashion by identifying those with acute coronary syndromes (ACS) is crucial for delivery of appropriate medical or interventional therapy and avoidance of catastrophies.[1,2] In addition to clinical, ECG and imaging data, use of an ideal biomarker would expedite the process of early diagnosis, risk stratification and management of such patients.[1-4] The recent introduction of high-sensitivity cardiac troponin (cTn) I or T assays aspires to achieve just that, i.e. to provide greater accuracy for diagnosis of ACS, but the question remains how well these assays can implement this task.[5,6] As the sensitivity of detecting cardiac troponin rises, the specificity declines and this poses several problems.[7] The introduction of such highly sensitive assays can effectively identify cardiac troponins in almost all patients with chronic coronary artery disease,[8] but also in healthy individuals, thus the major concern now remains how to define normal levels and establish clinically useful cutoffs. A higher threshold to diagnose myocardial infarction (MI) may be needed when using these newer assays.[7] The current consensus criteria propose a *typical rise and/or fall* above the 99th percentile of the upper reference limit (URL) in cardiac troponins in addition to other symptoms and signs of ischemia for the diagnosis of acute MI.[9] There may be an exception to the rise and fall pattern if the patient presents >24 hours after the onset of chest pain. Troponin values may remain elevated for up to 4-7 days for troponin I and 10–14 days for troponin T following the onset of MI.[10] In addition to aiding the diagnosis, cardiac troponins are also useful for risk stratification;[4,11] current guidelines recommend an early interventional approach in high-risk ACS patients as based on elevated cardiac troponin level.[3]

Although cardiac troponin is the most sensitive and specific biomarker of myocardial injury, it does not necessarily mean that the cause of such injury is an acute

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MI. Non-thrombotic myocardial tissue damage by a variety of mechanisms can raise cardiac troponin and a plethora of non-coronary conditions can also lead to troponin elevation (Table 1),[12,13] but they usually lack the typical rise and fall pattern of an acute MI and the *associated clinical, ECG and imaging criteria*. Thus, an elevated troponin in the absence of clinical evidence of ischemia, should lead to a search for other etiologies of myocardial necrosis, such as acute perimyocarditis, pulmonary embolism, aortic dissection, acute heart failure, renal failure or other non-ischemic conditions (Table 1).

According to the new definition of MI,[9] only type 1 MI is due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection, while type 2 is due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension. Both types of MI need to fulfill the criteria of troponin rise and fall pattern together with clinical, ECG and/or imaging evidence of ischemia. Conventionally, for MI type 4a (post-PCI) and 4b (stent thrombosis), increases of troponin greater than 3 × 99th percentile URL have been designated as defining PCI-related MI. For type 5 MI (post-cardiac surgery), increases of troponin greater than 5 × 99th percentile URL plus either new pathological Q waves or new left bundle branch block (LBBB), or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.[9]

Acute and chronic heart failure is notorious for its association with elevated levels of cardiac troponin, albeit at relatively low concentrations, which indicate an increased risk of morbidity and mortality in these patients, providing further prognostic information in addition to other conventional clinical and laboratory variables.[14] Again, the typical troponin rise and fall pattern of classical MI is contrasted with the persistent low-level elevation or gradual decline of troponin in heart failure, and, of course the chest pain and typical ECG changes

TABLE 1. Causes of Elevated Cardiac Troponin Levels

Acute MI	Critically ill patients
Coronary vasospasm	Renal failure
Pulmonary edema or heart failure	Strenuous exercise
Acute pericarditis	Chemotherapy (adriamycin, cyclophosphamide, etc)
Myocarditis	Left ventricular hypertrophy
Endocarditis	Diabetes mellitus
Heart transplantation	Post-operative noncardiac surgery
Cardiac trauma/Myocardial contusion	Acute rheumatic fever
Post-cardiac surgery	COPD exacerbation
Tako-tsubo cardiomyopathy (apical ballooning)	Lobar pneumonia
Tachyarrhythmias	Hypertensive emergency and hypertension (including gestational)
Radiofrequency catheter ablation	Acute aortic dissection
Cardioversion and CPR	Infiltrative diseases (amyloidosis, hemosiderosis, pompe's dis., sarcoid disease, etc)
Sympathomimetic drugs	Churg-Strauss vasculitis with eosinophilia
Pulmonary embolism	Animal bites (scorpion, jellyfish)
ARDS	Rhabdomyolysis
CVA/Intracerebral hemorrhage	Sepsis
Epileptic seizures	Extensive burns
Shock/Hypotension	False positive cardiac troponin testing (interfering mechanisms: heterophile antibodies from –occupational- exposure to monoclonal mouse antibodies or domestic animals, rheumatoid factor, macroenzymes in autoimmune or liver diseases, immunotherapies, vaccinations, or blood transfusions, etc)

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; CVA = cerebrovascular accident; MI = myocardial infarction

are herein missing. Other clues include the common (in heart failure) vs the occasional (in MI) occurrence of shortness of breath, the respective rare vs usual CK-MB elevation and the common vs rare BNP elevation, features useful to differentiate heart failure from MI.

In order to more effectively implement the correct use of troponin in ruling in or out an acute MI, a step-wise approach is recommended and presented in an algorithm in Figure 1. Whatever the steps being taken, clinical judgment should supersede any laboratory assay for biomarkers.[15] A most blatant clinical error would be to use troponin to exclude unstable angina. This is a clinical and ECG diagnosis and treatment should be started promptly without waiting for a troponin level, although some of these patients will eventually rule-in for non-ST elevation MI (NSTEMI). Unfortunately, it is this group, the first troponin-negative NSTEMI patients, who receive less aggressive therapy and thus have higher chances of sustaining a recurrent MI during short-term follow-up.[16] Emergency room

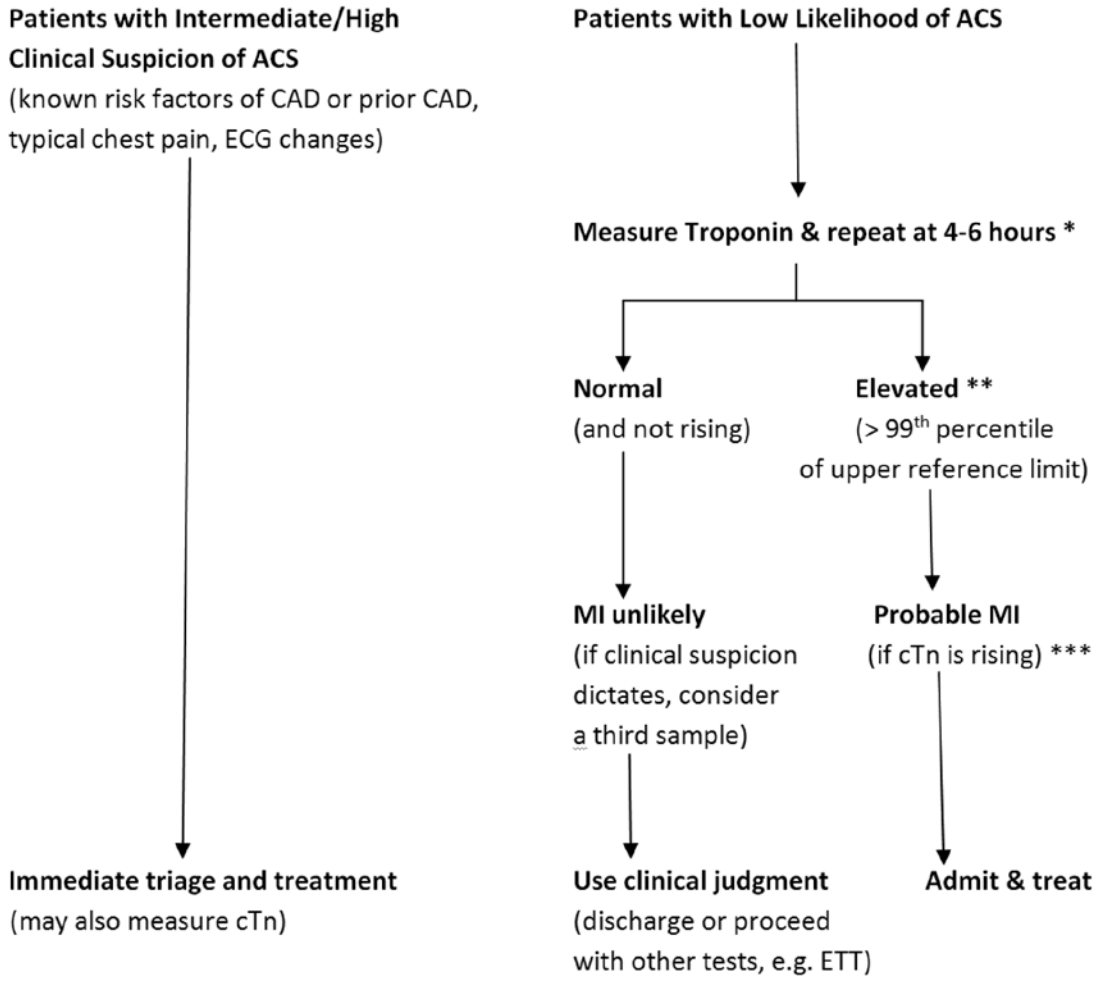

FIGURE 1. Algorithm for Management of Patients with Suspected ACS Using Cardiac Troponin. ACS = acute coronary syndrome (s); CAD = coronary artery disease; cTn = cardiac troponin; ECG = electrocardiogram; ETT = exercise tolerance test; MI = myocardial infarction.

* Do not use the troponin test to exclude unstable angina. To more safely rule out acute MI, document the time of onset of chest pain or at least the time of presentation to the emergency room in every patient. The sensitivity and negative predictive value of cTn is extremely high if measured at least 6 hours after the onset of chest pain.

** A rising troponin level is required to diagnose acute MI. In patients with baseline elevations of troponin (e.g. patients with chronic renal failure), two measurements are required to demonstrate a rising pattern. Troponin is considered negative when measured $\geq$6-9 hours after the onset of chest pain and ACS unlikely if no recurrent chest pain and no ECG changes. Troponin is specific for myocardial cell damage; however, the cause may be other than ACS (see Table 1).

*** if not rising, consider alternate etiology for elevated troponin

physicians and cardiologists should not be reassured by the first normal troponin and patients with the clinical syndrome and the ECG changes should be treated aggressively without waiting for the result of the second troponin measurement. Similarly, patients presenting with a typical clinical syndrome and ECG changes of an ACS do not need to be delayed for the result of a cTn assay; they should be promptly managed with an aggressive pharmaceutical and interventional therapy. It is only in patients with a low likelihood of an ACS that one should rely on cTn measurements for management decisions (Fig. 1).

With regards to the two types of cardiac troponin, cTn I and cTn T, there seems to be concordance in the majority of cases; however, discordant values have been reported, and some investigators have proposed that it might be helpful to confirm clinically equivocal increases or results unexpectedly below the cutoff value, obtained for one cardiac troponin by measuring the other.[17] A better approach remains with the clinician who should be relying on or guided by clinical judgment and use this high-sensitivity troponin conundrum to his/her own patients' advantage by requesting a cTn assay only when clinically indicated and interpreting the results in the context of the clinical presentation at hand, resisting inappropriate requests and erroneous interpretations. Inevitably, the use of high-sensitivity troponin assays in the emergency room will lead to an increase of diagnosed MIs, particularly NSTEMI. High sensitivity assays disclose small elevations in circulating cTn and therefore detect MI earlier than traditional assays. Using the 99th percentile of URL as the cut-off value will probably maintain a balance between sensitivity and specificity; MI can be effectively ruled out within 3-4 hours of onset of chest pain with a negative cTn, while repeat measurements will limit any initial false negative results and enhance the sensitivity for ruling in more MIs at a later time by documenting the typical rise and/or fall pattern of an MI, all, of course, in the appropriate clinical context. Even in those with initially elevated values, serial measurements will discern those with an MI (typical rise and/or fall pattern) from those with other etiologies for an elevated cTn (Table 1). For patients with intermediate or high clinical suspicion of ACS, cardiac troponins do not offer much help for deciding on therapeutic strategy, which should be aggressive from the start, without having to wait for the cTn result. On the other hand, in patients with low clinical suspicion of ACS, cTn assay could be crucial to guide further management steps as outlined in the proposed algorithm (Fig. 1).

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