

MYOCARDIAL INFARCTION & ISCHEMIA THERAPY UPDATE

The Role of High-Sensitivity Troponin in Diagnosing Acute Coronary Syndromes

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ABSTRACT

The development of assays to detect plasma elevations of cardiac troponins has revolutionized our current clinical practice in the diagnosis and management of acute coronary syndromes. Recently new highly sensitive assays for troponin measurement have been developed in an effort to detect even minimal elevations suggestive of subclinical injury providing thus the clinicians with additional diagnostic and prognostic information. These assays can facilitate an earlier diagnosis of myocardial ischemia or necrosis and add substantial prognostic information to improve our risk stratification and accordingly our treatment strategy. This increased sensitivity, however, may come at the expense of decreased specificity. Nevertheless, accumulating evidence suggests that high sensitive troponins, if used appropriately regarding proper timing and evaluation of serial samples and in conjunction with clinical data can improve clinical care of patients with acute coronary syndromes.

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INTRODUCTION

The development of assays to detect plasma elevations of cardiac troponins has revolutionized our current clinical practice in the diagnosis and management of acute coronary syndromes (ACS).^{1,2} This intracellular protein complex is released in the peripheral circulation after myocardial cell damage. Given the fact that both troponin T and troponin I are not found in skeletal muscles their release in the blood is thought to be highly indicative of myocardial injury.³ Indeed, this particular high diagnostic specificity has led to a re-definition of acute myocardial infarction (AMI) based on the rise of troponin above the 99th percentile of the upper reference limit.⁴ Recently new highly sensitive assays for troponin measurement have been developed in an effort to detect even minimal elevations suggestive of subclinical injury providing thus the clinicians with additional diagnostic and prognostic information.⁵ These assays can facilitate an earlier diagnosis of myocardial ischemia or necrosis and add substantial prognostic information to improve our risk stratification and accordingly our treatment strategy in patients presented with ACS. Studies have shown that of high-sensitivity troponins are more accurate in the early diagnosis of AMI.^{6,7} Moreover, the prognostic information offered by the new assays seems to be more robust compared to the old ones.⁸ This increased sensitivity, however, may come at the expense of decreased specificity. Since troponin is an indicator of the result but not of the cause of myocardial necrosis, this has challenged the widespread use of high sensitivity troponins due to the expected increased number of false positive results in the diagnosis of ACS. Nevertheless, ac-

LIST OF ABBREVIATIONS:

ACS = acute coronary syndromes
AMI = acute myocardial infarction
CV = coefficient of variance

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cumulating evidence suggests that high-sensitivity troponins, if used appropriately regarding proper timing and evaluation of serial samples and in conjunction with clinical data, can improve clinical care of patients with ACS.

CARDIAC TROPONINS: PATHOPHYSIOLOGY

Cardiac troponins regulate the calcium mediated interaction of actin and myosin filaments of muscular cells. The troponin complex consists of 3 subunits; troponin C binds calcium, troponin I inhibits the interaction of actin with myosin, and troponin T binds the troponin complex to tropomyosin facilitating this way muscular contraction. While troponin C is expressed in both myocardial and skeletal cells, troponins I and T are specific for cardiac muscle. This has led to the development of quantitative assays to detect elevations of troponin plasma levels as an indicator of myocardial damage.⁹ The majority of troponins is bound to the contractile apparatus of the myofibril, but approximately 7% of troponin T and 3-5% of troponin I remain free in the cytoplasm.¹⁰ This free cytoplasmic troponin is initially released after myocyte damage while the myofibril-bound component is released later and at a slower pace. This process accounts for the biphasic rise of serum troponin after myocardial injury.^{11,12} In the setting of ischemia, transmural myocardial necrosis requires at least 2-4 hours to occur. Accordingly, an earlier than that diagnosis of myocardial injury is not possible with the use of troponin. This is the reason that two blood samples are recommended to be drawn, one upon presentation and the other 4-6 hours later in order to optimize sensitivity and specificity in the diagnosis of acute myocardial infarction. Of note, the serum levels of troponin I and T remain elevated 4-7 and 10-14 days respectively after an AMI occurs. The exact mechanism of troponin elimination remains unknown. Although its large molecular size seems not to permit renal excretion, recent evidence suggests that fragments of troponin T can be renally eliminated and this could be a possible explanation for the high prevalence of troponinemia in patients with renal failure.¹³ Although this simple schema reflects our established knowledge about troponin kinetics, recent evidence suggests a more complicated production and turn over. Indeed, measurements with the use of the new highly sensitive analytical methods have clearly shown that low but detectable troponin levels can be traced in healthy individuals.¹⁴ Moreover, it has become evident that myocardial necrosis is not a prerequisite for the elevation of troponin serum levels. Mechanisms unrelated to necrotic myocardial damage but possibly related to ischemia include apoptosis, release of proteolytic troponin degradation products, increased cellular permeability and formation and release of membranous blebs.¹⁵ The above mechanisms are mainly implicated from experimental data, albeit with the use

of the high sensitive troponin assays some clinical evidence has started to emerge. Indeed, beyond normal population, transient rise and fall in troponin has been observed in marathon runners,¹⁶ as well as after induction of ischemia.¹⁷

CARDIAC TROPONINS: HIGH-SENSITIVE ASSAYS

The development of specific immunoassays to detect troponins has led to revolutionary changes in our diagnostic and therapeutic strategies for ACS during the last 10-15 years. A new universal definition of AMI was introduced. This new definition requires the detection of rise and/or fall of cardiac troponin above the 99th percentile of the upper reference limit together with evidence of ischemia.⁴ This cutoff point was selected based on studies which had shown that less than 1% of the population had detectable troponin which was, moreover, associated with the presence of or high risk for cardiovascular disease.¹⁸ In an effort to further increase precision at these very low levels of detection, it was also suggested that instead of the 99th percentile value the lowest value that an assay showed an imprecision (measured as coefficient of variance – CV) 10% should be used. Based on that, new generation assays have been developed to comply as much as possible with this recommendations.¹⁹ These “more sensitive” assays are able to detect troponins at much lower concentrations. A clear definition, however, of “high sensitivity” was only recently agreed among the experts. Thus, high sensitive assays should have a CV < 10% at the 99th percentile value in the reference population. In addition, concentrations below the 99th percentile should be detectable above the assays limit of detection in at least >50% (and ideally >95%) of healthy individuals in the reference population.²⁰ Based on the above, several troponin I and one troponin T high-sensitivity assays have been developed (Table 1). The wide variability in the characteristics of the troponin I assays does not permit direct comparisons among them. On the other hand, this is not an issue for the single prototype highly-sensitive troponin T assay. Beyond this, other analytical problems for the new high sensitive assays have also been underlined. One of them is the definition of the reference population. Indeed, the criteria of defining such a population have not been agreed upon. Concerns have been raised since it has been shown that the precision of these methods can be age and sex dependent.²¹ In addition, biological variability which is now easier to detect with this more sensitive assays is not known how much can affect their diagnostic accuracy.²² Indeed, this can be a particular problem when more than one values are necessary to be measured. The latter is required for diagnostic purposes in the great majority of the clinical cases and does not seem to have changed with the use of the new assays. Nevertheless, the highly sensitive assays have the potential advantage of allowing an earlier, faster and more

TABLE 1. Characteristics of the high-sensitivity troponin assays.

	Limits of Detection (ng/L)	99th percentile ng/L (CV)	10% CV concentration (ng/L)
Hs-cTnI			
Roche Elecsys	5.0	14(13%)	13
Hs-cTn-I			
Abbot ARCHITECT	1.2	16(5.6%)	3.0
Beckman ACCESS	2 to 3	8.6(10%)	8.6
Mitsubishi Pathfast	8.0	29(5%)	14
Nanosphere	0.2	2.8(9.5%)	0.5
Radiometer	9.5	23(17.7%)	39
Singulex Erenna	0.09	10.1(9.0%)	0.88
Siemens Vista	0.5	9(5.0%)	3
Siemens Centaur	6.0	40(10%)	30

CV: coefficient of variance; HS-TnT: high-sensitivity troponin T; Hs-TnI: high-sensitivity troponin I.

precise diagnosis of myocardial necrosis and ischemia although the later remains an issue of debate.

HIGH-SENSITIVITY TROPONINS IN THE DIAGNOSIS OF ACUTE CORONARY SYNDROMES

Acute coronary syndromes are a major cause of death and disability worldwide.²³ Given the fact that only a minority of the patients who present in the emergency department with chest pain have characteristic electrocardiographic changes, cardiac biomarkers play an extremely important role in the final diagnosis. Due to their high specificity, the conventionally measured troponins have long ago replaced the older biomarkers in the diagnosis of ACS, especially of AMI.²⁴ However, due to their inability to detect minor troponin elevations during the first few hours of the acute event, they still need repeated sampling which ends up in prolonged monitoring of the patient in the emergency department and delayed treatment of the true positive cases.

The high-sensitivity assays, by detecting also troponin in a substantial portion of the healthy population can provide clinicians with a more precise cut-off point of normality, leaving fewer cases in diagnostic uncertainty. Moreover, it is expected that they can lead to an earlier and perhaps "one-shot" diagnosis of AMI. Indeed, with the new assays the initial minor elevations of troponin can be detected within the first 90 to 180 minutes of the acute event.²⁵ In two large prospective trials performed in patients who presented in the emergency department, a single measurement of the high sensitive assays were more accurate than the conventional ones in the diagnosis or the exclusion of AMI within 3 hours

of the onset of symptoms.^{6,7} Due to their high specificity these assays were also able to reliably rule out AMI on the basis of a single measurement (negative predictive value 97-99%). More recent studies have confirmed these findings. Aldus et al²⁶ showed in a study performed in New Zealand, that high-sensitivity troponin T was more sensitive than the older assay in diagnosing AMI in patients presented with chest pain although optimal sensitivity was achieved 4-6 hours after the onset of symptoms. Similarly, Ahmed et al²⁷ showed that high sensitive troponin T measured in average 4 hours after presentation in the emergency department has an excellent negative predictive value (96%) for normal subsequent stress test while preserving a sensitivity of 90%.

Beyond their improved diagnostic accuracy, high-sensitivity troponins seem to offer also additional prognostic information for the patients with ACS. Early generation troponins had already shown to be a strong prognostic marker justifying an early invasive therapeutic strategy especially in patients with non-ST-segment elevation AMI.^{28,29} In a single center study of patients presenting in the emergency department with chest pain, a highly sensitive assay outperformed the conventional one in predicting cardiovascular mortality at 1-year follow up.³⁰ In another study performed in a cohort of 1635 patients with suspected ACS, highly sensitive troponin I measured immediately and 2 hours after presentation in conjunction with Thrombolysis in Myocardial Infarction (TIMI) risk score ≤ 1 could accurately identify patient who had a very low probability to sustain a major cardiovascular event in the 30 days of follow up.²⁵ More recently, in the LIPID Study (Long-Term Intervention with Pravastatin in Ischaemic Disease) it was shown that baseline sensitive troponin T levels was an independent predictor of subsequent cardiovascular death or AMI in patients who had suffered an episode of AMI or unstable angina.³¹ Of note,

even small changes of high-sensitivity troponin T (<20%) have been associated with increased long-term mortality in patients with non-ST-segment elevation AMI.³²

Based on the above it is reasonable to speculate that with the new highly sensitive troponins it is expected that our diagnostic accuracy in the assessment of patient with a suspected ACS will improve both in terms of an earlier and more reliable diagnosis, as well as, in defining a very low-risk population who can safely be discharged from the emergency department without further work up. Indeed, the recent guidelines recognize the superiority of high-sensitivity assays in their potential to earlier and more frequently diagnosing AMI. Nevertheless, several limitations in their clinical applicability are also been underlined.³³

HIGH SENSITIVE TROPONINS: LIMITATIONS

Beyond the fact that high-sensitivity assays have expanded the potential role of troponins and its use has been, accordingly, recommended from current guidelines, several issues remain open. From a pathophysiological point of view it has not been clarified if the minor troponin rises detected with the new methods indicate only necrosis or myocardial ischemia as well.¹⁵ If it is so, an interpretation problem of positive results may arise for the clinicians. Nevertheless, this should not obscure the clear prognostic role of even minor troponin elevations which should dictate an earlier interventional therapeutic approach. The issue of cut-off point (99th percentile) seems to be haven been agreed upon. However, an imprecision level higher than 10% (until 20%) has been advocated by some experts.³⁴ More importantly, the characteristics of the reference population have never been clearly defined. Recent studies have shown that different sample populations have also different 99th percentile values for the same assay.³⁵ In addition, these differences are age and sex dependent as it was shown in an analysis of the data derived from 3 large population-based cohorts.²¹ Biological variation is another not fully clarified issue. This was not relevant with the older troponin assays, since they lacked the sensitivity to reliable measure troponin in healthy individuals. With the new assays, however, specificity can be compromised due to biological variation especially in interpreting minor increases. Value differences due to biological variation can be detected on a daily, weekly or even monthly basis.³⁶ They can even be individual specific. Studies have shown that due to this variability short term changes up to 85% and long term changes up to 315% would be necessary to assure an abnormal highly-sensitive troponin elevation.³⁷

To overcome this problem serial measurements in the case of an initial positive value are necessary. However, even the

level of changes in serial measurement as well as the time of repeated sampling to verify the diagnosis of AMI remain also debatable issues. The proposed changes among serial samples have been ranging from 20-200%.^{38,39} It is nevertheless obvious, that the higher the initial troponin the lower the level of change required to consider the test results compatible with myocardial necrosis. On the other hand, both timing of repeated sampling and interpretation of the results have not also been standardized. The current guidelines suggest measuring one sample upon presentation and one sample 3 hours later. Current evidence suggests that this approach has a sensitivity and negative predictive value of 100%.⁴⁰ However, others have shown that a 6-hour period is required to firmly establish the diagnosis of AMI.⁴¹ Regarding the assessment of the changing pattern of troponins, general consensus is also lacking. Others have advocated the percentage change, the so-called delta troponin,⁴² while others have shown that absolute changes are of superior diagnostic value compared to the relative changes.³⁸ Finally, the issue of specificity compromise due to increased sensitivity is certainly not a negligible one. Since troponin elevation indicates the result (myocardial necrosis or ischemia) but not the case of it, there is a long catalog of conditions other than acute coronary thrombosis which have been associated with troponinemia (Table 2).⁴³ With the new sensitive assays the percent of non-coronary associated troponin elevation can dramatically increase. For example, patients on hemodialysis have shown minor troponin elevations at a percentage approximating 100%.⁴⁴

TABLE 2. Non-coronary causes of high-sensitivity troponin elevation

Cardiac Causes	Non-Cardiac Causes
Heart Failure	Renal Failure
Myocarditis / Pericarditis	Sepsis
Stress-induced Cardiomyopathy	Pulmonary Hypertension / Embolism
Post uncomplicated PCI	Drug Toxicity
Post uncomplicated CABG	Hypothyroidism
Myocardial Contusion	Stroke / Intracerebral Hemorrhage
Post uncomplicated Radiofrequency Ablation	Rhabdomyolysis
Tachyarrhythmias	Strenuous Exercise
	Hypotension / Shock
	Aortic Dissection

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

CONCLUSIONS

The new high-sensitivity assays for troponin detection offer the opportunity for a more rapid and accurate diagnosis of ACS leading this way to a potential increase in the number of patients who will benefit from an early invasive procedure. Moreover, a rapid “rule-out” for patients presenting with chest pain in the emergency department seems feasible. Nevertheless, studies to determine if incorporation of these new methods in clinical practice will improve outcome of the patients, are still lacking. Moreover, concerns have been raised for the possibility of over-diagnosing AMI in patients in whom other mechanisms than myocardial necrosis or ischemia are responsible for troponin elevation. This underscores the importance of using serial measurement of the high-sensitivity troponin assays, when they become widely available, and always in conjunction with a detailed clinical assessment particularly for those patients who now will have positive results while they would had been “ruled-out” with the conventional (less sensitive) assays.

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