High Sensitivity Troponin in Chest Pain and Acute Coronary Syndromes. A Step Forward?

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EDITORIAL

Historical Background

The measurement of cardiac troponins (cTn) first became available in the early 1990s. It is the first fully cardiospecific biomarker and for that reason has supplanted creatine kinase-MB (CKMB) as the biomarker of choice for the evaluation of patients with possible acute myocardial infarction (AMI). Of interest, even at the time of the first assays, it was clear that cTn was substantially more sensitive than CKMB. This has always been viewed as problematic because now with a totally cardiospecific agent that was sensitive, many additional situations where cardiac injury was present began to be defined. The first laboratory guideline suggested 2 cut off values for use in patients with acute coronary syndromes (ACS). One at a value equating cTn values and CKMB and a second where a diagnosis of unstable angina with minimal myocardial injury was present. This approach signaled even at that time concern about the increased sensitivity of cTn testing. These criteria were altered and the 99th percentile (99th) value chosen for the diagnosis of AMI in 2000. Cardiac Tn isoforms of troponin I (cTnI) and T (cTnT) have unique amino-terminal sequences that distinguish both of them from skeletal muscle isoforms. This fact alone increases sensitivity and thus, reduces the time to diagnosis. Presently, cTn measurements play a pivotal role in diagnosis, risk stratification, prognosis and the guidance of therapy in patients who present with ACS. However, as assays became more sensitive, it has become clear that more patients at risk were being identified, suggesting the need for still more sensitive assays. Thus, manufacturers began to develop successively more sensitive assays. Indeed, the multiple versions of cTn assays are a source of confusion in the field. Each successive step improved clinical performance. As an example, an assay with improved analytical sensitivity detected abnormal cTn values in the 50%-75% of initial samples from patients with AMI when only 15%-35% were detected with a less sensitive version of the assay.

The Year 2000 Guidelines. The cTn 99th Percentile

The modern day paradigm for the diagnosis of AMI was proposed in 2000. An elevated cTn value above the 99th of a reference population during the first 24 h of a clinical episode of coronary ischemia with a rising and/or falling pattern was taken to be diagnostic of AMI. At that time, the 99th for most assays was not often exceeded by subjects with cardiovascular risk factors or conditions such as arterial hypertension, diabetes mellitus, dyslipidemia, or heart failure. However, as assays became more sensitive, this was no longer the case. Zethelius was the first to show that the characteristics of individuals included in the reference population could influence the 99th value. cTn values appeared to increase with age not likely due to age per se, but because of the development of subtle cardiovascular comorbidities as shown by the adverse prognosis associated with these findings. Thus, not only was it clear that minor increases in cTn occur in response to cardiovascular risk factors such as hypertension and the like but these data also highlighted the need for caution in the selection of individuals who might be used to determine
normal values. This is a critical issue and one of the reasons, in addition to the use of different antibodies and analytical techniques why the 99th value varies so much between methods.

In addition, at the time of the 2000 guidelines the existing assays measured the value of 99th with excessive analytical imprecision. Thus, to reduce inaccurate results caused by imprecision, the guidelines recommended that imprecision should be lower than 10% (measured as coefficient of variation, CV) at the 99th value. Some interpreted that as an advocacy to use the 10% CV value and for the majority of the existing assays, this leads to a much higher cut off value (Table 1) and consequently, reduced sensitivity for the diagnosis of AMI. It is now clear that modest degrees of imprecision (up to 20%) do not cause false positive values. It does, however, make observing changes in cTn values far easier. It is also now clear from multiple studies that the 99th value identifies more patients at risk. For example, in TACTICS TIMI 19 the 10% CV value identified 49% of patients at risk of death or recurrent AMI by 30-days, whereas the 99th identified 10% more. This again is because contemporary assays are not close to real normal values as shown by Eggers. Indeed detectable values below the 99th are prognostic of future adverse cardiac outcomes in a long-term follow up studies of community populations or in patients after an ACS.

The diagnostic precocity attained using the cTn 99th with contemporary assays permits more rapid identification of patients with AMI and makes unnecessary measurement of the CKMB or myoglobin, the so-called “rapid” AMI markers. Accordingly, the biochemical guidelines on biomarkers of cardiac damage define cTn as the marker of choice instead of CKMB or myoglobin.

As indicated above, as cTn assays became more sensitive, it became clear that any cardiomyocyte damage could cause their release into the circulation. Thus, a variety of pathologies and not just ischemic injury can be associated with elevated cTn values (Table 2). These elevations are not “false-positives,” but mark alternative etiologies for cardiac injury. The vast majority predict adverse outcomes in these patients. The only way to distinguish one type from the other is clinically. This challenge has and will continue to increase as assay sensitivity improves still further.
TABLE 2. Causes of Troponin Elevation in the Absence of Ischemic Coronary Syndromes

<table>
<thead>
<tr>
<th>Cardiac diseases and conditions</th>
<th>Coronary vasospasm</th>
<th>Cardiac contusion</th>
<th>Cardiac surgery</th>
<th>Percutaneous coronary intervention</th>
<th>Post cardiac transplantation</th>
<th>Closure of atrial septal defects</th>
<th>Supraventricular tachycardia</th>
<th>Cardioversion</th>
<th>Implantable cardioverter defibrillator shocks</th>
<th>Radiofrequency ablation</th>
<th>Myocarditis</th>
<th>Pericarditis</th>
<th>Cardiac amyloidosis</th>
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<tbody>
<tr>
<td>1. Myocardial damage</td>
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<td>2. Heart enlargement</td>
<td>Dilated cardiomyopathy</td>
<td>Heart failure</td>
<td>Hypertrophic cardiomyopathy</td>
<td>Left ventricular hypertrophy</td>
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<td>Noncardiac diseases</td>
<td>Primary pulmonary hypertension</td>
<td>Pulmonary embolism</td>
<td>Pulmonary edema</td>
<td>Chronic renal insufficiency</td>
<td>Stroke</td>
<td>Subarachnoid hemorrhage</td>
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<td>2. General conditions</td>
<td>Critically ill patients</td>
<td>High dose chemotherapy</td>
<td>Sepsis and septic shock</td>
<td>Sympathomimetic agents</td>
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<td>Methodological causes</td>
<td>Fibrin clots</td>
<td>Heterophilic antibodies</td>
<td>Rheumatoid factor</td>
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**The Year 2007 Guideline. Serial cTn Measurements**

The cardiologic scientific societies updated the definition of AMI in 2007. This universal definition maintained cTn as the biomarker of choice, but because of recognition that more sensitive assays were now detecting other etiologies of both acute and chronic cTn elevations, additional emphasis was placed on observing a rise and/or fall of cTn concentrations in association with an elevation of cTn above the 99th value. A dynamic pattern cannot distinguish elevations from other acute etiologies promoting progressive cardiac injury such as myocarditis, pulmonary embolism or sepsis but when timing permits, it helps to distinguish acute from chronic etiologies for cTn elevations. Detecting variations in serial cTn measurements is challenging and the task force suggested the use of criteria such as a change equal to or greater than 3 standard deviations of the variation around the values. This requires the laboratory to report such a change since the criteria for such changes will vary according to the precision profile of any given assay. Specifically, at low values near the 99th, imprecision is often much higher than at higher levels. For some assays, a change value of 20%-30% may suffice, but this value will vary depending on the assay involved. Some have proposed using a calculation of biological variation which includes change related to biological alterations and analytic ones but that can only be done using normal subjects. The one study that did that, suggested a change of 47% rising short-term was needed for the novel (not yet released) Singulex assay. The need to detect serial cTn changes and more accurately calculate the 99th, as well as the knowledge that even at cTn values below the 99th value with present assays patients at risk were identified stimulated the development of more precise and higher-sensitivity cTn assays.

**High-Sensitive Cardiac Troponin Assays**

The designation “high-sensitive assays” is used to identify assays with an improved limit of detection which analytically is defined as the minimum concentration that can be distinguished from zero. There are no formal guidelines for the designation of high-sensitive (hs) and some assays have used the name for marketing purposes. 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 assays should be classified as guideline acceptable if imprecision is <10%, clinically usable if it is between 10%-20% and non acceptable if >20%. Then, 4 categories are assigned depending on the percentage of putatively normal subjects detected. The categories are <50%, 50%-75%, 75%-95%, and >95%. Table 3 shows that only 5 of the 16 current cTn assays detect the 99th with an imprecision <10% and only 1 of the current assays is able to detect cTn in more than 50% of reference individuals. In contrast, all but one of the high-sensitive assays fulfilled the maximum standards. According to these characteristics, none of the current cTn methods could be denominated as high-sensitive; an important issue that should be kept in mind when analyzing the results of recent publications using what are called “sensitive cTn assays.” One of those papers, compared 3
“sensitive cTn assays,” none of which would have been labelled high sensitivity per Table 3, with the investigational high-sensitive cTnT Roche assay. The investigational assay showed some differences with the current assays. The 99th value of the high-sensitive assay manifested a clinical sensitivity to detect AMI of 90% in samples drawn at admission, whereas the remaining assays showed clinical sensitivities of 85%, 75%, and 89% in the same samples. These differences were not statistically significant which may simply represent that given the broad group of patients in the study, including many with overt events, the diagnostic differences between assays in those with more subtle presentations may not have been detected. In addition, many of the assays used as comparators were the same assays being studied or ones that were similar in terms of sensitivity. Thus, the likely differences were related to the use of the 99th value in the study group to a greater extent than differences in the assays. Another paper published in the same issue of the journal compared two contemporary cTn assays. Although one of the methods is marketed as “Tn I ultra” it is not a high-sensitive assay according to the data in Table 3. It was more sensitive when used at the 99th value than the current cTnT assay used at the value obtained with a 10% imprecision. It is very likely that most of the differences shown relate to the use of the studied assays at the 99th value to a greater extent than intrinsic differences in the assays.

**Clinical Investigations With Novel High-Sensitive Troponins**

There are several recent papers showing important features of hs-cTn measurements in the management of cardiac patients. In general, they build on the saga previously depicted: diagnosis is earlier and more common, but increases in cTn due to non-ischemic cardiac issues are much more common.
**Reference Subjects**

The considerations around a normal reference population are even greater with these high sensitivity assays than with the current assays. The 99th percentile for the hs-TnT assay is between 13-16 ng/L (0.013-0.016 µg/L) compared with the undetectable value (<0.01 µg/L, <10 ng/L) found with current assay; there appear to be differences between men and women. This is similar for the Singulex assay. In contrast, the 99th percentile for the Beckman assay is of 8-9 ng/L compared with the value of 40 ng/L (0.04 µg/L) of the current Beckman assay. In other studies, there are no differences present between men and women. However, Kavsak did show minor differences according to sample type. These minor analytical differences were probably not key with prior assays but will be with these novel very high sensitivity assays. The 99th percentiles for these assays are 2.5 to 4.5-fold lower than the previous ones and are obtained with an imprecision much lower than 10%.

**Acute Coronary Disease**

Studies of hs-cTn in the evaluation of ACS are producing promising results, particularly when admission samples of the patients are evaluated. Both hs-TnT and hs-TnI manifest higher sensitivity to detect AMI (61%-72%) than the observed with the current assays (0%-8%) in the initial samples of patients, even those obtained 3-4 h after the onset of symptoms. As a consequence, the time to diagnosis is drastically reduced in one study from 247 to 71.5 minutes. The difference in hs-TnI values between samples drawn 3 h or 6 h apart showing maximal sensitivity for detecting an evolving ACS was of 177% and 243%, respectively. The minimum value that was of significance was not defined and will be a key metric. These values calculated by receiving operating characteristic analysis were much higher than the reference change value (RCV), i.e., the change exceeding the biological plus analytical variability, described by Wu for the Singulex hs-cTnI assay that is +46% for defining a rising cTn pattern and of -32% for a falling pattern.

In chest pain patients with low or intermediate likelihood of ACS, hs-TnT at admission had a sensitivity of 62%, a specificity of 89% and a negative predictive value of 96% for ACS compared with a sensitivity of 35% and a specificity 99% of the current cTnT assay. Overall, hs-cTnT detected 27% more ACS cases than current cTnT assay. These data are similar to those of Kavsak using the Beckman hs-cTnI assay. The increased frequency of AMI patients in these studies markedly diminished those with a diagnosis of unstable angina. One could even suggest based on the Wilson data that unstable angina might disappear. This speculation is consonant with the observations of Sabatine et al that an hs-cTn signal can be observed in individuals with positive stress tests. In that study, hs-TnI (Singulex assay) was detectable in all patients before testing. It remained unchanged in patients without ischemia and increased 24% in patients with mild ischemia and 40% in patients with moderate-severe ischemia. In contrast, no changes in cTnI were observed in patients using a current TnI assay. A 1.3 ng/L increase of hs-TnI was an independent predictor of ischemia. Taken together these data indicate the need to review the concept that cardiac ischemia can occur without biomarker release. However, they also suggest that eventually, ruling out AMI with these hs-cTn assays will also exclude the need for stress testing.

**Stable Coronary Artery Disease**

As with other increases in sensitivity, hs-cTn elevations occur in more patients with apparently stable cardiovascular disease. cTnT was above the 99th percentile in 11% and detectable in 97% of patients with stable coronary artery disease (stable CAD). Very few of these patients had elevations with contemporary assays. Of interest, hs-cTnT appeared higher in men than in female patients. In the stable CAD patients, hs-TnT was related to cardiovascular death, fatal and non-fatal congestive heart failure (CHF) and all cardiovascular deaths, except those caused by CHF; in accordance, hs-TnI could be helpful for risk stratification of stable CAD patients. These data are similar to those shown in heart failure by Latini et al. Similarly, abnormalities such as the presence and severity of coronary artery disease and left ventricular mass, reduced ejection fraction and regional dysfunction evaluated by 64-slice computer tomography were frequently associated with elevated hs-TnI values.

**Other Conditions**

The study of these novel assays is in its infancy. It is very likely that these assays will increase the frequency of abnormalities seen in the critically ill and others and help to define other novel situations where cardiac injury occurs. In that sense, the specificity of elevations for the diagnosis of ACS will diminish. Thus, such findings will increase the complexity of the clinical triage of such elevations. It is likely that defining a changing pattern will help immensely but this will be a challenging time.
Final Consideration. Future Use

The future is now or at least very close. These novel hs-cTn assays are currently available. Their use will require increased attention to pre-analytical and analytical issues since minor changes in some of these parameters might change values, causing false positive and false negative results. However, once we understand how to use such assays, their use should improve the rapidity of the evaluation of patients with chest discomfort and identify more patients who really have ischemic heart disease. These assays will however clinically challenge clinicians to distinguish elevations due to stable disease and/or subtle and perhaps novel disease entities different from those associated with acute ischemic syndromes.

REFERENCES


SUGGESTED READINGS
