Troponin testing at the point of care: What is needed, and when?

July 2012

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Despite the pervasive measurement of cardiac troponin (cTn) for the diagnosis of myocardial infarction (AMI) and acute coronary syndromes (ACS), the continuous evolution of assays and guidelines for their application has created uncertainty among laboratorians and clinicians: criteria for the choice of assay and cut-off values for clinical interpretation have yet to be clearly defined.

A recently proposed scorecard provides valuable information for the more accurate definition and utilization of sensitive assays. Point-of-care testing (POCT) represents a viable opportunity for the timely measurement of cardiac troponin, but its analytical accuracy remains mandatory.

Although a rapid testing process is required, it cannot impinge on diagnostic performance if patient care is to be safeguarded. Important requisites for assuring quality in POCT of cardiac troponin include the choice of the assay, appropriate training of operators, quality control and quality assurance programs.

The ability to measure the cardiac troponins (cTnI and cTnT) has produced a paradigm shift in the assessment of patients with suspected acute coronary syndromes (ACS). The availability of immunoassays for cardiac troponins, a milestone in the care of patients with chest pain, led to two new definitions of myocardial infarction and to the publication of several position papers and guidelines [1-3].

In fact, cTn elevations in blood are integral to the diagnosis of acute myocardial infarction (AMI) and the Joint ESC/ACF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction has advocated that the diagnosis of AMI be based on a rising and/or falling pattern of cTn in the appropriate clinical situation [2].

Almost identical guidelines have been issued by the National Academy of Clinical Biochemistry [3] and, in the updated American College of Cardiology/American Heart Association guidelines, it is recommended that, in patients with ischemic symptoms, at least one cTn concentration higher than the 99th percentile value during the first 24 hours after onset of symptoms indicates myocardial necrosis consistent with AMI [3].

In 2001 the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommended quality

specifications for analytical and preanalytical factors of cTn assays [4].

Taking into consideration the molecular heterogeneity of cTns, the IFCC document stated that "antibodies used for the development of reliable assays should preferably recognize epitopes that are located in the stable part of the molecule and are not affected by complex formation (such as ICT) and other in vivo modifications".

A second, and fundamental recommendation, concerning analytical reproducibility was "a total imprecision – as coefficient of variation (CV) – of less than 10 % at the myocardial infarction decision limit". Both concepts, quality of antibodies and analytical reproducibility, have strongly influenced the path towards standardization and improvement of cTns assays.

However, defining the decision limit has been a challenge, since initially two decision limits, one suggesting "a true myocardial injury" and the other "higher value suggestive of an injury to the extent that it qualifies as AMI" have been recommended [3].

The approach of defining an upper limit of normal at the 97.5th or 99th percentile as a reference population is the method used to establish cut-off values for many laboratory tests. For troponins, professionals societies initially suggested the 97.5th percentile [3] but thereafter consensually recommended the 99th percentile (i.e. a positive test for 1 in 100 persons in the reference group) as more conservative than the 97.5th percentile [2].

This cut-off value was chosen originally to minimize the number of false positive values that would potentially be included within the abnormal range, which could confound the diagnosis of AMI.

Both criteria, the adoption of the 99th percentile and an imprecision of 10 % or less at that cut-off value, have been accepted as fundamental characteristics of commercially available assays and have impacted on the improvement of available methods as well as the development of new and innovative assays that have been termed "contemporary", "sensitive" and "high-sensitive".

However, the evidence supporting the metric of a 10 % CV has been questioned for both theoretical and practical reasons. In theory, the easiest way to meet the 10 % CV metric would be to increase the assay threshold, thereby decreasing its clinical sensitivity.

In practice, it was demonstrated that modest increases in imprecision of more than 10 % (up to 20-25 %) at the 99th percentile do not lead to significant patient misclassification [5]. Therefore, precision cannot be considered the only useful metric in cTn assay evaluation.

Which cTn assays are appropriate for optimal patient care?

Advancements in cTn assay technology driven by the quality specifications defined and recommended in laboratory and clinical guidelines have created a conundrum for both clinicians and laboratorians.

In fact, the developments of assays with higher analytical sensitivity have the potential to allow the early detection of measurable cTn values in patients admitted to Emergency Departments with acute chest pain [6, 7], a more precise risk assessment [8] and effective patient monitoring.

Moreover, the improved analytical sensitivity allows the detection of measurable cTn levels in most reference ("healthy") subjects and, in turn, the evaluation of the biological variability of the marker [9-11].

On the other hand, increased analytical sensitivity may increase the risk of "false positive" as it is more frequent in patients without AMI but with a long list of diseases with myocardial involvement that should be grouped into two main categories: a) diseases not associated with myocardial ischemia, and b) conditions where the exact mechanisms are uncertain or multifactorial [12].

Finally, the introduction of the " new generation" of cTn assays in clinical practice did happen for the pressure of diagnostic manufacturers and before the development and diffusion of guidelines and practical information on the correct interpretation and utilization of laboratory results.

As underlined by Diamond and Kaul in a seminal Editorial [13], the aphorism "just as a tool is only as good as its operator, a diagnostic test can be only as good as its interpretation" appears apposite in describing the case for cTn assay. The more sophisticated the test, the more appropriate its diagnostic interpretation must be, and some basic tools may aid the search for a more rational utilization of cTn assays.

First, a scorecard based on a 2-tier analysis system has been proposed and widely accepted in the scientific community [14]. According to this assay-dependent scorecard, the two criteria to be used are the 99th percentiles and imprecision values at the 99th percentile.

Table I shows the scorecard designations of cTn assays, as proposed by Fred S. Apple. The scorecard is based on the designations of the total imprecision of each assay at the 99th percentile and on the number of specimens from "normal" individuals that have cTn concentrations measurable below the 99th percentile.

As only a few commercially available assays comply with both the requisites needed to define a "true high-sensitive" assay, the ultimate goal is for all assays to be "third generation (level 4), guideline acceptable", but in real life level 3 and "clinically usable" assays should also be used.

Second, recently published data, obtained in 643 consecutive patients admitted to the Emergency Department who had been discharged following serial measurement of conventional cTn assay, demonstrate that high-sensitivity cTnT is a strong prognosticator of intermediate and long-term mortality, but it was associated with a very low mortality rate (0.9 %) at 30 days and a 0 % rate of AMI.

Therefore, small increases in hs-cTn may suggest that patients without ACS require further investigations and treatments, but not necessarily immediate hospitalization [15].

Third, in our experience (data submitted for publication), in a unselected population of patients presenting with chest pain in the ED of a large academic tertiary hospital, a "last generation true high sensitivity assay" (hs-TnT) is highly accurate, but is not overall more accurate than a guideline-acceptable first-level assay (cTnI) and slightly better than a level 1 clinically usable cTnT assay for the diagnosis of ACS.

Therefore, the need to avoid the interpretation of a single cTn result, particularly in patients with small increases and negative ECG/clinical findings, and the importance of serial measurement (on admission, after 3 and 6 hours), not only high-sensitive but also guideline-acceptable assays could be used in clinical practice, namely for ruling in and ruling out patients admitted with acute chest pain.

Acceptance designation percentile, CV%	Total imprecision at the 99th
• Guideline acceptable	<10
• Clinically usable	> 10 to <20
• Not acceptable	>20
Assay designation	**Measurable normal values below the 99th**
• Level 4 (third generation, hs)	>95
• Level 3 (second gen., hs)	75 to <95
• Level 2 (first generation, hs)	50 to <75
• Level 1 (contemporary)	<50

TABLE I. Scorecard designations of cTn assays (from reference 14, modified)

Point-of-care testing for cTn: why and how?

The management of patients with chest pain is based on the well-known aphorism "time is muscle and time wasted is muscle lost". Delays in diagnosis and appropriate treatment are associated with poor clinical outcomes and a recommendation to treat all AMI patients within 60 minutes of their arrival in the ED was made many years ago [16].

The first available recommendation for the turnaround time (TAT) of cTns should be found in the NACB guideline, which suggested a target TAT of 1 hour or less [3], but this recommendation was not evidence-based.

In fact, a study conducted some years later by the College of American Pathologists (CAP) demonstrated that most physicians' expectations regarding TAT were more stringent: they wished to receive the results 45 minutes or less after the time they ordered the test [17].

In fact, few data are available on the relationship between TAT and patient outcomes. In a paper published in the Lancet several years ago, we stressed that "although TAT remains a crucial variable in cardiac marker testing, we disagree with the premise that faster is better, since a rapid response may compromise analytical quality" [18].

Rapid testing is certainly needed but it cannot be achieved to the detriment of diagnostic performance.

Laboratory professionals should therefore identify the best solutions to achieve quality and effective TAT in the specific clinical setting and in a close collaboration with clinicians. POCT is a viable option for cTn assay, particularly when clinical laboratories: a) cannot deliver results in the time consensually defined with clinicians (usually within 60 minutes), b) close at nights and/or weekends, c) are poorly connected with wards both for sample transportation and result communication, and d) the cost/benefit analysis confirms the value of this option.

If POCT is required, the choice of the method should be carefully made to avoid the risk of errors [19]. Quality specifications for POCT testing should be the same as those for centralized laboratories. In particular, the advantages of sensitive assays of cTns in allowing early diagnosis and prompt treatment cannot be side-stepped by using POCT methods with a low analytical sensitivity.

Therefore, according to the previously described scorecard, highly sensitive and guideline-acceptable assays that allow a good agreement with the results provided in the main laboratory could be used.

This is particularly important if serial results are obtained in the two different settings. In fact, according to current recommendations, at least three blood samples should be obtained at admission, 3 hours later and repeated 6 hours after admission in patients for whom the 3-hour values are unchanged but for whom the clinical suspicion of AMI is still high.

As the requirements for a "true high sensitivity assay" are not easily met, "clinically usable" POC assay for cTn should be effectively used in all institutions in need of POC testing option. Although no definitive data exist on the superiority of an absolute increase or relative changes in cTn, the comparability of results obtained at different times is mandatory.

Therefore, data on individual patients must be obtained using the same assay or different assays that guarantee the same analytic result. This should be assured by comparing clinical samples, not only on the basis of the manufacturers' claims. As a perfect correlation between POC versus Central Laboratory assays cannot be achieved, a comparison should be made by taking into consideration the respective cut-off levels.

This makes possible a comparison of data based on the clinical ground. Some further requisites should be taken into consideration when performing POCT testing.

First, quality control and quality assurance programs should be implemented. Second, a careful evaluation of the sample of choice (i.e. plasma or whole blood) should be made [20].

Third, an appropriate training for the operators should be available before starting the clinical practice and a program for continuing education provided. Finally, a continuous exchange of data and comparison of results between POCT and central laboratory should be performed.

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