Position Statement

IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays

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A B S T R A C T

In 2011, the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers (TF-CB) was formed, with the purpose of providing evidence based educational materials to assist all biomarker users, i.e. laboratorians, clinicians, researchers, in-vitro diagnostics and regulatory agencies, in better understanding important analytical and clinical aspects of established and novel cardiac biomarkers for use in clinical practice and research. The goal of the task force was to promulgate the same information conjointly through the in vitro diagnostic industry to the laboratory, emergency department and cardiologists. The initial undertaking of the TF-CB, which is comprised of laboratory medicine scientists, emergency medicine physicians and cardiologists, was to address two key issues pertaining to implementing high-sensitivity cardiac troponin (hs-cTn) assays in clinical practice: the 99th percentile upper reference limit (URL) and calculating serial change values in accord with the Universal Definition of AMI. The highlights of both concepts from IFCC statements are described. © 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Introduction

In 2011, the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers (TF-CB) was formed, with the purpose of providing evidence-based educational materials to assist all biomarker users, i.e. laboratorians, clinicians, researchers, and in vitro diagnostics and regulatory agencies in better understanding important analytical and clinical aspects of established and novel cardiac biomarkers for use in clinical practice and research. The goal of the task force was to promulgate the same information in the form of cards, posters and other educational prompts conjointly through the in vitro diagnostic industry to the laboratory, emergency department and cardiologists. The initial undertaking of the TF-CB, which is comprised of laboratory medicine scientists, emergency medicine physicians and cardiologists, was to address the two key issues pertaining to implementing high-sensitivity cardiac troponin (hs-cTn) assays in clinical practice: the 99th percentile upper reference limit (URL) and calculating serial change values in accord with the universal definition of AMI [1]. Prior to developing the handout materials, didactic documents containing the rationale for the advocacies that were taken were prepared. These educational documents are now posted on the IFCC website (http://www.ifcc.org/ifcc-news/2014-07-22-tf-cb-documents/). The highlights of both concepts from IFCC statements are described in these articles.

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99th Percentile URL.

The 99th percentile value is universally endorsed as the reference cut-off to aid in the diagnosis of acute myocardial infarction (AMI) [1]. As such, key components that are necessary to implement hs-cTn assays in practice include:

a) the 99th percentile should be determined in a healthy population [1,2];

b) the 99th percentile from either peer-reviewed literature or from manufacturers’ product information should be considered acceptable;

c) the 99th percentile for hs-cTn assays should be measured with an analytical imprecision of ≤10% (% CV; coefficient of variation) [1,2];

d) hs assays should measure cTn above the limit of detection in ≥50% of healthy subjects [2–4];

e) 99th percentile values should be reported as whole numbers only, in ng/L units.

Factors that influence an hs-cTn assay’s 99th percentile include:

a) age, because cTn values increase with increasing age, especially above 60 years [5];

b) gender, as men have higher values than women [3,4,6];

c) assay method, as the 99th percentile must be determined individually for each assay, as assays are not standardized;

d) specimen type, because the 99th percentile may be different for serum, plasma and/or whole blood.

99th percentile values should be established or confirmed with the appropriate statistical power for each sex (men and women) using a minimum of:

a) 300 male and 300 female subjects (by sex) [3];

b) 20 subjects if confirming 99th percentiles [3], using an appropriate 1-tailed nonparametric statistical method [2].

These analytical, educational suggestions proposed and endorsed by the IFCC TF-CB are the first of many steps to better harmonize the global use and reporting of hs-cTn assays in practice.

Calculating serial change values (Delta)

Determining the degree of serial changes in cardiac troponin values is the best way to differentiate between patients who have acute cardiac injury of any kind, including AMI from those that have more chronic elevations, many of which may be related to structural heart disease [1,7]. This approach is necessitated because there often are elevations of cTn values, particularly with those assays that are more sensitive, i.e., the “high-sensitivity” assays. Key to this determination is the assumption that the timing of the patient’s presentation allows for such an evaluation.

The development of criteria for such an analysis is complex. Important factors include the specific assay involved, the timing of the evaluation, spontaneous change in patients without acute cardiac injury, the anatomy that led to the acute problem, the criteria being used to make the “gold standard” diagnosis and whether one is attempting to improve diagnostic sensitivity and or specificity [7–12]. It is important to recognize that criteria that rely on more marked changes will improve specificity at the expense of sensitivity, whereas those that are less marked will improve sensitivity at the expense of specificity [8,9]. Thus, considerable thought and interaction between the stakeholders who use these assays is suggested.

The calculation of Delta change values (also called relative change values) for hs-cTn assays can be viewed as a simple task of generating criteria and then evaluating whether or not changes in either absolute or relative numbers are associated with higher diagnostic accuracy for acute events such as AMI. However, the reality is that it is a much more complex task. Issues that need to be kept in mind include [9]:

Problems related to the gold standard diagnosis of AMI:

a. The gold standard for AMI diagnosis should always be based on delta changes, assuming the timing allows for that. Delta changes are essential to rule out AMI in patients with chest discomfort. Solitary elevations alone are inadequate because there can be elevated cTns due to structural heart disease including coronary artery disease or non-cardiac diseases like infection, metabolic disorders, etc.

b. The gold standard diagnosis may not always be accurate. In a recent manuscript by Hammarsten et al., 26% of the patients diagnosed with MIs had less than a 20% delta change [13]. The authors reported that many of these patients had taken substantial time prior to reporting to the hospital and warned that late presenters might not manifest significant changes in cTn values. In addition, some of these patients may have had elevations due to stable coronary artery disease and may have been included as having AMI due to diagnostic misclassification [9].

c. If an insensitive diagnostic standard, such as an insensitive assay or high cutoff values is utilized to define acute events, then it will include only larger events and the values, whether calculated as percentages or absolute changes will be artifactually increased [14].

d. Most large events have very marked increases in cTn values and those individuals who have clearly non-cardiac events will not have any changes. Patients in between, such as those with atrial fibrillation but no coronary artery disease, need to be clinically identified and taken into account, they are likely to have some change in values [13]. Thus, the admixture of patients used as controls will influence the calculations regardless of the approach.

Problems related with spontaneous variation and timing.

a. Small delta changes could be due to spontaneous variation or analytic variation. Small changes with very low values lead to marked percentage changes and small absolute changes may cause values to cross the critical 99th percentile value. Thus, even modest analytical or biological variation can lead to spontaneous changes in patients with non-acute diagnoses. These changes have been shown to overlap those seen in patients with acute diagnoses [15]. This could be due to overlap in patients with disease but it also has at least the potential to include some normal subjects with high biological variation.

b. Timing is essential for an accurate Delta calculation [9,12]. The timing of most presentations should allow for the calculation of the delta. However, delta changes may be absent at or near peak values or when the presentation is late after an acute event. In addition, one needs to obtain samples frequently enough to make sure that the intermittent release known to occur in patients with acute coronary artery disease is not a confounder. Ideally, two values three hours apart might be considered but may not be applicable to all patients.

c. Comparing the value of delta changes across approaches and for clinical use should rely on fixed intervals.

d. cTn release is flow related. Thus, an event that occurs in a patient with an open artery, such as many patients with type 2 AMI, will have greater egress to the circulation rapidly than
will an event that occurs behind a totally occluded coronary vessel but both need to be accommodated within delta change rules. This provides some degree of difficulty because the timing of these 2 events may well be substantially different.

Problems related to assay methods

a. Change values will need to be developed for each assay. Assays are different, so the use of a conjoint set of criteria would be ideal but is not likely to occur in the near term [7,9].

b. All assays can have analytical and pre-analytical issues. These can increase or decrease values. When this occurs, it can have an effect on the calculation of the delta.

Problems related to the delta changes calculations themselves

a. Most “optimal delta values” have been derived by ROC analysis. This analysis makes the assumption that sensitivity and specificity are equally important. It may well be that in many circumstances sensitivity may be more important and in others specificity may be more important. Thus, a metric developed from ROC analysis may not meet the clinical needs of specific patient groups [13,14].

b. The calculations need to be taken under advisement in regard to the number of decimal points the values are reported to and whether or not rounding is appropriate or inappropriate.

c. There is a very uncomfortable issue of naming that has been as- siduously ignored in the literature. There will be some patients seen in whom the clinical diagnosis is unstable angina who have elevated troponins with a pattern that does not change. The appropriate diagnosis in these patients is unclear. They could have unstable angina with an elevated troponin due to structural heart disease or other comorbidities, or even due to coronary artery disease. Alternatively, they could be patients in whom the timing of the event under evaluation is unclear. How one designates these individuals diagnostically and deals with them therapeutically needs to be taken under advisement.

So, how does one calculate delta changes? The above suggests that no protocol for evaluation of delta change will be perfect. What is therefore necessary is information concerning the relative sensitivity and specificity of each of the approaches advocated. Then, one can utilize the pretest probability of disease to make a priori decisions about which metrics to use. Calculating the pretest probability is a clinical challenge, which will be supported by appropriate scores under development in the future.

At present, two approaches have been advocated for calculating a significant delta change. The first is a percentage change predicated usually on conjoint biologic and analytic variation, which has been called biologic variation (BV) [7]. This approach can be problematic because BV is in part dependent on the type of equipment used to generate the measurements. Some instruments are more precise than others even with the same assay reagents. Thus, for any given instrument, BV may vary [16], BV may also be dependent on the population studied. The studies thus far completed suggest that a range of reference change values calculated from BV is between 30% and 85%. This has led some to suggest that an appropriate mean value is in the range of 50%, and such algorithms have been published [17] but not prospectively validated. The majority of comparative data looking at this metric versus the second metric that has been advocated for use, one that utilizes absolute numbers, have suggested that absolute values may be superior [10,11]. These data are predicated on ROC analysis but find that values depending upon the assay in absolute terms are more valuable in terms of explaining and refining diagnostic yield despite the caveats indicated above. It appears that most of the benefit may be at higher values where marked percent-age changes might not be expected but where the absolute changes will be less than BV. Finally, an additional issue relates to the calculation itself and whether one wishes to use a one- or two-tailed test and whether logarithmic transformation is used to normalize what is usually not a normally distributed population of values.

For clinical use, the calculation of the delta change value is not simple and we have concerns over approaches using cohorts being evaluated in less than ideally comprehensive manners that do not adhere to the criteria delineated above. Good studies rigorously done are essential.

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