

# CALCULATING SERIAL CHANGE VALUES (DELTA) FOR HIGH-SENSITIVITY CARDIAC TROPONIN ASSAYS

## Level 1 concept – educational principle

Educational principle – Determining the degree of serial change in high-sensitivity cardiac troponin concentrations is the best way to differentiate between patients who have acute cardiac injury of any kind, including acute myocardial infarction (AMI) from those that have more chronic elevations, many of which may be related to structural heart disease.<sup>1,2</sup>

## Level 2 concept – summary

There often are elevations of cardiac troponin concentrations (cTn) and particularly those that are more sensitive including the so called “high sensitivity” assays in patients with structural heart disease of a variety of types. Thus, in order to distinguish acute elevations (acute cardiac injury) from those that exist more chronically, assessing a change in values over time is valuable assuming the timing of the patient’s presentation allows for such an evaluation. However, 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 and whether one is attempting to improve the specificity of for diagnoses related to changes or the sensitivity.<sup>2-7</sup> It is important to realize 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.<sup>3,4</sup> Thus, considerable thought and interaction between the stake holders who use these assays is suggested.

## Level 3 concept - detail

The calculation of delta change values (also called relative change values, RCV) for cTn assays can be viewed as a simple task of generating a variety of 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 much more complex task. Issues that need to be kept in mind<sup>4</sup> include:

### A/ Problems related to the gold standard diagnosis of AMI.

1. The gold standard for AMI diagnosis should be always 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 cTn due to structural heart disease including coronary artery disease or non-cardiac diseases like infection, metabolic disorders, etc.
2. The gold standard diagnosis may not always be accurate. In a recent manuscript by Hammarstam, 26% of the patients diagnosed with MIs had less than a 20% delta change.<sup>7</sup> 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 were included as having AMI due to diagnostic misclassification.<sup>4</sup>

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3. If an insensitive diagnostic standard for acute events is utilized, then it will include only larger events and the values, whether calculated as percentages or absolute changes will be artifactually increased.<sup>8</sup>
4. 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 like those with atrial fibrillation but no coronary artery disease need to be clinically identified.<sup>9</sup> Thus, the admixture of patients will influence the calculations regardless of the approach.

## **B/ Problems related with spontaneous variation and timing.**

1. Small delta changes could be due to spontaneous variation or analytic variation. Small cTn changes with very low values lead to marked percentage changes and small absolute changes may cause values to cross the critical 99<sup>th</sup> % URL 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.<sup>10</sup> 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.
2. Timing is essential for an accurate delta calculation.<sup>4,7</sup> 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.
3. Comparing the value of delta changes across approaches and for clinical use should rely on fixed intervals.
4. Cardiac troponin release is flow related. Thus, an event that occurs in a patient with an open artery such as many patients with type 2 MI 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.

## **C/ Problems related with assay methods**

1. 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.<sup>2,4</sup>

## **D/ Problems related to the delta changes calculations themselves**

1. 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.<sup>3,4</sup> It thus might be advised that an institutional decision should be made about this critical element by all of the stake holders involved. These considerations should be conjointly determined between the laboratory community and the clinical community.

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2. 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.
3. There is a very uncomfortable issue of naming that has been assiduously ignored in the literature. There will be some patients seen in whom the clinical diagnosis is unstable angina who have elevated cardiac troponins with a pattern that does not change. The appropriate diagnosis in these patients is unclear. They could have unstable angina with an elevated cardiac troponin due to structural heart disease 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.

## How to calculate delta changes

The above suggests that no protocol for evaluation of delta changes 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 biological variation (BV).<sup>2</sup> 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 piece of equipment, BV may vary.<sup>11</sup> 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 a 50% and such algorithms have been published<sup>12</sup> but not prospectively validated. The majority of the 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.<sup>5,6</sup> 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 percentage changes might not be expected but where the absolute changes will be less than BV. 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.

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