Delta Cardiac Troponin Values in Practice: Are We Ready to Move Absolutely Forward to Clinical Routine?

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The improved analytical characteristics of both sensitive and high-sensitivity assays for cardiac troponin I (cTnI) and T (cTnT) have substantially increased the diagnostic sensitivity for early detection of acute myocardial infarction (AMI) (1–3). With the ability to detect small increases in circulating cardiac troponins, any cause of myocardial injury will now produce a substantially greater number of analytically true positive findings not detectable by earlier generations of cardiac troponin assays (3–6). This evolution has led to a decrease in diagnostic specificity for the diagnosis of AMI, a concern to many clinicians who may incorrectly equate any increased cardiac troponin value to an AMI (7, 8). Observational studies, although conducted predominately with prior-generation assays, have consistently demonstrated that any increase in cardiac troponin due to almost any mechanism of myocardial injury carries an association with worse outcomes (3, 7). Nevertheless, because diagnostic specificity is pivotal to appropriate therapy, pragmatic approaches are needed to sustain diagnostic specificity with sensitive and high-sensitivity assays for cardiac troponin. In this issue of Clinical Chemistry, Mueller and colleagues (9) report on their experience with one such approach that uses the change in cardiac troponin over time (Δ).

First proposed by Fesmire in 2000 (10), diagnostic algorithms based on the Δ cardiac troponin have now been shown in several studies to improve diagnostic specificity, but not necessarily diagnostic sensitivity (11–13). When a sensitive contemporary assay (Ortho Clinical Diagnostics Vitros ES cTnI) was used, a 6-h Δ based on an optimized 30% change improved diagnostic specificity from 77% to 91%, whereas diagnostic sensitivity changed from 94% based on the 99th-percentile value, compared with 75% based on the Δ value (11). More recently, using the high-sensitivity cTnT assay (hs-cTnT), Reichlin and coworkers observed that a criterion of an absolute Δ over a 2-h period of >0.007 μg/L (7 ng/L) substantially improved the diagnostic specificity for AMI from 93% to 95% (13). A similar result was obtained with a sensitive contemporary cTnI assay (Δ, 0.020 μg/L; diagnostic specificity, from 91% to 96%; not significantly different compared with the hs-cTnT assay). Reichlin et al. found that a diagnostic criterion that used the absolute Δ provided a superior overall diagnostic accuracy for AMI, compared with relative (percentage) Δ (0.95 vs 0.72, P < 0.001). Together, these data strongly suggest that a diagnostic approach that uses serial cardiac troponin values measured with an analytically robust assay over a very short time period substantially mitigates the major concern of clinicians about high-sensitivity cardiac troponin assays.

Despite these encouraging findings, several challenges and unanswered questions regarding the clinical implementation of Δ-based strategies remain, and several are illustrated in the work by Mueller and colleagues (9). In contrast to previous diagnostic studies, Mueller et al. selected patients with definite acute coronary syndrome (ACS) and those with an increased hs-cTnT result unrelated to ACS. Patients without ACS and with an hs-cTnT result <99th percentile were not included in their analysis. The authors then tried to discriminate patients with AMI from those with non-ACS increases in hs-cTnT values and found that, analogously to Reichlin et al., an absolute Δ of 0.0092 μg/L (9.2 ng/L) from 2 samples obtained within 6 h performed better than using a percentage change (0.90 vs 0.75). Interestingly, use of the peak hs-cTnT alone from 0–6 h (area under the ROC curve, 0.83) performed better than the percentage Δ and offered perfect diagnostic sensitivity (100% at the 99th percentile). In addition, when categorized by the baseline concentration of hs-cTnT, the absolute Δ was superior only at the extremes, where either very low initial concentrations produced very large percentage changes or very high initial concentrations required large absolute changes to meet the relative Δ criterion. In contrast to previous...
In these respects, the findings of Mueller et al. add to the growing database supporting the use of an absolute δ criterion during the 3–6 h after presentation to enhance diagnostic performance in patients with suspected ACS. Specifically, the data from Mueller et al. show—more so than prior studies—an advantage of the δ in overall diagnostic accuracy for identifying AMI among a cohort of patients enriched with increased hs-cTnT via a variety of mechanisms. There are several limitations, however, to interpreting the findings that relate to the complexity of both the clinical implementation of the δ and such diagnostic studies.

First, it is important to acknowledge that each individual cardiac troponin assay will require a specific δ determination for both absolute and percentage changes in δ. A convenient approach to the δ value, such as the 20% relative change proposed by the National Academy of Clinical Biochemistry laboratory medicine practice guidelines in 2007 (3), does not perform as well as a δ optimized for the individual assay. This point is critical for both laboratories and clinicians, such that findings from the δ values set obtained with the Roche hs-cTnT assay in the study of Mueller et al. cannot be transferred directly for use by a laboratory that measures cardiac troponin with another high-sensitivity or sensitive cTnl assay, with an instrument from the same or a different manufacturer. In addition, although it is reassuring that the optimal absolute δ values for hs-cTnT revealed in the studies of Mueller et al. and Reichlin et al. are very similar, clinicians and laboratory workers should be cautious about placing high confidence in a δ originating from single studies, particularly studies that are small in size. Furthermore, such δ criteria based on small concentration changes over a short time period require the assay to be analytically sound. Both the imprecision (14) and biological variation (1) characteristics of individual assays need to be defined to ensure that derived δ values are clinically meaningful and not just “noise” originating from analytical or biological variability (BV). It cannot be stressed enough that each assay will have its own BV, as well as its own imprecision at low concentrations.

Second, the proposal to use different δ cutoffs for different studied populations, i.e., ACS vs non-ACS patients, will be confusing to clinicians. Different cutoffs for the same assay will not be reasonable for implementation into clinical practice. The findings of Mueller et al. reveal that determination of the optimal δ is dependent on both the distribution of presenting syndromes in the population studied and the timing of their presentation. We are hopeful that reasonable single-δ criteria can be developed for each assay and applied across the spectrum of patients encountered in clinical practice; however, this supposition will require validation.

Third, the primary aim of using a δ criterion has been to provide improved diagnostic specificity, compared with a single measurement and use of the 99th-percentile reference value (1, 11–13). In the study of Mueller et al., 100% of the non–ST-elevation MI and non-ACS patients had an hs-cTnT value in the first 6 h that was >99th percentile (14 ng/L), leaving no room for improvement on sensitivity. Because the area under the ROC curve was improved with the δ, compared with using 14 ng/L dichotomously, we presume that diagnostic specificity was enhanced, but this comparison was not explicitly reported. Notably, the deliberate selection of patients without ACS and with hs-cTnT values >14 ng/L for this study would be expected a priori to diminish the specificity of this single criterion; therefore, such a cohort would not be representative of the experience with the broader group of patients with chest pain who present to an emergency department. In addition, because the authors based their diagnostic gold standard on a 20% relative change that included values obtained later than 6 h, i.e., beyond the period for which the δ methods were assessed, the relative δ criterion was inherently disadvantaged in their analysis. This potential bias in comparing the methods is a limitation of essentially every diagnostic study in which the biomarker method being studied also contributes to the gold standard diagnosis and warrants consideration when assessing the strength of the findings.

Fourth, as we noted, BV will have an influence on determining optimal absolute and percentage δ values (1). In the study of Mueller et al., it was not clear whether δ values included both increasing and decreasing cardiac troponin changes over the 6-h period studied. Furthermore, they evaluated very few patients who had δ values due to changes from an initial cardiac troponin value below the 99th percentile to a value above the 99th percentile in the second sample. The influence of BV in the Mueller et al. data set will likely be different from that observed by Reichlin et al., who had a substantially greater number of patients presenting with an initial normal hs-cTnT value.

In addition to these limitations, several of which are acknowledged by the authors, the reader should recognize that there are several unanswered questions relevant to the clinical application of diagnostic strategies that use the cardiac troponin δ. Delta values for the time windows of 0–3 h, 3–6 h, and 0–6 h should be individually determined, because one overall goal of implementation high-sensitivity cardiac troponin assays is to decrease the time for ruling out AMI from 6 to 3 h. It is notable and sobering that approximately 25%
of the population in the study of Mueller et al. was ruled in for AMI beyond 6 h. The ability to identify patients who require serial testing beyond 6 h is of high clinical importance. Lastly, 51% of the patients with a final diagnosis of unstable angina had an hs-cTnT value >99th percentile but did not meet the authors’ gold standard 20% δ criterion for MI. This group reduced the diagnostic specificity of using the 99th-percentile value alone. Given symptoms strongly supporting the diagnosis of ACS, however, it is not clear to us that the δ criterion should be used to clinically differentiate this group from patients with MI. Application of a δ criterion may be most useful for those with an intermediate or lower probability of ACS based on clinical symptoms alone.

In summary, the introduction of high-sensitivity assays for cardiac troponin into clinical practice has enabled improvements of diagnostic accuracy via the use of serial changes, as demonstrated by Mueller and coworkers. Substantial investigative work remains to be done, however, before coherent evidence-based guidelines can be established for the full spectrum of available assays. Not all cardiac troponin assays, T or I, are alike, whether they are sensitive or high-sensitivity assays. Each assay and each platform on which cardiac troponin is measured requires the development of its own evidence-based δ criteria to support its optimal use for patients presenting with symptoms suggestive of ischemia. The data from Mueller et al. and others indicate that use of the δ is likely here to stay, but more work remains to be done before its widespread routine application.

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