What Constitutes a Relevant Change in High-Sensitivity Troponin Values over Serial Measurement?

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The universal definition of myocardial infarction (MI)2 requires both an increase in cardiac troponin concentrations and a rise and/or fall in values over serial measurement (1). It is noteworthy that there is no mention in the current consensus document regarding what magnitude of change in troponin values should be required to meet the definition for spontaneous MI. The conspicuous absence of criteria to define troponin concentration change in that document reflects important knowledge gaps and the lack of consensus with regard to this important component of the MI definition.

The introduction of high-sensitivity troponin assays has created both challenges and opportunities with regard to the universal MI definition. A major challenge is the observation that a substantial proportion of individuals without MI have troponin concentrations persistently above the MI detection limit (2). This is in part related to the effects of age, male sex, subclinical cardiac structural abnormalities, and renal disease on troponin concentration (3), but is also influenced by poor characterization of the 99th percentile threshold, particularly for the high-sensitivity cardiac troponin T (hs-cTnT) assay. Indeed, a recent study that included data from 3 large population-based cohorts has shown that the recommended 14-ng/L threshold value for defining MI by use of the hs-cTnT assay is actually well below the actual 99th percentile value for men ≥50 years and women ≥65 years old (4). On the other hand, higher precision of the high-sensitivity troponin assays should improve characterization of troponin concentration changes over serial measurement. Indeed, it has been argued strongly that assessment of serial high-sensitivity troponin changes is the solution to the “specificity problem” with these assays (1, 5); however, little guidance is available as to what constitutes a relevant change.

In the past few years, data have begun to emerge from 2 broad categories of studies to address this important knowledge gap. The first category comprises analytical studies designed to carefully distinguish what constitutes a troponin concentration change that is above “noise.” This is defined as the reference change value (RCV) and includes both analytical and biological variation. The second category includes clinical studies that associate temporal troponin release patterns with an adjudicated MI diagnosis and/or with subsequent clinical events. These clinical studies have generally shown that accounting for temporal changes in troponin concentrations, in addition to baseline values, improves specificity at the cost of decreased sensitivity (6–10). Moreover, absolute changes in high-sensitivity troponin concentration appear to outperform relative changes (7, 8), partly owing to better performance of absolute changes at extreme troponin values.

In this issue of Clinical Chemistry, 2 studies, 1 analytical and 1 clinical, shed further light on high-sensitivity troponin kinetics. Aakre et al. (11) collected blood samples from 19 hemodialysis patients and 20 controls at 90-min intervals over 6 h, and then weekly for 10 weeks. The hemodialysis patients were predictably older, with more comorbidities, and had mean hs-cTnl and hs-cTnI values persistently above the MI detection limit. In a rigorous analysis, within-person variation (CVi), RCV, and index of individuality (II) were calculated for both hs-cTnT (Roche Diagnostics) and hs-cTnI (Abbott Diagnostics) assays. The II, which indexes within-subject to between-subject variation, was low in both groups, supporting the potential utility of RCV in interpreting troponin trends even among dialysis patients. Over 90 min, asymmetric RCVs, which use different RCV values for increases and decreases, were −8%/5% for hs-cTnT and −18%/21% for hs-cTnI in hemodialysis patients, whereas a larger RCV was noted in healthy controls (−27%/29% for hs-cTnT and −39%/64% for hs-cTnI). These data indicate that the 20% relative change in troponin values endorsed for MI diagnosis by the National Academy of Clinical Biochemistry (12) will likely result in a high false-positive rate in low-risk patients with few comorbidities and low baseline high-sensitivity troponin, and that this may be a more substantial issue for hs-cTnI than hs-cTnT assays.

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2 Nonstandard abbreviations: MI, myocardial infarction; hs-cTnI, high-sensitivity cardiac troponin T; RCV, reference change value; II, index of individuality; APACHE, Advantageous Predictors of Acute Coronary Syndrome Evaluation.

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The similarly low mean CVi in hemodialysis patients compared with healthy subjects (1.9% vs 1.2% for hs-cTnT; 3.3% vs 5.0% for hs-cTnl) is reassuring, and suggests that RCV differences between healthy and dialysis populations depend mostly on the within-assay variation (CVa) for a given troponin value. If validated, this concept may allow reliable estimation of short-term RCV for dialysis patients, and potentially other disease states with increased baseline high-sensitivity troponin concentrations, by use of the assay-specific CVa only. It thus may not be necessary to calculate CVi across multiple patient populations with varying comorbidities. Because CVa varies across troponin concentrations, however, a universal RCV value may not be appropriate for all patients. It is important to note that an inherent limitation of this type of study is that although it can define what constitutes a troponin change above noise, it cannot determine what pattern or magnitude of change is clinically relevant.

In the second article, Simpson et al. (13) measured hs-cTnI (Abbott Diagnostics) in a real-world cohort with possible acute coronary syndrome. The patient population was optimized to create a rule-out algorithm, including 283 patients discharged without a diagnosis of MI and free from 14-day readmission, all with hs-cTnI below the upper reference limit (40 ng/L). Repeat sampling was used to determine total within-subject variation [CVt = (CVi2 + CVa2)1/2]. CVa was derived on the basis of a precision profile previously reported by the study authors, and CVi and RCV were then calculated. Mean CVi was 13.8% and asymmetric RCV was −36%/56%. The authors calculated absolute RCV on the basis of actual troponin values and determined that 92.2% of patients discharged without 14-day readmission had an absolute RCV <5 ng/L. Interestingly, in a subanalysis of the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) study, Mueller et al. identified a similar absolute change threshold of 5 ng/L as optimal for MI rule-out (7).

Several limitations of the Simpson et al. study (13) should be recognized. No demographic and clinical data are provided, making generalization of these findings difficult. As acknowledged by the authors, 14-day readmission is not a strong surrogate for underlying acute cardiovascular disease. Most importantly, the derived RCV is not applicable to patients with baseline hs-TnI >40 ng/L, who were excluded from this study. It is the troponin values above the 99th percentile threshold that create the most vexing interpretation problems for clinicians.

How might information reported by these 2 studies be of value for clinical practice? Clearly, assessment of high-sensitivity troponin changes over short periods of observation will form a centerpiece of any MI diagnostic strategy. The RCV aids in differentiating real change from noise, which is essential for distinguishing acute from chronic troponin increases. However, acute increases may occur in conjunction with multiple other conditions; hence changes that fall outside the RCV-derived cutoff do not necessarily represent MI. Indeed, although the average troponin increases are larger with MI than with other causes of acute cardiac injury, overlap between diagnoses is substantial (14). Thus, RCV studies will likely be most useful for determining optimal MI rule-out strategies. However, even this approach has caveats, as it is clear that MI may occur with very small changes in troponin over serial measurement (14).

Several strategies have emerged that use different change criteria for rule-out and rule-in of MI. Reichlin et al. (10) derived and internally validated an algorithm using different cutoff values for rule-out and rule-in that incorporated baseline and absolute hs-cTnT changes with the first hour. Their rule-out criteria had sensitivity and negative predictive value of 100%, and the rule-in criteria had a specificity of 97% and positive predictive value of 84%, whereas 23% of patients did not meet either of these sets of criteria and would be recommended for further observation and testing. Diagnostic strategies such as this one, which leave a diagnostic gray zone necessitating clinical judgment and/or additional testing, may be the most pragmatic way to manage the tradeoffs of sensitivity and specificity inherent to any discussion of cutoff values.

Although this and similar algorithms are promising approaches for incorporating baseline and change values, the studies used to derive the algorithms are subject to important measurement biases. For example, in studies in which the MI gold standard is clinical diagnosis that does not require a rise and/or fall in troponin, biomarker strategies that use troponin changes may underperform. In contrast, studies that require a dynamic troponin pattern as part of the MI adjudication process may exaggerate the performance of troponin changes. Lack of a biomarker-independent gold standard for diagnosing MI (15) remains a major impediment to determining which patterns of troponin increase and change are most informative for MI. As high-resolution imaging modalities such as computed tomography and MRI continue to evolve, they may offer one potential solution for overcoming this limitation.

In summary, carefully performed reference change value studies, such as those reported in this issue of Clinical Chemistry, will help to provide a platform for improving MI rule-out with high-sensitivity troponin assays, useful in diagnostically challenging subsets of patients such as those on hemodialysis. As well, complex algorithms incorporating different baseline and change values for MI rule-in may help to improve spec-
ificity and positive predictive value, but even these strategies have important limitations. It is increasingly clear that identification of a simple strategy for accurate MI diagnosis with high-sensitivity troponin assays will prove to be an elusive goal. As a result, we must remember that the diagnosis of MI is a clinical one, and troponin measurements are only one piece of the diagnostic puzzle.

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