Can Changes in Troponin Results Be Useful in Diagnosing Myocardial Infarction?

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In 1979, the WHO defined 3 specific criteria for use in the diagnosis of myocardial infarction (MI): (a) clinical symptoms typical for ischemic heart disease, (b) specific electrocardiogram changes, and (c) a typical change in serial measurements of cardiac enzymes (1). Later definitions have continued in the mold of listing specific criteria, and in the current definition of MI, a characteristic increase and/or decrease in a cardiac biomarker with at least 1 result >99 percentile of a healthy population and evidence of myocardial ischemia (either specific symptoms or electrocardiographic or ultrasound findings) are mandatory (2). During the last decade, troponin T or I molecules, which are found only in myocardial cells and released after cell necrosis, have been the preferred cardiac biomarkers because of their high sensitivity and specificity (3), although myocardial cell necrosis can be seen in conditions other than myocardial ischemia (renal failure, sepsis, treatment with cardiotoxic drugs, myocarditis, and so on). A common problem in clinical practice is how to diagnose an acute MI in a patient who already has increased troponin concentrations. The National Academy of Clinical Biochemistry has suggested that a 20% increase in troponin results can be used to diagnose an ischemic event. This recommendation is based on analytical variation for troponin analysis alone, without taking biological variation into account (4).

Recently, troponin assays with better analytical sensitivity have become commercially available. These assays not only have opened up new diagnostic opportunities but also have challenged our understanding of ischemic heart disease, because the assays can detect low troponin concentrations, even in the healthy population (5, 6). The natural fluctuations of troponin concentrations around a homeostatic set point (i.e., within-person biological variation) as well as the between-person biological variation can be established, as is reported by Vasile et al. in this issue of Clinical Chemistry for a highly sensitive troponin T assay (7) and was reported in 2009 by Wu et al. for a highly sensitive troponin I assay (8). A low ratio of the within-person (plus analytical) variation to the between-person variation (as seen in these 2 studies) would suggest that the circulating concentration of troponin is a highly individualistic measure. For this reason, this ratio has been termed the “index of individuality,” and the results of tests with low ratios are quite person specific. Given a low index of individuality for troponin, it is easy to understand how an MI may occur in persons whose natural troponin concentration is quite low and in whom a troponin concentration indicative of MI might still fall below the 99th percentile. Likewise, because of this individuality, an increased troponin result in some persons might not imply an MI, despite being >99th percentile (5, 9). Thus, after the implementation of the new, more-sensitive assays, one can anticipate that the problem of differentiating between troponin increases due to nonischemic causes and those due to true ischemic events will occur more frequently (10).

With the highly sensitive troponin assays, it is conceivable that measurement of changes in troponin results might provide a better—or an additional—way to diagnose MI. To judge whether changes in serial test results reflect true differences, one must know the biological variation of the measured constituents, especially the within-person biological variation (CVi). Although data on CVi exist for many constituents, these data need to be interpreted with caution because not all have been obtained with a strict methodology. For example, in a recent study of urine albumin, the CVi information for the albumin/creatinine ratio obtained from a review of >25 reports ranged from 4% to 103% (11). It is therefore of the utmost importance that reports on biological variation strictly define the methods used to obtain the data (e.g., exclusion of outliers, tests for homogeneous variances, sampling time, posture, preanalytical conditions, time of measurement, and storage of the samples before measurement). Different critical-appraisal forms exist for evaluating reports of diagnostic accuracy (12), and similar critical-
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appraisal forms also need to be developed for reports dealing with biological variation. Developing such form is, in fact, 1 of the tasks of a newly established working group in the European Federation of Clinical Chemistry (13). With respect to troponin, it is surprising that the CVi data for highly sensitive assays of troponin T (CVi, 48%) and troponin I (CVi, 9.7%) studied over time periods of a few hours are so different for similar populations (7, 8). Such differences may reflect real differences in the biology of the 2 troponins or differences in the methods used to obtain or treat the data.

The use of data from studies of biological variation permits calculation of the reference change value (RCV):

\[ \text{RCV} = z \times \sqrt{2} \times \left( \frac{1}{2} \text{CV}_a^2 + \text{CV}_i^2 \right), \]

where \( z \) is the standard deviate for a certain probability of the gaussian distribution, the factor \( \sqrt{2} \) derives from summing the variation of 2 measurements with the same mean biological variation, and \( \text{CV}_i \) is the underlying analytical imprecision. The RCV for interpreting a measured difference is thus based on the \( \text{CV}_i \) and the \( \text{CV}_a \), as estimated from healthy (or diseased) individuals during steady state, assuming gaussian distributions and variance homogeneity. For biological data, \( \text{CV}_i \) is often calculated after a lognormal transformation. It is important to emphasize that the RCV provides only a measure for judging the probability that a difference in consecutive results can be explained by the analytical and within-person variation seen in patients in a stable situation. It does not provide a measure for judging the probability that a true change has occurred. For a thorough evaluation of the difference between 2 troponin results, it is important that both of these aspects be taken into account. Petersen et al. have suggested a model (14) in which one assumes 2 frequency distributions of differences, one for a stable steady-state situation and one for a certain true change. A measured difference will thus represent a “false change” for a patient in a stable situation but a “true change” if the patient’s condition really has changed. The ratio between these changes (true change/false change) will be the likelihood ratio (LR) that a change in the test result is caused by the disease, similar to the LR of a diagnostic test (true positive/false positive). The LR for the disease increases with increasing measured differences between the 2 results. When the LR is combined with the pretest probability (prevalence of disease), the posttest probability of a true change (i.e., the disease) can be calculated with Bayes theorem.

Use of a slight modification of this model with data for the highly sensitive troponin T assay presented in (7) and given a \( \text{CV}_a \) of 10%, a 200% increase in a result (e.g., from 3 ng/L to 9 ng/L) will produce an LR of about 48 with a corresponding posttest probability for MI of 72%, 92%, and 97% if the pretest probabilities were 5%, 20%, and 40%, respectively. If the \( \text{CV}_a \) is 50%, the corresponding LR will be 7.2 with posttest probabilities of 27%, 64%, and 83%, respectively. This example underlines the importance of knowledge of both analytical and within-person variation for these calculations. Application of these calculations to the data for the highly sensitive troponin I assay of Wu et al. (8), who observed a much lower \( \text{CV}_i \), would have produced a much higher LR. A change of only 20%, however, would have only a marginal effect on the probabilities for MI. The use of lognormal-transformed data will produce slightly different results. The \( \text{CV}_a \) should be less than one-half the \( \text{CV}_i \) in these calculations to minimize the effects of analytical imprecision on the estimated probability for disease (15). Therefore, the goal for \( \text{CV}_a \) should be < 24% in the data of Vasile et al. (7) and < 5% in those of Wu et al. (8).

With this Bayesian model or similar models of differences in serial test results, MI can be diagnosed more easily in patients whose troponin results fall within the reference interval or in patients with chronic troponin increases.

Data on the biological variation of troponin concentrations, such as those of Vasile et al. (7) and Wu et al. (8), will facilitate our understanding of ischemic heart disease, and the use of RCVs expanded with LRs and probabilities for diagnosing MI should be evaluated carefully and modified as necessary on the basis of clinical optimization and outcome studies. Studies that use a strict methodology to estimate the intraindividual variation should be performed for the troponins in different patient groups as well as in healthy individuals. Samples from patients for whom the model is to be applied should be subject to the same preanalytical conditions as the study population.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.
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