CZE is reported to be superior to agarose gel electrophoresis for the separation of albumin and to allow detection of more cases of baisalbuminemia (11).

The present case of baisalbuminemia and benign monoclonal gammapathy appears to be the second description of such an association. Both patients had IgG-κ (8). Baisalbuminemia occurring with paraprotein has also been reported rarely in patients with myeloma and plasmacytoma, but the genetic origin was not investigated in these cases (8, 10). Baisalbuminemia in these cases may be a coincidental finding. In our patient, myelodyplastic syndrome was also suspected; the occurrence of this disorder with baisalbuminemia has not been reported.

Our observations further support the previous report (11) that CZE has an advantage over agarose gel electrophoresis in albumin separation, allowing the detection of more cases of baisalbuminemia.

References


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To the Editor:

There is currently substantial debate about how cardiac troponin concentrations should be reported. We would like to offer an alternative strategy to recent recommendations.

In a recent editorial, Apple and Wu (1) proposed that the concentration of cardiac troponin that corresponds to an analytical imprecision (CV) of 10% be used as a medical diagnostic guide.

Panteghini et al. (2), in their document on quality specifications for cardiac troponin assays, state that “the detection limit ... of cardiac troponin ... should be significantly lower than the clinical discrimination limit used”. The main reason for this is that patient risk stratification based on results generated by assays not meeting this requirement would be compromised by considerable imprecision.

In contrast, a recent article on the proposed new definition of myocardial infarction states that “A review of currently available data demonstrates no discernible threshold below which an increased value for cardiac troponin would be deemed harmless” (3). Thus, the first two views (1, 2) focus on ensuring that reported results are real, and the third (3) is intent on extracting the maximum clinically useful infor-
tion. Is it possible to reconcile these imperatives?

Current commercially available assays for cardiac troponin cannot detect the picomolar concentrations of protein that are reportedly present in the blood of healthy persons (4). This point is supported by recent work from Roche Diagnostics in their efforts to establish a reference value for cardiac troponin T. Among 1951 apparently healthy persons, only 19 had troponin T concentrations above the minimum detectable concentration of 0.010 \( \mu \text{g/L} \) (Roche Diagnostics, information on file). No information was available on the clinical outcome in the 19 apparently healthy individuals (0.014 – 0.039 \( \mu \text{g/L} \)). Regardless, the fact that >99% of this study group had undetectable cardiac troponin T concentrations argues strongly that the appropriate reference interval for cardiac troponin, at least with currently available commercial assays, is below the detection limit. In support of this, Pagani et al. (5) could find no measurable troponin I in 120 healthy persons. We would question the upper reference limit quoted for some troponin assays (Table 1).

How then should cardiac troponin concentrations measured by currently available commercial assays be reported? If we accept the clinical observation that any troponin detectable is of pathologic significance, then the question becomes at what concentration is cardiac troponin detectable? To answer this question for each assay, we can determine the apparent troponin concentration of 10 or more replicates of a zero calibrator (within-run) and calculate the troponin concentration at 2 or 3 SD above the mean of these results. Above this value, any cardiac troponin present would be considered clinically significant. Between this value and the concentration that corresponds to a day-to-day CV of 10%, the concentration should be reported as “detectable”; above the 10% CV value, the actual quantity should be reported. We choose 10% because expert opinions from the National Academy of Clinical Biochemistry Committee (6) and the IFCC Committee on Standardization of Markers of Cardiac Damage (C-SMCD) (2) recommend a CV of 10% at the clinical decision limit for troponin measurement. This is at variance with the increasingly common clinical practice of using the “functional sensitivity” (CV) of 20% as the practical cutoff for reporting numerical values (7). The only concern with using a CV of 20% as the minimum requirement for a clinically relevant troponin value would be if it fell close to the detection limit. Reference to the data in Table 1 indicates that in all cases for which data were available, the 20% CV value is clearly above the detection limit. Although there is no evidence for the use of a CV of 20%, it has become established in clinical practice, at least for immunoassays. It would certainly be inappropriate to replace it with other criteria for which there is clearly opposing clinical evidence (8).

In practice, manufacturers of commercial troponin assays determine the detection limit as the concentration corresponding to a signal 2 SD above the mean of replicate within-assay measurements of a zero calibrator (Table 1). Another way suggested by Panteghini et al. (2) is to calculate the troponin concentration that is approximately one-fifth of the analytically valid clinical decision limit, i.e., one-fifth of the troponin concentration with a CV of 10% (Table 1). Alternatively, the minimum detectable concentration can be derived from the imprecision data obtained at low troponin concentrations, including at least two troponin concentrations that cover the range between the detection limit and the clinical decision limit of the assay. Using the three-parameter variance function, \( \sigma^2(U) = (\beta_1 + \beta_2 U)^J \), where \( \sigma^2(U) \) denotes variance, \( U \) denotes concentration, and \( \beta_1, \beta_2, \) and \( J \) are the parameters, the between-run imprecision data determined at six or seven troponin concentrations were used to calculate the parameters for an assay system. These were then substituted into the variance equation with \( U \) equal to zero to determine the minimum detectable concentration (9, 10). Using the Roche Diagnostics cardiac troponin T system as an example, the minimum detectable concentration at the 99.9 percentile, which corresponds to the troponin concentration with a signal 3 SD above zero, was 0.009 \( \mu \text{g/L} \) (Table 1). This concentration was near the quoted detection limit of 0.01 \( \mu \text{g/L} \) and close to the troponin concentration that was one-fifth the concentration at the clinical decision cutoff, i.e., 0.007 \( \mu \text{g/L} \).

In six other widely used cardiac troponin I systems, the detection limit values agreed reasonably well when estimated by the three methods (Table 1). The mathematical model gives added confidence to the reporting of troponin as “detectable” when the signal lies between those corresponding to the detection limit and the troponin concentration at a CV of 10%. Precision data obtained from our own field laboratories and applied to the mathematical model give a real-life measure of the detectable concentration of troponin in currently commercially available assays and highlight analytical and subsequent clinical differences that exist between these assays (Table 1).

The reporting of any analyte depends on the use of some valid criteria for the boundary between detection and nondetection, taking into account the degree of assay imprecision that does not affect clinical interpretation. For cardiac troponin, if we use a decision point of 3 SD above the zero calibrator, we might falsely label ~1 in 100 persons as having minor myocardial injury. Is there a greater potential for harm or good as a consequence? Two potential benefits arise. One is that the patient is given life-saving therapy, using the rationale that any troponin in the setting of coronary ischemia is associated with a worse prognosis. The other is the ability to accumulate data that enable us to test the hypothesis that any cardiac troponin associated with ischemia carries a worse prognosis. The potential downside is that patients may be started on therapy and experience an adverse reaction.

The old definition of myocardial infarction used decision thresholds for myocardial markers. This definition
Table 1. Reported characteristics of cardiac troponin I and T assay systems.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Quality specification</th>
<th>Bayer Centaur cTnI, μg/L</th>
<th>Dade Behring Dimension RxL cTnI, μg/L</th>
<th>Abbott AxSYM Access cTnI, μg/L</th>
<th>Beckman-Coulter Stratus CS cTnI, μg/L</th>
<th>Dade Behring Vitros ECi cTnI, μg/L</th>
<th>Ortho Clinical Diagnostics Elecsys cTnT, μg/L</th>
<th>Roche Diagnostics Elecsys cTnT, μg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection limit</td>
<td>calculated as the mean cTn value of 10 or more replicates of the zero calibrator plus 2 SD</td>
<td>0.03b</td>
<td>0.04b</td>
<td>0.30b</td>
<td>0.01b</td>
<td>0.03b</td>
<td>0.02b</td>
<td>0.01 (3 SD)b</td>
</tr>
<tr>
<td>Minimum detectable cTn concentration calculated using a mathematical model (3 SD above zero)</td>
<td>0.10d (1 SD, 0.032)</td>
<td>0.038d (1 SD, 0.125)</td>
<td>0.38d (1 SD, 0.128)</td>
<td>0.014d (1 SD, 0.0046)</td>
<td>0.017d (1 SD, 0.0057)</td>
<td>0.08d (1 SD, 0.026)</td>
<td>0.009d (1 SD, 0.0030)</td>
<td></td>
</tr>
<tr>
<td>IFCC C-SMCD recommendation for detection limit: cTn one-fifth the clinical decision value</td>
<td>0.06b</td>
<td>0.12d</td>
<td>0.028b</td>
<td>0.026d</td>
<td>0.3d</td>
<td>0.012b</td>
<td>0.016b</td>
<td>0.07b</td>
</tr>
<tr>
<td>cTn with a total imprecision (CV) of 20%</td>
<td>0.15b</td>
<td>0.3d</td>
<td>0.16d</td>
<td>0.08d</td>
<td>0.7d</td>
<td>0.032b</td>
<td>0.04b</td>
<td>NA</td>
</tr>
<tr>
<td>IFCC C-SMCD recommendation for clinical decision point: cTn concentration with a total imprecision (CV) of 10%</td>
<td>0.30b</td>
<td>0.58d</td>
<td>0.14b</td>
<td>0.13d</td>
<td>1.6d</td>
<td>0.06b</td>
<td>0.08b</td>
<td>0.36b</td>
</tr>
<tr>
<td>Manufacturer’s quoted upper reference limit (95, 97.5, or 99 percentile)</td>
<td>≤0.07 (99)</td>
<td>0.05 (97.5)</td>
<td>0.5 (95)</td>
<td>0.03 (97.5)</td>
<td>0.07 (99)</td>
<td>0.10 (97.5)f</td>
<td>0.01 (99)</td>
<td></td>
</tr>
<tr>
<td>Suggested range: “detectable cTn”</td>
<td>0.2–0.5</td>
<td>0.07–0.13</td>
<td>0.6–1.5</td>
<td>0.04–0.05</td>
<td>0.07–0.08</td>
<td>0.10–0.35</td>
<td>0.010–0.034</td>
<td></td>
</tr>
</tbody>
</table>

a cTnI, cardiac tropinin I; cTnT, cardiac troponin T; NA, data not available.
 Data derived from manufacturer’s package insert or obtained directly from manufacturing representatives.
 The mathematical model uses the between-run imprecision data determined at several troponin concentrations and substituted into the three-parameter variance function, \( \sigma^2(U) = (\beta_1 + \beta_2 U)^2 \), where \( \sigma^2(U) \) denotes variance and \( U \) denotes concentration, to calculate the parameters, \( \beta_1, \beta_2, \) and J. At the 99.9 percentile, i.e., the value at 3 SD above zero, the minimum detectable concentration was calculated after substitution of \( \beta_1 \) and J into the variance equation at a concentration of \( U \) equal to zero (10).
 Data were obtained by local field laboratories from the daily repeat measurement of troponin using manufacturers’ controls and patient sera (Centaur) or heparin plasma (Dimension RxL and AxSYM) containing low concentrations of troponin (n = 7–49 runs; imprecision was determined at six or seven troponin concentrations).
 Data from Quinn-Hall et al. (12).
 Based on serum samples.
 Based on heparin- and EDTA-plasma samples (upper reference limits for different specimen types are not available for other assay systems).
was flawed in that despite stratifying persons into those with myocardial infarction and those without (unstable angina), the death rates were identical after 2 years (11). The prognostic importance of a very low concentration of cardiac troponin has recently been confirmed by Morrow et al. (8), who found that troponin concentrations that were detectable but below that corresponding to an analytical CV of 10% had adverse prognostic significance. Thus the clinical evidence is in disagreement with the proposal from Apple and Wu (1).

The sole purpose of laboratory medicine is to provide clinically useful information. In this context, it appears that the clinically useful information is that any detectable cardiac troponin has pathologic significance. With the procedures we have outlined here, clinically significant low concentrations of cardiac troponin can now be defined with some confidence.

References
10. Sadelka WA. A new WN32 computer program for estimating immunoassay variance function.