Is It Time to Do Away With the 99th Percentile for Cardiac Troponin in the Diagnosis of Acute Coronary Syndrome and the Assessment of Cardiac Risk?

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The concept and use of the 99th percentile for interpretation of cardiac troponin was introduced with the redefinition of myocardial infarction in 2000, a time when few assays could detect cardiac troponin at the 99th percentile and none could meet the criteria of an assay CV of 10% at this concentration. There have been many reports of the 99th percentile providing useful information toward defining a population at high risk of future myocardial injury (1).

However, as we increase our knowledge regarding cardiac troponin, it is apparent that the 99th percentile has limitations. Cardiac troponin may be released in response to minor noncardiac illness, and this can cause confusion. Further, with the new high-sensitivity (hs)6 assays becoming available, it is apparent that most healthy persons have low concentrations of cardiac troponin present in their blood. Thus we have to come to terms with the concept that cardiac troponin may be released by physiological mechanisms as well as pathological ones. As assay quality has improved, the use of cardiac troponin in a clinical setting has become more complex and confusing.

We list below some of the ways in which 99th percentile has problems and how we may be better served by other criteria when using cardiac troponin for the assessment of individual patients.

Cardiac Troponin below the 99th Percentile May Also Identify Persons at Risk of a Major Coronary Event

Many studies that use conventional and hs cardiac troponin assays have demonstrated that there is a progressive rise in risk from the assay limit of detection (2, 3).

This is logical when one considers the nature of the acute coronary syndrome, where in the vast majority of cases there is rupture of a plaque, leading to emboli causing cardiac myocyte ischemia and death. The number of cells affected might range from very few to very many, and this will be reflected in the relative cardiac troponin concentration. There is no magic threshold at which a person suddenly becomes at risk of a cardiac event. Putting an arbitrary cutpoint into a continuum of disease is not ideal.

Variability between Assays

Cardiac troponin I (cTnI) assays are not standardized. Results with early assays could vary greatly in the reported concentrations from the same sample. Although there is much less variability between current assays, there will always be some variation, because of the different forms of cTnI that exist in plasma and because monoclonal antibodies recognize different sites in these modified proteins to a variable extent. This variation between assays for cTnI likely will continue to exist into the future.

There is only one manufacturer for cardiac troponin T (cTnT), but even here, as the fourth-generation assay was replaced by the fifth-generation hs-cTnT, there was considerable variation at lower concentrations, with 0.01 µg/L (10 ng/L) as determined by the old assay corresponding to approximately 35 ng/L with the new, a value that is substantially above the documented 99th percentile for the hs-cTnT assay (4). Even with the new hs-cTnT assay, adjustments to the calibration curve have caused substantial increases in concentrations at lower levels, and uncertainty exists as to how these changes may affect the reported 99th percentile for this assay. Although it is claimed that the recalibration of cTnT has not caused a change in the 99th percentile (5), a relative 35% increase in cTnT results has been reported for concentrations around this threshold following the recalibration of the assay (6).

The net result is that it is difficult—indeed, nearly impossible—to transfer 99th percentile values across generations of a particular assay and even more of a problem between assays from different manufacturers.

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6 Nonstandard abbreviations: hs, high-sensitivity; cTnI, cardiac troponin I; cTnT, cardiac troponin T.
Reproducibility of High Cardiac Troponin Results

Studies in children with very low cardiac risk showed that a high cardiac troponin result was not repeatable on subsequent sample collection (7), whereas in older adults high cardiac troponin concentrations were more likely to be repeatable and were associated with increased mortality (8). At what age does a cardiac troponin concentration above the 99th percentile become a reliable predictor of cardiovascular disease?

Index of Individuality for Cardiac Troponin

The within-person biological variation of cardiac troponin in healthy individuals is relatively small, and several studies show that the index of individuality is consistently <0.6 (9). When it is this low, changes due to within-person biological variation occupy only a small portion of the reference interval, and delta changes become more important. This is an important consideration when assessing patients with a possible acute coronary syndrome, as a clinically important rise in cardiac troponin concentration might occur without exceeding the 99th percentile. It appears that the delta cardiac troponin—the change over a 3- to 4-h interval—will become more important, and the actual value for the 99th percentile will be less so. This is also influenced by how the 99th percentile is derived as considered in the next section.

Population Definition for Calculating the 99th Percentile

Different studies, even when using the same assay, may derive quite different numbers for the 99th percentile. There are many possible reasons for this, including sample size, age, sex, and ethnicity.

However, it appears that an important contributor to a high apparent 99th percentile may be subclinical disease. There are several studies demonstrating that further screening with health questionnaires, estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide, and echocardiography can decrease the determined 99th percentile by approximately 50% (10, 11). Consequently, cutpoints lower than the 99th percentile will be more robust estimates, as they are not affected to the same extent by extreme values. The elimination of extreme values in population studies by the use of more extensive screening studies, however, will add to the costs of such studies. Requiring echocardiography, for example, to definitively define cardiac health would make population studies of the 99th percentile prohibitively expensive.

If We Were to Do Away With the 99th Percentile, What Would We Put in Its Place?

We have noted in our studies on healthy children that log transformation of the data gives a gaussian distribution of cardiac troponin concentrations (12). Gaussian or near-gaussian distributions have been noted in adult populations as well (8, 13). It appears that truly healthy populations have an underlying concentration of cardiac troponin that reflects physiology and not pathology, and that assessment of health or otherwise in a population should assess how closely that population’s results lie to a gaussian distribution. If cardiac troponin results can be made gaussian, why not have standard reference intervals defined by the central 95% and the upper reference level set to the 97.5th percentile, as is done with other biomarkers? This was proposed by the National Academy of Clinical Biochemistry already in 1999 (14). However, cardiac troponin has for many years been inappropriately used as an absolute diagnostic test, not as an aid to diagnosis. Setting the cutpoint to the 97.5th percentile will likely cause anxiety considering that 2.5% of individuals would be regarded as having an abnormally high cardiac troponin. Accordingly, as emphasized by 3 eminent cardiologists working in this area, there is a strong need to educate physicians that cardiac troponin concentrations and their changes must be interpreted in the context of the clinical presentation of each individual patient (15). In an appropriate clinical setting, looking for a delta change in cardiac troponin may be the best way to define the presence of an acute coronary syndrome. Whether this delta change should be an absolute increment or a percentage change, and over what time period the delta change should be calculated, remains to be clarified.

In summary, we have identified several important problems with the 99th percentile and offered an alternative. The 99th percentile presents problems in that it uses an arbitrary cutpoint inserted into a continuum of disease. However, in addition, the evidence is that within-person biological variation of cardiac troponin is small, and clinically significant changes could occur without exceeding the 99th percentile. Transient noncardiac illness, age, male sex, and subclinical cardiovascular disease may all push up the determined 99th population percentile artifically. On top of this, variation between assays and problems with population selection make the 99th percentile an unreliable boundary to use in assessing patients with presumed acute coronary syndrome.

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References


