

False positive troponins

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Abstract

The measurement of the troponins T and I has revolutionized the diagnosis of acute myocardial infarction. However, as the assays have become more sensitive, they inevitably have become less specific for acute myocardial infarction; the consequence is an increased prevalence of “false positive troponins.” This article explains how this has come about and describes the strategies that can be used to improve specificity. ■ *Heart Metab.* 2018;75:37-39

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What is “false positive”?

Cardiologists have a love-hate relationship with troponin! The use of troponin has revolutionized the management of patients with suspected non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) and the identification of patients with non-ST-segment elevation myocardial infarction (NSTEMI). This revolution has been led by the increasing analytic sensitivity of the troponin assays. However, when sensitivity increases, specificity always declines. Thus, an increased prevalence of “false positive” troponins is an inevitable consequence of our desire for extreme sensitivity. To dissect how to deal with false positive troponin, we first need to define what we mean by “false positive.” This is the crux of the problem; the threshold at which troponin becomes abnormally elevated (positive) is set at the 99th percentile,¹ while, as cardiologists, we view “positivity” as the identification of a culprit atherosclerotic plaque. Below, I will attempt to set out why this gap between definition and expectation can never be bridged. The best we can do is to understand the problem. Through a

better understanding, we can adopt strategies and apply a framework to maximize the identification of type 1 NSTEMI (acute plaque events) and other forms of acute myocardial injury.

Concept of the 99th percentile

For most assays, we define the normal range as that encompassing 95% of the healthy population. Troponin has evolved differently since the early assays lacked the analytic sensitivity needed to accurately measure low concentrations of troponin in the blood (*Figure 1*). Therefore, it was impossible to define the lowest 2.5% of the presumed normal distribution of troponin. There were also concerns of “false positives” and, for this reason, the threshold at which troponin was deemed to become positive was defined as above the 99th percentile of the “healthy” reference population.¹ The adoption of this criterion was fairly arbitrary, but it became immortalized in the first and subsequent universal definitions of acute myocardial infarction (AMI). The 99th percentile threshold for positivity did not upset the cardiology

community when the troponin assays were imprecise, which is difficult to understand without doing the thought experiment depicted in *Figure 1*. In essence, the imprecision of the early assays meant that the 99th percentile was high since the concentrations returned by the assays encompassed the biological variance of the population together with the analytic variance of the assays, and the noise of the latter drowned the former. Thus, the 99th percentile threshold only identified patients with substantial myocardial injury and a high prevalence of AMI (type 1). As the troponin assays became analytically more

sensitive, they began to return the true distribution of troponin in the general population, which is when the frustration of “false positive” troponins surfaced. Robert Jesse encapsulated this by saying “when troponin was a lousy assay it was a great test, but now that it’s becoming a great assay, it’s getting to be a lousy test.”² With improved analytic sensitivity, we also realized that troponin was not distributed normally, since all studies have shown a positive skew (*Figure 1*),^{3,4} which has further diminished the statistical validity of the 99th percentile.

Differentiating acute from chronic myocardial injury

Having set the upper limit of normal at the 99th percentile of the healthy reference population, we have an immediate and predictable consequence. The distribution of troponin in the population at risk for type 1 AMI is not the same as that of the healthy reference population! Consequently, approximately 15% to 20% of patients presenting to emergency departments without an AMI have troponin concentrations above the 99th percentile of the reference population. This percentage increases the more rigorous selection of the healthy reference population (eg, excluding patients with high blood pressure, raised cholesterol, abnormal electrocardiograms, etc), and it increases as the risk of the population presenting with suspected NSTEMI increases, since advancing age, male sex, structural heart disease, and renal dysfunction each significantly increase the median troponin concentration. So, the “false positive” rate is always likely to be at least 20% if we use the 99th percentile as a cut point (*Figure 1*). Patients with troponins that are elevated chronically and stably above the 99th percentile are defined as having chronic myocardial injury. The latest European Society of Cardiology rapid rule-in / rule-out guidelines attempt to minimize the impact of chronic myocardial injury in two ways.⁵ First, the 99th percentile is replaced by a much higher rule-out threshold (*Figure 1*). Second, for patients in the grey zone (between immediate rule-in and immediate rule-out thresholds), the troponin concentration on a second blood draw is subtracted from that of the first blood draw to calculate the absolute delta change value, the magnitude of this change in concentration can then be used to determine if the troponin is constant or acutely changing.

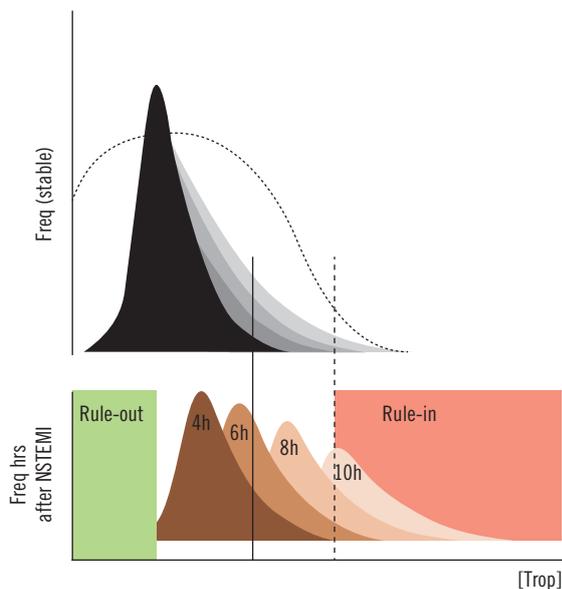


Fig. 1 The effect of the reference population and assay performance on the troponin 99th percentile.

In both panels, troponin concentration is on the x-axis and population frequency is on the y-axis to show the distribution of both troponin in stable populations (upper panel) and troponin over time in a population experiencing an atherosclerotic plaque rupture event at time zero that has initiated an NSTEMI (lower panel). **Upper panel.** The solid black depicts the true distribution of troponin in a healthy reference population. The dotted line curve depicts the effect of an insensitive troponin assay on this distribution. The vertical lines represent the 99th percentile cutoff concentration for the true troponin distribution and that returned by an insensitive assay, respectively. As assays have improved, analytic variance has diminished and the 99th percentile concentration has dropped. In lighter shades of grey are troponin distributions in stable patients with increasing prevalence of cardiovascular risk factors, which is more representative of patients presenting with suspected NSTEMI. As much as 25% of the stable population at risk is above the 99th percentile determined in the healthy population. **Lower panel.** Although median troponin concentrations increase over time, many patients with AMI still lie below the 99th percentile cutoff and many patients without AMI (grey distribution in upper panel) lie above it, resulting in unacceptable sensitivity and specificity. The latest ESC guidelines⁵ advocate a high rule-in threshold (red) akin to the vertical dotted line and a low rule-out threshold (green), rescuing specificity and sensitivity. However, these thresholds, widely spaced on either side of the 99th percentile, leave most patients in an indeterminate zone between cut points.

Causes of “false positive troponin” other than chronic myocardial injury

The adoption of a rule-in threshold above the 99th percentile and the use of delta change values increases the specificity of troponin for the diagnosis of NSTEMI to about 75%.⁶ These NSTEMI diagnoses include type 2 AMI, which is when there is no identifiable culprit plaque. Despite including type 2 AMI, which some cardiologists would view as a false positive diagnosis by itself, at least 25% of the patients above the immediate rule-in threshold do not have an AMI. The causes for these remaining “false positive” troponins are heterogeneous. Troponin release is not restricted to ischemic myocyte necrosis and it occurs with any form of injury, including viral myocarditis and cancer chemotherapy. Thus, troponin release almost always reflects true myocardial injury.⁷ The only exceptions are so called analytic false positive troponins from assays that misread the concentration for a variety of reasons, all of which are rare with contemporary assays and the appropriate quality controls that exclude hemolysed, clotted, and lipemic samples.

Conclusions

Various conditions, other than an acute atherosclerotic plaque rupture event, cause troponins to be released from the heart and to enter the circulation.

These conditions cause frustration and create the impression that the assays are at fault and prone to false positive reads, which is not the case! Rather, we are at fault for assuming the assays are able to determine a binary assignment into AMI and no AMI. The solution is a better understanding of how troponin can be used in a clinical framework that still requires an assessment of the pretest probability of disease and of individual risk. Troponin aids, but does not replace, clinical assessment. ■

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