# Lab: What have we done for you lately? The Troponin Issue

## Normal troponin

For most laboratory tests, the reference interval ('normal range') is selected to encompass the central 2 standard deviations (2SD) of a normal population. 2SD includes approximately 95% of an ideal population.

For troponin I (TnI), the definition of normal has evolved. Current international guidelines suggest that the reference interval include all values *up to the **99th percentile** of healthy adults*. Thus, an 'abnormal' TnI would be any above the 99th percentile. In our lab, this is any above 0.04 ng/mL.


Myocardial ischemia cannot be excluded with a single normal troponin. But the evidence is abundant that an admission and 3-hour TnI together may facilitate early exclusion of AMI. In fact, recent studies utilizing high-sensitivity TnI assays indicate that after the 3-hour TnI measurement, you can exclude MI with nearly 100% sensitivity, and that the subsequent 6- and 12-hour measurements are minimally informative. On the other hand*, a significant change in the TnI level from admission to **3 hours** may help establish an MI diagnosis*, even in patients with very low TnI.

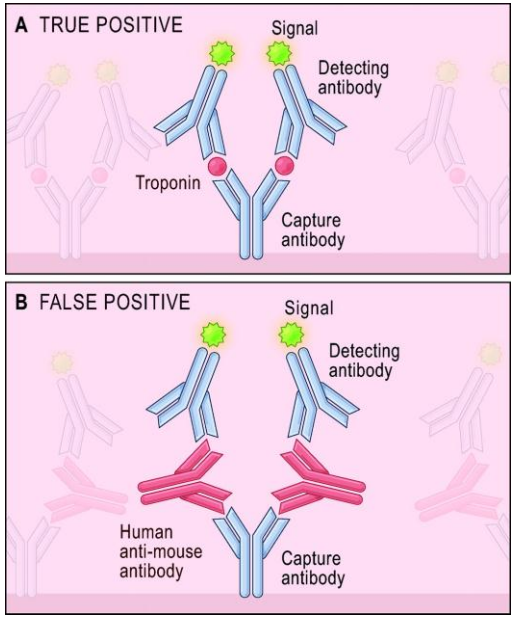
## Abnormal troponin

Most of the time, of course, this means myocardial ischemia, but sometimes not. Sometimes the laboratory detects TnI above the 99th percentile in a patient without myocardial ischemia. How could this be?


There is a large body of literature on the subject of patients with elevated troponin and no other evidence of myocardial ischemia; i.e. 'false positive' troponin. In a variety of single-institution retrospective reviews, the rate of these 'false positives' ranges from 0.2% to 4.8%. These 'false positives' fall into 4 categories.

1. Non-ischemic pathology: Acute pulmonary embolism, myocarditis, pericarditis, heart failure, intracranial insults, rhabdomyolysis, sepsis, shock, and renal insufficiency.
2. No pathology: the 1% of healthy adults whose TnI is normally above the 99th percentile.
3. Wrong patient's blood in the tube. Crazy, right? Happens all the time (up to 4 in 1000 blood draws). Was your nurse distracted? Did he or she label the tube at the bedside? Do the labels in her pocket belong to your patient? Or to the one in the next bed (the one clutching his chest)?
4. Analytical false positives

'Analytic false positive' equals 'Lab screw-up', right? Yes and no. Yes, it is a number with no basis in reality. No, it is usually not the result of poor laboratory practice. Widely reported in cardiology and emergency medicine literature, analytical false positive troponin is a phenomenon that is an inherent weakness of the available assays. There is a variety of causes that, like most lab stuff, is stimulating enough to serve as general anesthesia. So, rather than bore on, allow us to alarm you with this instead: Whereas, non-ischemic causes of TnI elevation (renal insufficiency, CHF, toxin, etc) are generally associated with low-level elevations (0.05-0.9ish), *most analytic false positives are actually quite high*. We have observed them as high as 0.56.

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## Normal but detectable troponin


It used to be that any measurable troponin was abnormal, because early assays were insensitive to very low levels of troponon. But troponin assays have evolved. A decade ago, no assay on the market could measure troponin at the 99th percentile with reasonable precision. Now, commercially available troponin assays can reliably measure troponin as low as 0.01 ng/mL, and some in development as low as 0.001 ng/mL. Our troponin assay, the Beckman assay available at BHS, can precisely detect TnI as low as 0.01 ng/mL. *As of June, 2012, we will begin reporting TnI down to this level.*

So what about the patient with detectable TnI at a concentration beneath the 99th percentile? A patient with TnI of 0.2 or 0.3, for example? It's still unclear, but it seems that patients with detectable TnI have higher 1-year mortality than matched patients with undetectable TnI. The published studies have findings similar to those of high-sensitivity C-reactive protein.

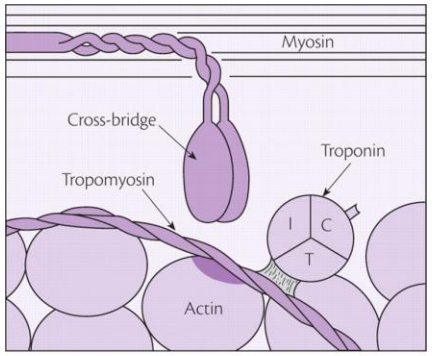
So what do you do with a patient who has detectable TnI below the 99th percentile? The same as you do with any other patient: modify risk factors and hope for the best.

## This next part is boring but important.

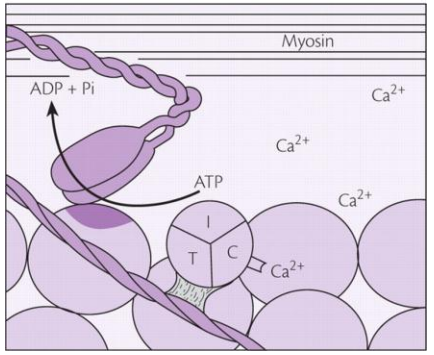
The rate of false positives for any test is inextricably affected by the prevalence of disease in the tested population. Without changing anything about the test itself*, the rate of false positives is **higher** if the prevalence of disease is **lower***. So, if you test every patient in the ER who has pain above the waist, then you must be prepared to deal with a lot of false positive troponins.

## The part where we summarize

1. The troponin test has changed dramatically over the past 10 years, so much so that *the way it is used must change also.* Troponin assays have achieved a level of sensitivity so high that there must be a careful approach to detectable and raised troponin values. In the words of the esteemed cardiologist Robert Jesse, "*When troponin was a lousy assay it was a great test, but now that it's a great assay, it's getting to be a lousy test*."ǂ




2. Assessment for non-ischemic pathology is required in patients with low-level TnI elevation, and in these patients a second 3-hour TnI may be enlightening.




3. Know that analytic false positives, some quite impressively high, do occur and will continue to occur for the foreseeable future. While we know that time is of the essence, question and repeat any test you do not believe.

4. A single negative troponin does not exclude MI. But there is increasing evidence that two troponins 3 hours apart, particularly with the new highly sensitive assays, might.

## At what level is troponin critical? Explain.

We would like to re-consider the troponin critical value, with input from cardiologists, ED physicians, and whoever else cares. If you have an opinion on this issue (and let's face it, who doesn't?), please email ddmais@baptisthealthsystem.com.

ǂ Jesse RL. On the relative value of an assay versus that of a test: a history of troponin for the diagnosis of myocardial infarction. *J Am Coll Cardiol*. 2010;55:2125–2128.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