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What Constitutes a Relevant Change in High-Sensitivity Troponin Values over Serial Measurement?


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Guests:
Dr. James de Lemos and Dr. Houman Khalili are both from the Department of Cardiology at the University of Texas Southwestern Medical Center in Dallas.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

The universal definition of myocardial infarction requires both an increase in cardiac troponin concentrations and changes in values over serial measurements. However, exact criteria regarding the magnitude of change in troponin remain elusive. In the June 2014 issue of *Clinical Chemistry*, two studies on biological variation of serum troponins helped shed further light on the kinetics of this important cardiac marker.

These papers are accompanied by an editorial written by Drs. Houman Khalili and James de Lemos on just what constitutes a relevant change in high-sensitivity troponin values. They are both from the Department of Cardiology at the University of Texas Southwestern Medical Center in Dallas, and they both join us in today's podcast.

Dr. Khalili, we'll start with you. What are the potential advantages of high-sensitivity troponin assays and where are these new assays currently being used?

Dr. Khalili: Given that these high-sensitivity assays can detect troponin levels that are less than 10 nanograms per liter, they have a very high sensitivity and discrimination for diagnosis of myocardial infarction relatively early after onset of a chest pain. For example, in a study that was done by Januzzi and published in *Circulation* in 2010, high-sensitivity troponin assays were able to detect about 27% additional cases of myocardial infarction that would have been otherwise missed by conventional cardiac troponin assays.

They also have a very high precision. Less than 10% coefficient of variation around the 99th percentile cutoff point, which allows for a much better characterization of changes in troponin values which are the measurements.

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As far as where they're being used right now, they're used in many parts of the world currently, including Europe and Asia, but not approved for use in the United States. The FDA, particularly over the past couple of years, has been stricter in approving new assays. The concerns of high false positive rates with these assays have definitely played a role in that regard.

Bob Barrett: What defines a myocardial infarction and why do new sensitivity troponin assays pose a challenge in its diagnosis?

Dr. de Lemos: MI is now defined using the universal definition of MI which is a consensus document from multiple professional societies. It requires, really, three components to meet the MI definition.

The first is an elevated troponin level that's defined based on a troponin value exceeding the 99th percentile value from the normal population. The second criterion is a dynamic pattern of the troponin elevation, so there's a rise and/or fall in levels indicating that the elevation is acute and not chronic. Third, and very importantly, it requires context from clinical information to define the acute troponin elevation as due to cardiac ischemia. That can be a good history for ischemia, or it can be EKG evidence of ischemia, or echo or other imaging evidence that would support the ischemic diagnosis.

The challenge is that as the assays get sensitive, many things besides acute MI can cause acute cardiac injury. With more sensitive assays, these are increasingly a problem. The other challenge is that it's highly contingent upon where the 99th percentile value is defined. Our group has recently published a paper that suggests that the 99th percentile value that's being used in most parts of the world for the high-sensitivity troponin T assay is in fact far too low, and that all men above 50 and women above 65 actually have a considerably higher 99th percentile value. This feeds in to the concerns that clinicians already have that the current assays are too sensitive.

The big problem we're having with MI diagnosis, really, isn't that the current assays aren't sensitive enough. It's that we have challenges interpreting whether the elevations are in fact due the MI or other causes. It's actually our view that the big advantages of the high-sensitivity assays probably won't be an MI diagnosis but in other disease states where increasing sensitivity may offer new opportunities for using cardiac injury as a prognostic marker. The one caveat that I want to come back to and just finish with is that, as Dr. Khalili said, these high-precision assays that are also highly sensitive offer the ability to characterize small changes over time, which is the potential advantage.

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Bob Barrett: Well, according to the current guidelines, how are significant changes in blood troponin concentrations defined?

Dr. de Lemos: Amazingly, they're not. There's really no information in the universal definition that provides guidance to clinicians about how to define a change, despite the fact that the guidelines require a change. There is some guidance in the National Academy of Clinical Biochemistry -- recommendations suggest that a relative change of 20% in troponin values over two measurements may be considered a significant change.

This was based not on any clinical validation but only on the appreciation that a 20% change would exceed analytical variation of the assay.

One challenge is that with these high-sensitivity assays, one can have a fairly substantial relative change over serial measurements even in the absence of acute injury. We've demonstrated this for example just with rapid atrial pacing in patients without ischemia, that you may have relatively substantial increases. So there really isn't a lot to guide the guideline writers with regard to what defines a significant change which is why these papers might be so important.

Bob Barrett: Well, let's talk about defining reference change value. What is that and how important is it when interpreting troponin concentrations?

Dr. Khalili: Reference change value, it can be a great tool in assessing what constitutes a significant change above "noise" in between two assay results that are obtained on two occasions. RCV, reference change value, it takes into account both the analytical imprecision and biological variation. The analytical imprecision is the inherent random fluctuations that you see with any assay. On the other hand, biological variations are these natural fluctuations of the biochemical maker that occur around a set point over time within an individual. We call that within-person biological variation. There are also differences between different individuals' set points, and that's referred to as between-person biological variation.

Knowing these variables, the analytical imprecision and biological variation, one can calculate a reference change value. This is typically expressed as a percentage; a change in the assay results that's greater than or less than that percentage can be considered, potentially, a significant change.

Now, reference change values are particularly useful when it comes to analytes where between-person variance exceeds

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that of the within-person variance. We call this the index of individuality or biological individuality. In other words, if you have two consecutive assay results that fall within the population base reference limit but yet the difference between two measurements, the delta change exceed the reference change value, that there may be a significant change. This could have been considered as a normal result with conventional reference intervals, but again, the delta change is exceeding the RCV so it's potentially a significant change and may warrant further evaluation or testing.

One can also envision a scenario that's the other way around where you've got two consecutive results that fall above the population base reference limit but on serial testing, there was only a small delta change. RCV can be of great use here as well.

Potentially, for high-sensitivity troponins, where again, given the sensitivity of these assays, you're going to have a lot of different patients with different medical conditions that have troponin levels that are above the population base reference limit. We can look at a consecutive testing of troponins in these patients and look at the delta change and perhaps use that information to guide further testing and evaluation.

Bob Barrett: Doctors, your editorial accompanied two papers, one from Norway and another from Australia. What were the major findings of these two studies?

Dr. Khalili: The study from Norway by Aakre et al, they collected blood samples from patients with end-stage renal disease who were receiving scheduled hemodialysis. Diagnosis of myocardial infarction using biomarkers including troponin is quite challenging in this patient population. They tend to have an elevated baseline level of troponin. So in a very laborious extensive analysis in their study, they looked at 90 minute reference change values for both high-sensitivity troponin I assay, and troponin T assays. They calculated the reference change value, the RCV, at negative 8 plus 5% for troponin T and negative 18 plus 21% for troponin I. What's really interesting, and I think, important, about these results is also that they found reference change values are lower than what is recommended by the NACB, which we alluded to earlier about a 20% relative change.

The study from Australia, Simpson and colleagues, they examined a group of Emergency Department patients that were assessed for acute myocardial infarction using high-sensitivity troponin I assay. These patients were discharged from the ED without admission given they had a low concern for acute MI. They used their previously published precision profile to estimate an open precision and then used repeat

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sampling as most of the previous study to calculate within-person biological variation as well as reference change value.

What's really interesting about this study is that it's a real-life study. The sampling intervals ranged anywhere from 1.5 hours to 17 hours. Despite this, the within-person variation didn't change much with different sampling intervals. They also calculated the absolute change in troponin measurement with the majority of patients, over 90% of them, having an absolute change value that was really small, less than five nanograms per liter. These findings can potentially be helpful to apply in these high-sensitivity troponin assays and some sort of algorithm for evaluating patients with chest pain in the ED.

Bob Barrett: How do the results of those two papers in *Clinical Chemistry* help in overcoming challenges with high-sensitivity troponin assays, and what are some potential strategies to use high-sensitivity assays effectively in a clinical setting?

Dr. Khalili: With the study from Norway, what's really interesting is that the relatively small within-person variation that was observed in the end-stage renal disease patient population. If that holds true, it suggests that the differences that we see in reference change values between ESRD patients and healthy patients is really mainly due to differences in analytical variance at different troponin levels rather than the intrinsic differences across different disease states. This could really make estimation of reference change value a much easier task if we know the analytical variance for a given troponin level as that may be enough without really having to know the biological variance for different disease states that are associated with elevated troponin levels.

As for the Simpson study, if biological variation and component RCV cutoff don't change significantly with collection times, it broadens the applicability of easy relative troponin changes in clinical settings with different testing intervals rather than having to check troponins at set intervals.

Having said this, we have to be cognizant of the fact that diagnosis of myocardial infarction is really not based solely on cardiac enzyme pattern. Utilizing different cutoffs for relative change in troponin over time is pretty useful in any diagnostic strategy. But it's not "be all end all." RCV can be certainly helpful in discriminating chronic elevation of troponin from an acute change in troponin, but there are multiple different acute medical conditions that can lead to acute elevation of troponin and MI, myocardial infarction, is only one of them.

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So in essence, RCV can be a great tool to use for ruling out MI in an MI rule-out strategy, but it may be too nonspecific for a rule-in strategy. To this end, there have been several novel strategies using different cutoff points for ruling out and ruling in MI to have proved effective in a small population studies, but they really need to be validated in a much larger cohort.

Bob Barrett: Well finally, doctors, let's look ahead. Where does the conversation go from here?

Dr. de Lemos: Well, I think this is a nice early step in attempting to figure out how to assess change, which is so front and center in the MI diagnostic algorithms. As Dr. Khalili said, I think that the RCV concept is going to be useful to establish that no change has occurred, in particular, that's clinical or analytically meaningful for rule-out MI strategies. But even that needs to be validated. What has to happen for the RCV-based rule-out strategy are much larger studies of relevant real-world ED populations that demonstrate that individuals that have serial measurements that fall below the RCV value in fact are not at risk for complications down the line, and with adjudicated panels, don't rule in for myocardial infarction.

It's going to be much more complicated with regards to using RCVs for MI rule-in and for identifying high-risk individuals. Clearly, many other conditions besides MI will lead to acute troponin elevations above the RCV value. Again, we believe that clinical validation and not just proof in principle studies like these are going to be needed to establish what levels of change in sensitive troponins are necessary to be confident that the patient has in fact had a myocardial infarction.

Having said that, the data here suggests that it may be an easier road than we had feared because this may not have to be done across every disease state based on the Aakre paper; we may be able to do this in a large representative ED-based population and then apply that more broadly. I think that's very encouraging and these are both important studies that to help us get closer to where we need to go.

Bob Barrett: Dr. James de Lemos and Dr. Houman Khalili are both from the Department of Cardiology at the University of Texas Southwestern Medical Center in Dallas. They've been our guests in today's podcast from *Clinical Chemistry* on interpreting high-sensitivity troponin assays. I'm Bob Barrett, thanks for listening.

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