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Diurnal Rhythm of Cardiac Troponin: Consequences for the Diagnosis of Acute Myocardial Infarction

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Guest: Dr. Steven Meex is a clinical chemist at the Central Diagnostic Laboratory at Maastricht University Medical Center in the Netherlands.

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.

Clinical practice recommendations call for use of serial measurements of high sensitivity troponin, a cardiac biomarker, to diagnose acute myocardial infarction. The interpretation of these results relies on the assumption that concentrations of troponin randomly fluctuate around an individual's homeostatic set point. If instead troponin shows diurnal variation, meaning its concentration changes in a given pattern throughout the day, this could impact its diagnostic performance.

Researchers from the Netherlands recently tested this hypothesis for the two troponin isoforms and evaluated the effect on diagnosis of acute myocardial infarction. The results of this study appear in the December 2016 issue of *Clinical Chemistry*. We're joined for this podcast by the article's senior author, Dr. Steven Meex. Dr. Meex is a clinical chemist at the Central Diagnostic Laboratory at Maastricht University Medical Center in the Netherlands. He heads the unit General Clinical Chemistry there and performs research on cardiac biomarker.

So Dr. Meex, a number of hormones exhibit diurnal variation, but it does seem unexpected that Troponin T would show this pattern. Why do you suspect the diurnal rhythm for Troponin T?

Dr. Steven Meex:

Yeah, that's a very good question. It was quite unexpected for us as well. This whole study actually started with a previous publication of our group in 2014 in the *Journal of American College of Cardiology* and in a very small group of patients with Type II diabetes. Actually, in seven patients we found quite unexpectedly that Troponin T was exhibiting a diurnal rhythm, and that was a very preliminary observation that we did not really understand. Based on this initial observation, we decided to follow up on this pattern because we didn't understand it and in theory, it could have currently relevant consequences. So, that was actually the start of the study. What we were not sure of at

the start is whether this diurnal dip pattern that we found in male Type II diabetes patients is whether that would extend to the general population. So both males and females, also people with old Type II diabetes, and that's why we decided to actually follow up in this finding and study this in a more extended study that we now publish in *Clinical Chemistry*.

Bob Barrett: What was your approach to investigate this hypothesis?

Dr. Steven Meex: We did in fact two separate studies. The first study was actually a classical biological variation study. Here, what we did, was recruited 24 individuals, and we sampled a lot in these individuals for a period of 25 hours in all these subjects. What we did then is we just sorta into biological variation. We measured Troponin in all samples, Troponin T and I, and we measured them in all the samples and we just looked at what the pattern was during the day for both Troponin T and Troponin I. Then we conducted a second study and that was a collaboration with the group of Christian Mueller, Dr. Christian Mueller in Basel, Switzerland. That was actually a prospective diagnostic study using the APACE score, and APACE stands for Advantageous Predictors of Acute Coronary Syndrome Evaluation study. What we had there was actually a population comprising 2,782 consecutive patients presenting to the Emergency Department between 2006 and 2013 with symptoms suggestive of myocardial infarction. For all those subjects that were in the study, there was adjudicated diagnosis of either myocardial infarction or something else.

So, what we did in the second study is we evaluated based on the first study, is whether the diagnostic accuracy was different depending on whether Troponin was high during the day, physiologically high or physiologically low. Those were the two approaches that we did.

Bob Barrett: So please talk about your findings.

Dr. Steven Meex: Well, the first study was going back to the biological variation study. It was actually a confirmation of our original finding in 2014 and an extension of that. So what we found is that actually all patients exhibited a diurnal Troponin T rhythm. Meaning that that Troponin T was highest in the morning, gradually decreased during the day, and rose again during the night, to peak again in early morning. This was independent of sex, independent of age, and the higher the baseline Troponin value was, the stronger the rhythm that we observed. Interestingly, it's when we looked at Troponin I and we measured those with two different assays, the high sensitive assay from Abbott and a sensitive assay from Bachmann, we found actually no rhythm at all. So there was just random fluctuation of

Troponin I during the day with no systematic variation as we saw that for Troponin T.

So that was actually confirmation and strong proof that it is actually a general phenomenon that is present in all subjects.

Bob Barrett: So, what was the effect of the diurnal Troponin T rhythm on the diagnostic accuracy of Troponin T for acute myocardial infarction?

Dr. Steven Meex: Yeah. That was actually what we tried to evaluate next in the second study. What we found there is when you consider the whole population, there was not a big effect on the diagnostic accuracy for the population as a whole. So that is actually part of a fortunate finding because the impact for the clinic would be quite dramatic if we would have found that patients presenting at the Emergency Department in early morning would have a different diagnostic accuracy than in the evening, but that was not the fact and that is a fortunate finding I think.

What we did find is that in patients presenting very early after symptom onset, that there was a small difference in diagnostic accuracy in early morning compared to evening, which is in line with the diurnal rhythm that we found for Troponin T. However, it should be stressed that this finding was statistically significant because of the high number of subjects included in the study, but the true value in terms of diagnostic accuracy was so small that the clinical impact, if any, is actually very limited. That means actually that both Troponin T and Troponin I remain excellent biomarkers to diagnose myocardial infarction and that the effect of the diurnal rhythm that is there, that is confirmed in the study, that it is actually limited for the clinical and the biomarker diagnosis of myocardial infarction.

Bob Barrett: So, it does seem fortunate that the impact is so limited. Are there other clinical settings where the Troponin T rhythm may be relevant?

Dr. Steven Meex: Well, one of the settings that may be relevant which is becoming more and more actual these days is in prognostic medicine. So Troponin T and I are not only interesting for diagnosis of myocardial infarction, but more and more people are researching their potential as prognostic markers.

Well, given the rhythm in all subjects, it is definitely worth researching what the effect would be in large epidemiological studies where the value of Troponin T is evaluated as a prognostic marker, to which extent that it is impacted by the diurnal rhythm. That is something that has

not been done so far but it is definitely something that should be followed up. We just don't know what the effect would be, but given the size of their diurnal rhythm, it is not unlikely that there is some kind of an effect there. That it may also mean that the prognostic performance in samples taken in the early morning may be different in samples taken in the late evening for example.

Bob Barrett: Well, finally, Dr. Meex, why is there a rhythm for Troponin T but not for Troponin I?

Dr. Steven Meex: Well, that's a very interesting question and it's something we're not quite certain about yet either. So, this study definitely shows that it is restricted to T because we tested in total three I assays. We measured Troponin I with Abbott, Troponin I with the Bachmann, and using the cohort from Dr. Mueller of Switzerland, we saw that there in that cohort, it was measured with Siemens, and we found also a confirmation of the absence of rhythm.

So, it seems quite reproducible. Why it is its not completely clear to us? What is in fact, however, is that both molecules have different sizes and perhaps different way of degradation in the body. So, probably the root of how the molecule is degraded is different and that impact perhaps the half-life of the molecule in the body and hence, the presence or the absence of a diurnal rhythm. But that is quite speculative and we actually don't know yet whether that is really true and that is definitely something to follow up in the future research.

Bob Barrett: Dr. Steven Meex is a clinical chemist at the Central Diagnostic Laboratory at Maastricht University Medical Center in the Netherlands. He has been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.