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High-Sensitivity Cardiac Troponin T for the Detection of Myocardial Injury and Risk Stratification in COVID-19

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Guest: Dr. Yader Sandoval is Director of the Coronary Artery Disease Clinic and Associate Professor of Medicine and a Consultant in the Division of Interventional Cardiology and the Department of Cardiovascular Medicine at the Mayo Clinic in Rochester, Minnesota.

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

The COVID-19 pandemic has resulted in substantial morbidity and mortality worldwide. While pulmonary complications are frequent with SARS-CoV-2 infections, studies suggest that myocardial injury is also common, in particular among those with chronic cardiovascular conditions and more severe COVID-19 presentations, and these may be associated with poor outcomes. Yet, limited data exists on high-sensitivity cardiac troponin for risk stratification in cases of COVID-19.

A paper appearing in the August 2021 issue of *Clinical Chemistry* describes a multicenter study of myocardial injury and risk stratification in COVID-19 patients. To help address that very question: the senior author for that study is Dr. Yader Sandoval. He is Director of the Coronary Artery Disease Clinic and Associate Professor of Medicine and a Consultant in the Division of Interventional Cardiology and the Department of Cardiovascular Medicine at the Mayo Clinic in Rochester, Minnesota and he is our guest in this podcast.

First of all, Dr. Sandoval, so that all of our listeners are on the same page, what is myocardial injury and what is its relevance to COVID-19?

Yader Sandoval: Yes Bob, thank you for the opportunity to chat about our paper in *Clinical Chemistry* on this issue of myocardial injury and high-sensitivity troponins in COVID-19. So myocardial injury is defined by the fourth universal definition of myocardial infarction, and even before that document has been defined for some time as such, but it's defined just from an analytical biochemical perspective as any troponin concentration that exceeds the 99th percentile of presumably healthy reference cohort.

It can be acute, chronic that it shows irrespective of the etiology just has concentration above the 99th percentile defines myocardial injury. And part of the issue that relate to

COVID is that from early in the pandemic, some of the original studies that were coming out, a number of publications have indicated that in patients with COVID, when they were being evaluated with cardiac troponin assays, whether they were conventional, contemporary, or high-sensitivity, that it was not infrequent that they had evidence of myocardial injury as identified using this test.

Some of the original studies were not necessarily using the 99th percentile. Others were using other variations of non-guideline definitions of what is myocardial injury. For example, they were using ECG abnormalities, for example, or other imaging abnormalities. But the definition per textbook, it's just an analytical one on the basis of the cardiac troponin increases. And that was part of what we did in our study, which we can discuss further, but essentially myocardial injury is defined by cardiac troponins above the 99th percentile and the distinction from infarction is that for you to have infarction, one needs to have clinical evidence of myocardial ischemia.

Bob Barrett: What are the mechanisms leading to myocardial injury in general and in cases of COVID-19 infection?

Yader Sandoval: That's an important question. As we discussed before, myocardial injury is justified by cardiac troponin increases above the 99th percentile and that definition upfront tells you that quite an array, a whole list of potential mechanisms and etiologies, and that it's very broad term. We did the original work that I can discuss where further that was published in *Clinical Chemistry*, but we had actually tabulated also last year in JACC with some of the authors from this paper, also a conceptual approach as to how to think of myocardial injury in COVID-19.

And when you think about the mechanisms and etiologies, I think in general one wants to think: "is this an acute process or is this a chronic process, irrespective of whether it's related or associated with COVID-19?" Because the reality is that what we have learned is that a number of patients that are having particularly more severe illnesses with COVID-19 are often those that are more elderly, those that have comorbidities, those that have chronic cardiovascular disease, for example, such things such as heart failure or hypertension or cardiomyopathy, so it is those patients that are elderly with comorbidities that are often having a less favorable outcome.

And the reason that's relevant is because we know from the extensive literature on cardiac biomarkers and on high-sensitivity troponin that this population by itself, irrespective of the issues that came with COVID, these populations often can have increases in cardiac troponin concentrations above

the limit of detection or quantitation or well above the 99th percentile.

So now the COVID-19 pandemic, once that initiated and we were seeing these patients in the hospital, the first question when we think about mechanisms is: is this an acute process or it's a chronic process, because patients with this chronic conditions such as chronic heart failure, cardiomyopathy, hypertension, advanced renal disease, all of these patients often can have increases above the 99th percentile and they can certainly also present with concomitant COVID-19 infection. So in that case they may have chronic myocardial injury that is part of their chronic illness and not necessarily because of a direct association with COVID-19. So that is one mechanism.

The other mechanism that we want to think is that they said if it's not chronic, is this acute? And if it's acute, the big question, at least clinically speaking, in relationship to the universal definition of myocardial infarction and also with interpretive biomarkers is, is this an infarction or is this just plain non-ischemic myocardial injury?

And what helps facilitate this distinction is essentially the clinical context and clinical information. So if what we are looking for is, is a patient having clear unequivocal ischemic sounding chest pain or angina? Is the EKG, the electrocardiogram showing clear signs of ST depression, new diagnostic T-wave inversions, ST elevation, so clear diagnostics of the abnormalities? Are there new imaging changes such as regional wall motion abnormalities or I think some more severe cases has occurred, is there a presence of, for example, thrombosis in the coronary arteries?

So if we have features, objective features of myocardial ischemia, then there are some patients with COVID-19 that can have concomitant acute myocardial infarction. In some cases it may be an association. In some cases it may be secondary to it, and that sometimes can be very clinical to distinguish.

Something that we addressed in our paper from *Clinical Chemistry* was this issue of type 1 versus type 2 MI, because not much data has addressed the incidence of myocardial infarction. And conceptually, conceptually speaking, because patients with COVID-19 often are critically ill and they have respiratory failure, and hypoxia, and in more severe cases they can have full-blown sepsis and hypertension and tachycardia and tachyarrhythmia, the idea was that this was in a scenario where all these things would combine and we would see a lot of type 2 myocardial infarction caused by all these imbalances in supply-demand mismatch.

On the other hand, there has been a number of case reports in series suggesting that there might be some prothrombotic nature to COVID-19 that may promote also coronary thrombosis or microvascular artery disease and whether some of those cases can be more type 1 myocardial infarction and their expressions have failed after a thrombosis and this can be very hard to distinguish.

In our particular study that we evaluated 367 patients with COVID-19 that underwent troponin, we actually found that about half, 46% of them, had myocardial injury. But interestingly enough, when we went ahead and we classified all these cases following the criteria from the universal definition of MI, what we learned was that the vast majority, 95% of the cases that we evaluated were just plain isolated myocardial injury. They did not have overt evidence of myocardial ischemia. We only identified a handful of type 1 or 2 myocardial infarctions. So despite those initial concerns, it appears that most of the injury that we identify in patients with COVID-19 is just isolated myocardial injury which can be acute or chronic, but not necessarily infarction.

And that of course brings us to the question as to what is the nature of this acute non-ischemic myocardial injury, and when we think about that, I think what we are trying to think is, is this a primary cardiac or a primary non-cardiac illness? And I think in a lot of these patients there is often a lot of also concomitant primary non-cardiac issues, whether that's critical illness by itself, whether it's sepsis; there has been of course a lot of data on pulmonary embolism that can occur. There can be stress cardiomyopathy. And there is of course cases and some data to suggest that there can be myocarditis and even potentially direct SARS-CoV-2 injury.

In our particular experience, clinical, our clinical data that we evaluated in this study, we evaluated all this cases with cardiac troponin increases, things that have raised previous concerns such as myocarditis, those things were actually fairly rare in our study. And as I say most of the experience was just isolated non-ischemic myocardial injury with things such as myocarditis being fairly infrequent.

Bob Barrett: Dr., besides its application as a diagnostic tool to detect myocardial injury, does high-sensitivity cardiac troponin offer other information among patients with COVID-19?

Yader Sandoval: Yes, that's a very important point. So in our paper on high-sensitivity troponin for the detection of injury and risk stratification in COVID-19 that we now present in *Clinical Chemistry* led by our colleague Dr. Laura De Michieli, and a number of our colleagues at Mayo Clinic, we specifically addressed that, because we wanted to look at both issues; the ones that we have been talking about thus far as to what

is the frequency of myocardial injury and what are the mechanisms and so on.

But we know from a number of recent studies that high-sensitivity cardiac troponin assays are a great risk stratification tool, both in the acute setting as well as for intermediate and even long-term data.

There is in particular numerous studies and meta-analysis that have suggested that a single sample of cardiac troponin measured, whether T or I assays in patients coming to the emergency department with symptoms suspicious for ischemia or for myocardial infarction that if we measured a single sample, that can be tremendously informative in understanding whether patients are at high or low risk for subsequent cardiovascular events.

With that history and that background of information that we knew about troponin, we therefore went ahead and probed whether this applied to patients with COVID-19. There had been data published early in the pandemic that troponins were an adverse prognostic feature and that is not surprising if you have myocardial injury and marked troponin increases, the higher the worse that you are able to perform and have an unfavorable outcome.

But what we were particularly interested in, at the other extreme, can this be a good tool to triage and risk stratify patients at both extremes? So we probed that, and we probed that and we identified that indeed consistent with other studies and other observations that troponin is associated with adverse outcomes; and they have higher risk for mortality, higher risk for major adverse events and both troponin increases as well as myocardial injury.

But a particular application and what we feel is a contribution from our study, is that we identified the patients that had a high-sensitivity cardiac troponin T that was below the limit of quantitation of 6 ng/L, had a very favorable outcome. Actually, in our study we identified that 26% of patients with COVID-19 that had a value that was below 6, none of them died. There was no mortality in that patient subset. And actually had a negative predictive value of about 95% for major adverse events.

So it appears to be a tool that if one has seen the early unidentified patient in which one tries to understand where they stand in their course, whether this is somebody that is at high risk or low risk, of course there is a number of clinical parameters and other biomarkers that have been evaluated, but troponin can be another important, very accessible and a widely available tool that can be used to risk stratify these patients.

I think it's important to highlight also that while we showed that a troponin below 6 was not associated with mortality itself, by the same token, these patients can still of course have respiratory issues or respiratory failure, but at least identified patients that were at a very low likelihood for mortality, with a good negative predictive value sensitivity for major adverse events.

And that is a tool that we find informative for clinicians at the front end when they are trying to risk stratify and triage patients with COVID-19.

Bob Barrett: Well, finally Dr Sandoval, every study has its strengths and its limitations. How would you characterize those for this particular study, and what future studies do you believe are needed moving forward?

Yader Sandoval: Similar to other studies, our study was observational in nature and retrospective. So we relied on patients that underwent clinically indicated cardiac troponin measurements and patients that had COVID-19. And that already tells us that there is of course some selection bias, and this has been the case for most studies in this field. While on one hand that is a limitation in that it's hard to speak with confidence as to what is a true incidence of myocardial injury in COVID-19 unless there is consecutive measurement of troponin in patients with COVID-19.

By the same token, there is some strength in this observation, and the strength is the following. These were patients that there was a clinical need for troponin to be measured. So they were probably at some degree of higher risk, even though they were higher risk suspected by the clinicians for them to order the test, when we adjudicated them, they were infrequently identified to have myocardial infarction or things like myocarditis. When we curated these cases and adjudicated them and classified them, as we discussed before, 95% of them had isolated myocardial injury. Only 5% met criteria for infarction type 1 or 2, and conditions such as myocarditis were pretty infrequent.

So while there was some selection bias, it tells us that in those that we select troponin, the conditions that early on we had some degree of higher concern, that was, at least in our observation, that was not frequently encountered.

What studies are needed in the future? I think specifically studies that evaluate this more in a consecutive fashion. We want to understand in the overall consecutive all commerce with COVID-19, what is the frequency of myocardial injury? That I think continues to be a question.

Likewise, another limitation is that while we did have some analysis based on delta and serial measurements, ideally one would want to know if myocardial injury occurs, what happens in serial measurements. Are these patients manifesting more acute or flat chronic patterns? And if acute injury occurs, when does it resolve? So we need studies that hopefully have more cardiac troponin samples and other biomarkers over time, both in the inpatient setting and even with doing follow-up to have a better understanding of the analytical trends and patterns of this concentration. So more information is needed in that aspect.

Bob Barrett: That was Dr. Yader Sandoval from the Department of Cardiovascular Medicine at the Mayo Clinic in Rochester, Minnesota. He has been our guest in this podcast on Myocardial Damage and COVID-19. He is senior author of a paper describing a multicenter study detecting myocardial injury and risk stratification in COVID-19 patients that appears in the August 2021 issue of *Clinical Chemistry.*

I am Bob Barrett. Thanks for listening.