The Importance of the ECG in Interpreting Troponin

Announcer: Welcome to Mayo Clinic's ECG Segment: Making Waves, continuing medical education podcast. Join us every other week for a lively discussion on the latest and greatest in the field of electrocardiography. We'll discuss some of the exciting and innovative work happening at Mayo Clinic and beyond with the most brilliant minds in the space and provide valuable insights that can be directly applied to your practice.

Dr. Kashou: Welcome to Mayo Clinic's ECG Segment: Making Waves. We are so glad you could join us today. Today, we have an exciting episode planned for you as we look at the utility of cardiac troponin in clinical evaluation. We'll be joined by one of the leaders in the field who has done extensive work on the topic. So, let's get started. Cardiac biomarkers can be used to expedite the workup for patients with suspected Acute Coronary Syndrome or ACS. Many screening and triaging protocols used in practice today for ruling in or ruling out ACS rely on a rising or falling pattern of cardiac troponin levels. The development of high sensitivity cardiac troponin assays has helped triage patients with ACS more accurately and rapidly compared to prior assays. At the same time, understanding how to interpret, integrate other diagnostic tools, and respond to various value changes and high sensitivity cardiac troponin during evaluation is important but can be difficult. In today's episode, we will look at how to do just that. We will discuss how to best use high sensitivity cardiac troponin levels in suspected ACS and the utility of the ECG in such cases. We'll also look at how this evaluation of cardiac troponin levels in various patient populations can be done in the acutely ill patients and the postoperative patients, as well as those with chronic medical conditions. We have a lot in store for you today and we are fortunate to have an expert in the field joining us to help us better understand this clinically important topic. Let me introduce you today's special guest, Dr. Allan Jaffe. Dr. Jaffe is a professor of medicine in cardiology as well as a professor of laboratory medicine and pathology at Mayo Clinic in Rochester, Minnesota. He has been involved in the development and validation of the use of a variety of cardiac markers including cardiac troponin during his long career. He's one of the principal investigators involved with the development of the universal definition of MI as a result of his primary clinical activities related to diagnosing and treating patients with ischemic heart disease. Dr. Jaffe, what a true honor to have you joining us today.

Dr. Jaffe: Tony, it's my pleasure to be here.

Dr. Kashou: Now, there's so much I wanna discuss with you today, so let's get to it. Now, you're aware that the cardiac biomarkers are widely used today in clinical practice. Yet, they can give pause to many clinicians when attempting to interpret their clinical significance to the patient they're actually caring for. Perhaps you can share a little bit about how to best use high sensitivity cardiac troponin levels, especially in suspected ACS, and maybe share how to integrate these levels with the ECG to make it most valuable.

Dr. Jaffe: Glad to, Tony. I think we need to take a step back and understand where we came from. For years and years, with insensitive markers like CK-MB, the idea was any elevation of CK-MB, by definition, was an MI. And that worked reasonably well. There were maybe 10% of analytic and false positives due to skeletal muscle disease, but bio-enlarged CK-MB was relatively insensitive, but big increases are what you see usually with ischemic heart disease. So,

when you had an elevated CK-MB on a statistical basis because it wasn't very sensitive, you could say, well, likely ischemic heart disease, likely an MI. And this fed a paradigm that clinicians got used to. Patient comes in, has an elevated CK-MB, probably needs to go to the cath lab and have their coronary arteries investigated. That paradigm changed with cardiac troponin and it started many years ago. Even the first iteration of cardiac troponin assays were far more sensitive than CK-MB. They identified initially in the preliminary assays that we developed, maybe 30% or more patients who didn't have elevated CK-MB who had elevated troponins. And it was clear those patients had the same propensity to have an underlying cardiovascular problem, often coronary disease initially, and had an adverse prognosis. And it was for that reason why over time troponin replaced CK-MB, not only because it identified additional patients but because it had a nearly perfect specificity for the heart. That is to say CK-MB could be elevated when one had skeletal muscle disease. And there were eventually, over time, a large number of circumstances in which people had concerns over what a given elevation meant. And the question was, for example in hypothyroidism, is it due to poor clearance of CK-MB? And it probably was. In rhabdomyolysis, you would see the CK-MB go back up 'cause skeletal muscle would re-express the B chain. So there were a large number of areas where there was a problem with specificity. So troponin, in addition to being more sensitive, was more specific. And that's the reason most of us were interested in developing it in the first place. Over time, what has occurred is these assays have gotten better and better and better. They are more precise. They are more accurate. And therefore, the numbers are more meaningful. In addition, it's gotten more sensitive and as these assays have gotten more sensitive, we've found that there are a large number of circumstances that can cause elevations of cardiac troponin. And that bothers clinicians 'cause no longer can they say, "Elevated biomarker, go to cath lab." Because the truth is that the frequency of MI in the United States emergency departments is less than 10%. In our own institution, when we looked, it was 8.1%. Parkland has recently published their experience. The frequency of MI was 2.1% from all the- And that includes all the people in whom they got cardiac biomarkers and troponins. So the reality has become that the most common cause of an elevated troponin is not ischemic heart disease. It's something else. I would call it, for want of a better term, myocardial injury. And the question is then, how do clinicians sort these things? Well, the first thing that you have to do when you sort something is start out with a pretest probability so that you can think about it properly. If you just get the troponin and you haven't thought about how it fits the patient, then the troponin drives the car. If you've thought about what the pretest probability of ischemic heart disease, for example, is in a given individual, then you drive the car. And when the troponin comes back, if you think this was a very poor story and the troponin is elevated, you're sensitized to say, "I should look for the other ideologies of myocardial injury." But if you don't do that, you say, "Could it be?" And sure, it always could be. And if you look... And I'll just use data from our own emergency department. Of the people who have troponins tested, about 40% have an elevated troponin. As I told you, about 8% have MIs. So 80% of the people with an elevated troponin aren't having acute ischemic heart disease problems. So, how do you sort that? Well, there have been several proposals to how you sort that. Proposal number one is the higher the value, the more apt you are to have ischemic heart disease. That works really well if you just cone your population down and you say, "I'm only gonna take the people who present with clearcut chest pain and whom my only question is, are they having an MI?" A value with troponin, T, which is what we use and 52 as a predictive value. At the first value in that particular population, about 70%. And if you use a 100, which is what we use here, it's over 90%. However, if you apply that principle to the overall number of

people who have cardiac troponins drawn, doesn't work nearly as well because elderly people have elevated troponins. If indeed you were to use those cutoffs of 50% and 100%, you'd be admitting 50% or more of your dialysis population because they tend to have chronically elevated troponins. So there are a variety of structural disease. The critically ill often have... About 25% of patients who are critically ill will have an elevated troponin. So if you add them, our most recent analysis would say that sensitivity for MI is about 22%. Not the 80%. So that doesn't work, ideally. One thing that helps is to look and see the pattern of troponin. Does it change? Increases in troponin or decreases. Say, something acute has happened. And it may well be if it's a down slope that had happened 12 hours or so before. But if it's rising, it says there's something acute going on. So you can improve specificity by looking at the pattern. And rising pattern or falling pattern for that minute means that there's acute myocardial injury. A fair number of individuals will not have any change. And within a couple of exceptions that you have to be careful of, like somebody late after the presentation of an MI. Because the down slope of the time concentration curve is slower than the up slope, generally you have chronic myocardial injury. So you can start by looking at the Delta. And with the caveat I gave you of the late presenter, if indeed you don't have a Delta, then you likely have chronic myocardial injury. Structural heart disease of some sort, which we'll get to in just a moment, a few moments-

Dr. Kashou: And how about the timeframe though between those zero to two? I know there's something-

Dr. Jaffe: We'll get to that in just a minute. For the acute changes, if you have an acute change, you have an acute myocardial injury. Now, some people want to do that at one hour. We decided not to do that analysis at one hour and the reason for it was that when we looked at the imprecision profile of the specific assay that we were using here, we said the distinction between three and five which is what the guidelines would suggest, too tight. And we're gonna have some people misclassified based on imprecision alone. So, we went to a two-hour protocol. All that said, that's much different than the six or eight-hour protocols we had in the past. So you can look for a rising pattern because patients with MIs should have a rising pattern. So, you improve specificity with a rising pattern. But you don't make it perfect still because the critically ill can have a rising pattern. You can have a rising, so you have sepsis, acute respiratory failure. Patients with pneumonia can have stress-related increases. We saw a huge number of increases with COVID. Why? All those patients weren't critically ill anywhere, but there's underlying cardiovascular disease that is exacerbated by an underlying disease process. So, what else then can you use? Well, there are multiple things you can use. One is the clinical information, history, physical examination. If they're taken well, they can be terribly informative. The physical exam. I can't tell you, I work in the ED periodically, how many patients I've seen where an elevated troponin was due to aortic stenosis be? But it wasn't appreciated because a good physical exam hadn't been done. The ED is a tough place. It's noisy, hard to listen, hard to hear, hard to have enough time to scrutinize. And this is where the electrocardiogram also becomes terribly important. Someone has ST elevation. It's easy,. But often, you can look then for ischemic looking changes: plain RST depression, deep symmetric T-wave inversion. All of then would tell you, well, assuming there is an electrolyte abnormality here, we need to be really careful because this might be the ischemic presentation that we've liked troponin to help us with so that additional level of specificity can come from the ECG. And quite honestly, I think in the long run, we need to figure out what are the changes that are most apt to be ideal. And that's an

opportunity for those of us who work on ischemic heart disease to lever the ECG findings and say, "What are the patterns that ought to make us think of ischemic heart disease to a greater extent than anything else?"

Dr. Kashou: And that's exactly what I was gonna get to with. What are those clinical scenarios where cardiac troponins can be used to actually improve the clinical utility of the ECG?

Dr. Jaffe: Well, I see it the other way around. You see, I don't see the cardiac troponin as helping the ECG. I see the ECG as helping the cardiac troponin. So if the troponin is elevated, for example, and you have ECG changes that suggest ischemic heart disease. Wow, that's good. But then again, where is that injury coming from? There have been a variety of cases that have been presented at national meetings. Now I no longer speak up at those when I hear these case presentations. But they present a case of a patient who has an elevated troponin. A wonderful story for ischemic heart disease and an unimpressive looking electrocardiogram. And what do I want you to think? Well, if you really think it's ischemic heart disease and the 12 Lead electrocardiogram looks okay, maybe posterior leads would be informative. And in point of fact, those are the sorts of cases they have presented. And those are real world cases. We miss circumflex occlusions all of the time in triaging and explaining cardiac troponins.

Dr. Kashou: That's a really good point because... You know, getting the extra leads. Actually, that's something I learned when working with you as a resident, of getting those posterior leads because the left circumflex is often silent. I wonder how about something like reperfusion patterns that... You know, they have these huge ECG changes yet we get the troponins and they could be completely normal. Any thoughts on, say, De Winter pattern where you get these magnificent ECG patterns and you're like "wow" and then you get the troponin. It may be early on. It's normal. Any thoughts to that?

Dr. Jaffe: Well, we did a study some years ago and I'll take a little bit of issue with you. And the patients I've seen with De Winter's pattern, they almost always have an elevated troponin. And we actually asked the question, how often do you have an ST elevation MI and a normal troponin at baseline? And even with the prior iteration of assays, it was really small. And the reason it's really small is not because the protein washes out of the myocardium so early. Because in point of fact, if you have a totally occluded vessel, it has trouble getting out. It's because, as we'll talk about later when we start to talk about chronic disease states, all of the comorbidities that lead to atherosclerosis cause increases in cardiac troponin, usually within the normal range. But somebody comes in with diabetes, hypertension, hyperlipidemia. All right. Without the MI, it's gonna have a slightly elevated troponin anyway. So you almost always see a signal. The important part to my way of thinking is then to say, where' is that signal coming from? And that's where an ECG that says, "this looks like De Winter's sign" all of a sudden becomes actionable. Because if indeed you're not sure if it's De Winter's sign but the troponin is elevated and the story is reasonable, you got a pretty good way to move forward. On the other hand, if you're ambivalent about the ECG and the troponin is totally normal and the story isn't really strong, you have a different way to move forward. So, taking these things and putting them together is what can give you modifications. The same thing, and I think, is very important. There's some patterns which several people have articulated are associated with an occluded coronary artery. And there's a subset of patients with non-STEMI who have total occlusions. If you look at DA

Wood's original work, it was only about a third, 33%, in the original DA Wood's study. And even that today with more sensitive probes, it's probably not huge. But if you look and there's several recent reviews, those patients do poorly. So one of the challenges and one of the ways we need to move forward is if you have a high pretest probability for ischemic heart disease. You've got an elevated troponin and you've got an ECG that is suggestive of one of those circumstances. And I would argue that we need better processing to identify those patterns because although I like ECGs so I think I can identify many of them and I have friends and colleagues who can identify a lot of them, the vast majority of people can't. And so this is an area where those of you who are interested in the processing of ECGs could really help us by helping to identify in an automated way when the ECG should lead us to say, "This is a high risk non-STEMI." As opposed to waiting, as we often can, whether it's six or eight hours. This is a high risk STEMI that should go in one or two.

Dr. Kashou: That's really interesting, and we've already almost touched on that. I don't wanna go down the whole AI route because that could go into another discussion for us. But I see a tremendous value in if we can automate that. Just as you said, really identify some of these subtle patterns that may be suggestive of ischemic heart disease or occlusion MI that most providers can't see. Now we've already touched on some of the patient populations, but I wonder if you could tell us a little bit how to use the high sensitivity cardiac biomarker in those that are acutely ill, and you've mentioned some of it. But even postop patients. What's the best way we look at it?

Dr. Jaffe: Well, there are two or three... There probably are two bins. The critically ill, often have an elevated troponin. And the way in which we have thought about them, I would argue, is not as good as it could be. We say, are they having an MI? Well, most of them are not having a Type 1 event anyway that would lead you to want to take them to the cath lab without showing you either ST elevation or some human inimic instability that is severe. They might be having a Type 2 MI, but in the absence of really seeing evidence of ischemia, often these patients can't talk to you. So, you have a choice of either getting that evidence via the ECG or via imaging. And I would argue that the ECG fails fairly rapidly there because it's taken in a time when often the patient is stable and it may be five minutes later that they're ischemic. And the same principle holds for the postoperative situation, which we'll talk about in a minute. So in that situation, if indeed you have ischemic heart disease which you're looking for, having a rising pattern of troponins helps some but it doesn't help enough because the rising pattern can be due to acute myocardial injury. And one of the things that bothers me since we always are thinking of, "Oh, no heart attack. I can go away." It keeps us from thinking of the alternatives. So for example, some years ago, a collaborator in Israel and I, called by the name of Georg Landsberg, looking at patients who were septic saw that troponin seemed to correlate best with those who didn't get adequate fluid resuscitation during their septic course. And we said, "Why is that?" And we looked at their diastology. And lo and behold, they had abnormal diastolic filling. So Georg went ahead and he went and did 250 consecutive patients who were septic with 3D Echo. And lo and behold, the best correlation for an elevated troponin was not ischemic heart disease, was not Type 2 MI, it was diastolic abnormality and an enlarged RV, suggesting that some of likely the cytokines, TNF, all of the heat shock proteins that are elaborating in sepsis may well have an effect on myocardial stiffness and diastolic filling. And when we only think of these patients as having coronary disease, or we don't care, we lose the ability to start to think about these mechanisms. Maybe slowing heart rate, not necessarily with a beta blocker. I'm not ready to say

we ought use beta blockers in septic patients, but there may be ways of slowing heart rate that may be uniquely helpful. And those patients who didn't get volume expanded enough, didn't get volume expanded enough because they couldn't, because their heart rates were too fast and their ventricles were too stiff. So if we lose that... So that's the way we have to think about it in the critically ill. We have to look for mechanisms over and above ischemic heart disease. The periop situation is different. The vast majority of those individuals, we think, have Type 2 events. The problem is that we don't know how to treat those Type 2 events because therapeutic trials have not been done. There was one done by PJ Devereaux called MANAGE, where he used the big trend to try and help and had combined endpoint of some sort of vascular event that seemed to reach statistical significance, but not as convincing as one would like. So it's not necessarily... It may be that you need to address the coronary disease since many of these are supply-demand relationships. And many of those patients will have coronary disease but many won't. And so what needs to happen is we need to figure out an intelligent way to bend those individuals. And they're often asymptomatic just like the critically ill 'cause they can't talk to you. They are sedated and getting pain medicine. The ECG again is taken randomly. That said, in both of those situations, both the acutely ill patient and the perioperative patient, maybe if we were smart enough to look for the subtle changes that perhaps something like AI might show us, maybe there are signals. We're just not smart enough to know what they are. But still, we need to figure out in those settings how to treat those patients. Aspirin? Statins? Statins, people are enamored with because they have pleiotropic effects and maybe will help and there are data that suggests that they do reduce mortality in the perioperative period. But otherwise, beta blockers. Well, if there are a supply-demand imbalance, maybe a beta blocker is a good thing. But as you know, giving a beta blocker pre-surgery is associated with a reduction in the number of events of Type 2 MI, but with increased mortality in the subset of patients who either have neurologic disease or become septic. So maybe we gotta wait 'til after surgery. But how do we identify those patients? We could identify them... We identify them now with troponin. It has shown us there's a signal, but that's not good enough. You can't monitor troponin all the time. At least not today, maybe. Maybe soon but not today. So maybe the studies that Georg Landsberg did originally 20 years ago using continuous monitoring of the STT waves are the way to go to identify those postop patients who are at risk. In order to do that, we would have to reconfigure a lot of our thinking of what we wanna do in the perioperative circumstance. But I think there's an opportunity there. Perhaps to use and lever that to learn more and probably another use for the ECG. The problem is with the continuous monitoring is there's so many changes where the patient changes their side, their position, coughs, et cetera, that one has to have a sensitive detector system to be able to screen those out as well.

Dr. Kashou: Very interesting. And I think we could spend a lot of time getting into each one of those. I do wanna touch on some of those chronic conditions because there are a lot... A lot of our patients have those and I wonder, are there... You know, there's so many chronic conditions. You mentioned aortic stenosis. Are there other common ones we should think about and how to use them? And then do age and sex- How do they play a role with the troponin interpretation?

Dr. Jaffe: Well, first of all, and maybe it's a good example of this is a paper that we have in review right now where we took patients who came into the Mayo Clinic with atrial fib relation or flutter and ask the question- And an elevated troponin and ask the question, if they have an elevated troponin, does that happen just from the atrial fibrillation and the rapid ventricular

response? Or is there something else? And in almost 100% of patients, we found there was something else as well. So if you've got an arrhythmia and you have an elevated troponin, it tells you that you probably have underlying structural heart disease. And interestingly, although a fair percentage had coronary artery disease, eventually, the mass majority and actually the most common etiology were patients who had left ventricular hypertrophy had likely poorly-controlled hypertension. So that one of the things that troponin is telling us by giving us a signal for the heart is injured in some way is you gotta look elsewhere outside the coronaries even though that's what worries so many clinicians. An LVH is a very common one. And there's good data from the group in Dallas that if you have LVH and you have an elevated troponin, your prognosis is terrible. They call it malignant LVH. And if you look at MRIs, those are the patients that tend to have additional fibrosis associated with their LVH. So, you could go through each one of the chronic structural heart diseases and do the same thing. If you take amyloid patients, years ago we showed that amyloid patients with elevated troponin do much worse than amyloid patients without an elevated troponin. But that said, you've gotta then find the mechanism. And after the mechanism, then you have a chance to find the therapy. In regard to sex and age, I like both, obviously. We now know with high sensitivity troponin assays that there are different normal values for men and women. It's hard to explain exactly why, but that's the truth. In addition, men and women have different types of heart disease. For example, women tend to have more diffuse coronary artery disease. When they have coronary artery disease, tend to have more microvascular disease, tend to have multiple lesions. Whereas, men tend to have these often solitary, easy to bypass, easy to interact with lesions. And women present at a much older age. So using sex specific cutoffs with troponin is critical. And again, it's critical not only because it identifies more women. And there are good data to say that it identifies more women who are at risk. Interestingly, the argument in the field is not. Doesn't identify more women who are at risk but it doesn't change prognosis, and it doesn't. And the reason it doesn't is because most people tend to ignore that. That's not right. So we now need to work hard to figure out what are any ideologies. So we can then begin to craft the therapies 'cause it's very likely, since these women are at risk, that we could do something good to help them if indeed we are astute to the etiology, but we have to study them. And here's another area where the ECG could be helpful. Which is to say elderly individuals of all type, both men and women, present atypically in over the age of 80. Less than half have chest pain when they're STEMI and the ECG and objective information becomes key. So you guys have to get a separate analysis of the older patients who come in who have STT wave changes, and in particularly women, to see whether or not there are unique signals that could be levered. In regard to age, I'm all in favor of it. It beats the devil out of the alternative for sure. But it does turn out that there are increases in troponin with age. The question is, why? Our own data set here, which we analyzed some years ago from a study that was called Pavin that they have collected the samples in a punitively healthy population, was that when we corrected for comorbidities, 'cause we had imaging, we ran NT-proBNP, eGFR, hemoglobin A1C. Almost invariably, those patients had comorbidities. When we corrected for those, the values came down remarkably, not all the way. And maybe that means that some of these comorbidities are things we can't detect. So your wall when you were born, maybe four millimeters, it gets to be 11. Still normal. So we don't call that a comorbidity but in point of fact, it's a change over time. So my position is that the changes in the elderly are comorbidities and we should not change cutoff values for that group. In addition to not changing cutoff values, I would argue because they're comorbidities, you would also... If you change the cutoff values, which some people have actually suggested for troponin, you would disadvantage those of us who work

every day and exercise every day to try and stay healthy and who don't have an elevated troponin. We'd have an elevated troponin but below that threshold of the others who are sicker and you'd ignore me, and I don't want that to happen either. So, I'm of the opinion that we need to use a changing pattern in the elderly. That said, we need additional tools. Those additional tools are no longer the history and physical, unfortunately. They are a good physical exam because often these patients have comorbidities that you can detect on a good physical exam. And another area where ECG is specifically targeted in an older age group looking for the more subtle changes that we all miss might well be helpful.

Dr. Kashou: There's so much that we could get into. I don't want to go down another route 'cause this is so exciting and there's a lot that I wanna get into. But before we end, there's something I like to ask and you've accomplished so much in your academic career. I've seen a lot of it over the years here at Mayo Clinic and it's been truly admirable to me and I know many others. Before we end, what career or even personal advice would you share with those in medicine today?

Dr. Jaffe: Well, I think young people nowadays are trying to think out what it is they wanna do with their lives. They wanna try and anticipate what the future is gonna look like. Is this group... Is this particular field going to be well reimbursed? Not well reimbursed? It's too hard. So what I would say to young people is do what you have a passion for. If you love it, it may never be lucrative. It may never be... You may never be as successful in the financial realm as you wanna be, but you'll every single day be doing something that you really enjoy and love. And if you do that, your likelihood of doing it at a higher level of sophistication, being more satisfied with your results, and having much more fun is far greater.

Dr. Kashou: Thank you. I know many of us can certainly hold onto that because we do need that. So cardiac biomarkers have provided a means to detect myocardial injury and manage patients accordingly. High sensitivity cardiac troponin has added a chance to further improve triage in patients with acute coronary syndrome. Understanding how to interpret and use this biomarker in correlation with other diagnostic tools such as the ECG, as well as for different patient populations, can have a tremendous value in the delivery of care for our patients. Dr. Jaffe, thank you so much for taking the time today. It's been a true honor. And on behalf of our team, thank you very much. I've learned so much and you've opened my eyes that I have so much more to learn. Thank you.

Dr. Jaffe: My pleasure.

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