Emerging ECG Methods for Ischemia Detection

Announcer: Welcome to Mayo Clinic's ECG Segment: Making Waves. We're so glad you could join us. Today, we have an exciting episode planned for you as we discuss emerging ECG methods for ischemia detection. We have an expert discussant joining us, and he's going to help us better understand this topic and the future of the field. So let's get started. The 12-lead ECG is one of the most widely used non-invasive assessments of acute myocardial ischemia. It helps to detect, diagnose and manage these patients. But how well does it do? In this episode, we will discuss ECG detection of acute myocardial ischemia, including the very basis of the ECG findings, limitations inherent to the ECG and approaches to improve the ECG's sensitivity. We're fortunate to have an expert in the field, Dr. Salah Al-Zaiti to discuss this with us further today. Dr. Al-Zaiti is an Associate Professor of Nursing, Emergency Medicine and Cardiology, as well as the Vice Chair of Research at the Department of Acute and Tertiary Care at the University of Pittsburgh. He brings 15 years of experience as a clinician, scientist, innovator and entrepreneur. His academic career has focused on the biomedical modeling and phenotyping of physiological signals in coronary artery disease, myocardial infarction, heart failure and cardiomyopathy with special emphasis on novel ECG signatures of cardiac ischemia. Dr. Al-Zaiti currently leads two NIH funded observational trials that focus on developing and deploying artificial intelligence ECG clinical decision support tools to triage patients with chest pain at the emergency department. Dr. Al-Zaiti has been very productive academically with nearly 100 scholarly publications in peer-reviewed journals and more than 50 scientific presentations at national and international forums. He's a fellow of the American Heart Association and he has developed... has helped developed the 2020 AHA scientific statement for preventing and mitigating the risk of exercise-related adverse cardiac events, as well as the upcoming 2023 AHA scientific statement on the role of artificial intelligence, so AI, in improving cardiovascular outcomes. He is the Conference Chairman of the upcoming 2023 International Society of Computerized ECG Annual Conference and he currently serves on the editorial board of the Journal of Electriocardiology. Dr. Al-Zaiti, what a true honor to have you with us today. Thank you so much for joining.

Dr. Al-Zaiti: Thank you so much, Dr. Kashou. The pleasure is mine. Thank you for having me.

Dr. Kashou: It was so nice to get to know you back at the recent conference where you were co-chair, and now chair. I am so excited and proud of what you've accomplished and what I wanted to get your insights were on kind of the ECG and the ischemia detection. And so I guess, firstly, you know, we know that the ECG is key in the evaluation of suspected acute coronary syndrome. You know, for instance, the patient's coming to us in the emergency department with substernal chest pain. However, we know it's not perfect. And so firstly, I wanna know, what are your thoughts on the accuracy of the 12-lead ECG in detecting ischemia and where do you see the potential pitfalls in its performance?

Dr. Al-Zaiti: Okay, thank you. And this is a very great question actually, to start with, and with the context. So we know that chest pain is very common, almost seven to 10 million people complain of chest pain and they come to the emergency room every year, in the U.S. alone and we do a 12-lead ECG and it would be great if it gives us an answer upfront and say, "Oh, this patient's having some coronary occlusion. This patient does not." However, it's not doing that

great. It does it wonderfully for a small subset that's defined by the ECG itself, which are the STEMI groups. So now, if you took these STEMIs away, which are one to two percent of the general chest pain population, what do you do with the rest of the 98% of patients with chest pain who do not have that feature? Research is very controversial. Many meta analyses were done on the field, but I wanna focus on one of them that looked at around 24,000 patients with non-specific chest pain, excluding these STEMIs. It gives us an overall average accuracy of sensitivity of 68%. Specificity's not that great as well, 77%. And this is controversial again, this is just like an average. The range is like 23% to 100%. So some studies report that ECG is only sensitive 23%. If you put at that in a context, out of every four patients who come with a true occlusion of their coronary arteries, an ECG might miss three of them. That's the reality. That's what we are dealing with here. And that's why when you think about clinical workflow, if the ECG is negative, that's not known to the patient in the emergency room. You do troponins, you do biomarkers, you do stress tests, you do numerous things. Sometimes you admit the patient for observations and it might be, like, one or two days before you even declare whether there is infarction or not. And sometimes, you send them home, it might be false positive, they come a week later with more serious infarctions. So we are really dealing with an accuracy that's, on average, at 68%, but it might be as bad as 23% sensitive.

Dr. Kashou: So quite the range, in terms of what we're missing. And those patients are having some underlying substrate, even myocardium that is now vulnerable and potentially infarcted, meaning the dying of the tissue. Where do you see the pitfalls? Are there any thoughts to why it doesn't do so well or even just reaching that 60 some percent threshold?

Dr. Al-Zaiti: Mm-hmm. So this is really, like, a sense of the problem. I completely agree. What are the pitfalls? And if I wanna try to group the different causes together, I would say you can think about it as at three levels. One of them is conceptual limitations. There are technical limitations, there's what you call clinical limitations. So in terms of concept, when you try to diagnose a coronary occlusion using surface ECG, you are really talking about two different entities here. Occlusion is a problem of blood flow and surface ECG is a manifestation of the action potential that's happening in the heart. Now, although they are related, but it's an indirect measure. So technically, what happens is, you get a coronary occlusion, it disrupts the metabolism at the myocardial level, that disrupts the action potential, action potential transmits from the myocardium to the surface ECG. During that transmission, it goes through tissues, there are the lungs, there is space, there is hair. Eventually, it manifests, you know, on the surface ECG. So just the concept of moving from what really happens from the occlusion itself to the surface, the concept itself explains why the ECG is not perfect. It's an indirect measure. It's not like you are putting someone in a cath lab, looking with a microscope, looking in their arteries to measure whether there is occlusion or not. That's one of the pitfalls why, in concept, in general, people are okay with saying it should not be 100% sensitive because conceptually, it's an indirect measure. But there are more sides to the story. You wanna think about the technical aspects of it. Well, there's a lot of technical specifications here. We put electrodes on the chest and these electrodes are facing the myocardium from different directions. And we all know the basics of 12-lead ECG and why we have precordial leads and the limb leads because we wanna have all these different views of the heart. But if you think about it, when you get metabolic derangements in certain areas that are ischemic, they generate distortions in the action potential. These distortions are... they vary from side to side. So there is what we call spatial heterogeneity

from one side of the myocardium to the other. These start generating injury currents. Now, these injury currents might simply align with the normal pathway of activation or recovery, in other words, depolarization or polarization. So they will be completely masked from the ECG. Now, if these ischemic currents hit in a different axis compared to the normal pathway, depending on where that axis is, if it is perpendicular to the axis of the ECG, it just makes a waveform a little bit smaller. However, when they start heading in different directions, that's where a changes start... The ECG's summative, they start canceling each other; that's where you might see some more bigger changes on the ECG. Still, if these changes are happening in a location where an electrode is not facing, they're gonna be completely masked or they might cancel each other if there is one injury current from this side of the heart, there is a completely opposite direction of another injury from another side of the heart, like when you have an inferior and some posterior or even inferior. These start canceling each other, and that's the nature of the technology. It's vector-based. So they start canceling each other, so you do an ECG, it doesn't show up anything. That's another pitfall. And the last thing I wanna comment on is there are clinical pitfalls. Clinical pitfalls would be what guidelines tell us. And right now, we are all familiar with the STEMI, non-STEMI guideline. And if you think about it, the STEMI is really putting a mindset on the ST segment and tells us if the ST segment is elevated, then you are dealing with STEMI. So it's really putting us in that tunnel vision, really focusing on the ST segment. However, when you think about ischemia, there are changes that happen across that continuum of the ECG. The QRS, we're all familiar with the Q wave, widening of the QRS, fragmentations of the QRS, loss of the S wave, of course, what happens to the T wave. So it's not just the ST segment. So when you say that the ECG is that much accurate, it depends on what criteria you are using. If you are following the universal definition of MI and looking at it from that way, of course you're not gonna be perfect. So we consider that more of a clinical limitation in terms of how would we actually define that criteria of the ECG to pick up ischemia that might be going on? When you take all of these aspects together, you end up understanding why the ECG is not that perfect and some people are okay with that. They say, "It should not be actually 100%. It's an indirect measure, and we have all of these limitations." So that's where we lie right now.

Dr. Kashou: It's really fascinating to... And thank you, you even got to my next question, which was the basis of some of these findings. But to kind of take some of what you mentioned of these pitfalls in the different areas, and when we say the accuracy, there is the potential pitfall of how we define ischemia, which is an important thing. And so, maybe if our definitions improve, maybe our accuracy might be a little better. And that's so interesting, but that gets to our next thing and that's actually from this commentary paper you had in the Journal of Electrocardiology, where you start to discuss some of these approaches to improve the ECG's sensitivity to ischemia. And you mentioned four techniques. You know, the first one... And I'll list them and then maybe we could go through each one of them.

Dr. Al-Zaiti: Mm-hmm.

Dr. Kashou: The first technique based on novel ECG signatures of ischemia, beyond the ST segment and T-wave abnormalities, as you mentioned just recently with how we define, and maybe we get honed in and so focused on the ST segment. The second technique of maximizing the spatial coverage of the ECG you discussed. And then the third one is based on the ECG imaging. And finally, the one based on AI or artificial intelligence and machine learning

techniques. So maybe we could look at each one of these because they're quite fascinating. So let's start with using the novel ECG signatures of ischemia as an intuitive approach. Maybe you could elaborate further on this one.

Dr. Al-Zaiti: Okay. So this is a very great starting point. And I agree with you, it's the most intuitive way since the way how we define ischemia, to some extent is limited, with the ST segment. Let me make a comment and elaborate further on why we look at ST segment, you know? So from a clinical standpoint, we are really interested in finding the patients who would benefit from immediate reperfusion. And earlier studies have shown us that what technically happens when you get a complete coronary occlusion, that leads to what we call transmural ischemia across the spectrum of the myocardial wall and that what leads to significant ST elevation. So with that classical understanding, we always linked ST elevation with a STEMI, "These are the ones that need reperfusion," and now you have that sort of paradigm in practice where we say, "If it's not a STEMI, it doesn't really matter. Why would the ECG need see this? Because these patients are not gonna need immediate reperfusion." Now, you can actually answer that question from two different perspective. One of them would be, well, at least we need to rule out. Ruling out in emergency practices is as important as ruling in. If you rule in one to two percent with STEMI, what do you do with other 98% that you cannot rule out on the spot? And that leads to resource utilization, unnecessary admissions, unnecessary and provocative testing, et cetera. So we're gonna need to think about rule out. But another way to think about that question is, that classical understanding of transmural ischemia leading to ST elevation is not really 100% accurate. We recently put a scoping review together where we looked at literature that correlate STEMI, non-STEMI with the magnitude of coronary occlusion. And in that scoping review, we looked at 80,000 patients from, I think, 15 different studies. And what we found is that among those who have a STEMI ECG, 25% of them do not have total coronary occlusion. And what's more worrisome is, among those who do not have a STEMI, or what we call non-STEMIs, 40%... Or actually, I reversed them. I think it's 40% of small STEMIs do not have occlusion and 25% of those who do not have a STEMI pattern actually do have total coronary occlusion. And that's why when you think about guidelines, even in non-STEMIs, there's what we call early risk stratification to identify among the non-STEMIs who would benefit from immediate reperfusion because we know that we don't wanna send them all to cath but some of them would actually need. And it turns out to be these 25%. So now, when you go back to the basics, well then, ST elevation itself is not really capturing you know, total occlusion versus not total occlusion. So then, the question becomes what else on the ECG would capture that? That takes us to the first intuitive approach of... There are signatures on the ECG. Now, to put this in a simple context, if you look at an automated algorithm to interpret an ECG and say, "This algorithm is reading these ECGs and it's giving this accuracy." If you look at any paper in the literature that compares an automated software against a cardiologist, and that's where they start putting these fancy titles, cardiologist level detection, cardiologist level interpretation, we always find out that a cardiologist beats an automated algorithm. So now, lets think about that for a second. Well, this is a completely unfair comparison because do you know what a cardiologist does? They read everything on the ECG. Look at Q waves, you look at QRS, you look at slurring, you look at the shape of the T wave, you start looking at reciprocal changes between electrodes and when you take all of these into account, of course you're gonna beat an automated algorithm because an automated algorithm simply looks at the ST segment. Is it elevated with that much in these leads? Yes, no. It's rule based. So with that in context, well, why wouldn't we

quantify the features that can be detected by visual inspection? And have we done that? Of course, massive literature out there. I will just comment on one paper, I think from 2009, that was put together as a consensus statement from the International Society of Computerized ECG, leaders in the field, who put that commentary together right after the third universal definition of MI, I believe, where they said, there are pitfall in there because if you look at the universal definition of MI, it talks about ST elevation, ST depression and Q wave version; they put it in a very tiny table. And they identify eight different patterns. I don't wanna comment on all of them, but they start talking about things like ST depression in V1 through V3, or even V4, like Wellens sign. We know what Wellens sign is. But they also comment about tiny T-wave inversions in V1 through V4. And they also talk about hyperacute T waves and they map these specific visual patterns to certain occlusions. They say, "Oh, this is an occlusion of the marginal branch. This is occlusion of OM branch," et cetera. And I think you previously had Dr. Smith in here and with his occlusion MI and non-occlusion MI, he also defines around seven different patterns and they overlap nicely with this consensus statement where he started identifying ST depression V1 through V4, et cetera. So many of these features overlap. So when you think about it, there are more signatures on the ECG to indicate ischemia than simply ST segment elevation, depression. Now, the downside of this is these are patterns based on visual inspection and there is a lot of subjectivity between providers. So when we put them out there in guidelines, some providers might be better than others. And this integrator variability between ECG interpreters is very well documented in the literature. So how can we overcome that? And this is the other interesting part about, can we quantify, in an objective manner, these distortions that we see on the ECG without the need to visually inspect the ECG? In other words, in computational approaches. And yes, there are numerous features out there. I will just comment on one of them and this feature, I really love, and I published previously on this one. It's called PCA ratio or standing for Principal Component Analysis of the ECG. So to put this in a simple context, if you look at a wave form, right from the onset of the QRS to the offset of the T wave and you align all leads, all 12 leads together, you get sort of like a superimposed 12 different peaks. Now, if you run what we call principle component analysis, which is a mathematical operation that identify perpendicular independent eigenvalues in the ECG, it starts identifying and isolating patterns among all these 12 different leads. And what it does is, it looks for uniformity and deviations. And when you think about activation and recovery in the heart, we anticipate that the activation of the myocardium follows a main pathway and the recovery follows another main pathway. Now, if you remember the injury currents I mentioned earlier when we said there are injury currents that are either distorting the activation or the recovery of the heart, these injury current, they are not following the main uniform pathway of this activation. So when you run something like a principle component analysis on these 12 leads, you end up with what we call eigenvalues. What would be the most representative waveform followed by the next, the third and the fourth? And if you take a ratio between them, if this is a healthy heart with a uniform depolarization and a uniform repolarization, you will find there is one giant eigenvalue that explains everything. This is the first eigenvalue. However, the more injured vectors you have, that's where you start seeing there is a second eigenvalue, there's a third eigenvalue. So when you start taking ratios between them, the bigger the ratio, it means there is more distortion across the waveforms, across the signals on the ECG. This is called the Principal Component Analysis or the PCA analysis, and it can easily quantify all the different lead to lead variations that someone can see on the ECG as a clinical expert simply by calculating a number and just putting it on the ECG and saying that's how much distortion we have. And in our prior work, we have shown that looking at these T

wave complexities or PCA ratios in a dynamic fashion can give you a sensitivity and specificity at least 82%. So when you compare that to the 68%, I mentioned initially on average, this is still a very nice gain by simply doing a simple calculation, computing a simple ratio, giving you almost 80% sensitivity and specificity on the ECG.

Dr. Kashou: That's really fascinating to think of. I think we have that idea that there are signatures, that you mentioned, and that have been published that are not really well used or well recognized that we have to teach, almost, people about. And so I appreciate you mentioning those because for those of us that look at ECGs all the time, we can start to see them, but it takes time and it's that recognition. And so it makes sense why a clinician, a cardiologist that's seeing them over and over they start to ingrain these signatures and do a little better than the computer. I wanna get to that second technique that you mentioned about maximizing the spacial coverage of the 12-lead ECG. How do you see that... I guess, maybe can you explain that? And then, how would that enhance the sensitivity to detect ischemia on the ECG?

Dr. Al-Zaiti: So in this technique, we are mainly talking about body surface potential mapping here, and the reasoning is simple. Since ischemia might happen at any location in the heart and the whole idea of having 12 leads is to have 12 different views of the heart, you can easily miss up on smaller areas of ischemia that might be quite tiny or in a location that's weakly sensed by the 12 leads. So when you start expanding that spatial coverage with something like a body surface potential mapping, conceptually, of course, you're gonna enhance the sensitivity. And in my commentary paper, I mentioned two main studies and one of them is occlude MI, in, I think, 2009, looking at 80 electrodes with a vest that's put on their chest. And it showed that they were able to pick up 27% more STEMIs just by adding these 80 leads compared to 12 lead. And the follow up study a few years later have shown that they can reach almost 90% sensitivity for ischemic detection just by body surface potential mapping. Now, as always, there is a downside here and the downside is, this requires more equipment for hospital to start getting body surface potential mapping plus it's not easy to interpret and it's very laborious and that's why their clinical utilities is really diminished; I don't see that happening in the future. And that leads me to a brief discussion about a very innovative technique called the VSEL specific ECG leads, which stands for V-S-E-L, VSEL. So this technique was developed by researchers from U.S. and Canada in collaboration with Phillips and some of the legendary experts in the field, Dr. Galen Wagner, who was part of the initial TIMI studies, and he was the Editor-in-Chief in the Journal of Electrocardiology for a long time. He passed away almost 10 years ago. He was one of the initial innovators of this technique. So this technique tries to bring the value of body surface potential mapping simply by using the 12-lead ECG. So what they have done, and this is computationally smart way of doing it, they did on a series of patients, both a body surface potential map and a 12-lead ECG. First... And this, I think, were angioplasty studies where you inflated balloons so you have a gold standard ischemia and you know exactly where it's happening. If you are in inflating it in the LAD, then you know if this is an LAD occlusion pattern. And what they were doing is, they were recording the maximum area of distortion on the body surface that comes with LAD occlusion. Same thing with LCX. Same thing with RCA. Now, they were able to easily pick these up because they had 80 electrodes with body surface potential mapping. And what they did is, they created computationary coefficients, conversion coefficients. How do I estimate these areas on the chest simply by using the 12-lead ECG, using coefficients or conversion coefficients? And they were able to do that. So technically, the way

how this technology works is, you take a 12-lead ECG, you read that signal from this 12 lead and you can generate three new leads. One of them is called LAD lead, RCA lead and LCX lead. And what these leads are are approximations of how an occlusion of LAD using body surface potential mapping would look like if you really have the right electrodes in the right spot. So they can be derived from the 12-lead. And we have tested that in a series... In our current NIH-funded study on around 4,000 ECGs and it was very amazing when you give a clinician a 12-lead say, "Do you see anything?" They say, "No, there's nothing in there." Then you give another 12-lead that includes these three additional vessel leads and he says, "What are these?" And you say, "Oh, this is the LAD, or this is a lead tailored to the LAD" and say, "Where did that elevation come from?" And you can easily start picking up on that. I think we recently presented that at the American College of Cardiology and it did boost the accuracy and sensitivity to 85% and the negative predictive value up to 95%, just simply using the 12-lead ECG itself, but reproducing what we call vessel leads, which uses the concept of body surface potential mapping to maximize the spacial coverage around the heart, to really start reaching out to where the ischemia is supposed to look like on the body surface.

Dr. Kashou: That's amazing, honestly. I've seen some of that work where they're mapping the vessel and that's probably even helpful to the interventionalists if they're gonna cath, to have an idea of what things look ahead of time. And so, the body surface potential adding that additional coronary artery layer to it, you could see the value there. And so, we've talked about the novel signatures, the maximizing the spatial coverage. And now, I wanna get to that third technique that you talked about with the ECG imaging and how that could be used to detect ischemia.

Dr. Al-Zaiti: Mm-hmm. Okay. So ECG imaging... So let me comment on what ECG imaging is. So this is based on the inverse ECG solution. So what does that mean? So we know that if... You know, the best way to look at that action potential alterations is just simply to put electrodes on the myocardium itself; this is the electrogram. Electrophysiology or EB doctors, they do that all the time when they do the ablation or any sort of EB procedure. You don't rely on the surface ECG, you go directly on the action potential on the electrogram. Now, there has been a lot of research over decades, "Can we actually estimate how the action potential looks like simply by measurements on the surface ECG?" And that's what they call the inverse solution. So they are trying to regenerate the action potential simply by looking at a 12-lead. That comes with limitations because you have to take into account the torso, the shape, the geometry, the size of the heart, size of the chest, the lungs, et cetera, because they all get distorted as confounders during that conversion. And a lot of research has been done in that area. And that's what they call ECG imaging nowadays, where you take the 12-lead ECG based on a torso or a body in geometry, you try to map what's happening on the surface of the heart or the myocardium itself. Now, with that work, there has been a lot of research about, "By doing so, are we able to make measurements on the action potential itself as derived from the ECG to say whether there's ischemia or not?" You teach ECG all the time and you know there are phases. There's phase one, phase two, phase three, phase four, and you know exactly what happens with ischemia in phase three. So, the argument's simple. If I take 12-lead and do inverse ECG solution, and now I have an approximate action potential in front of me, can I measure phase three, for example? The time, the slope, the shape? And can I use that to predict ischemia? This has been done, and I think you have some interesting primary results and their sensitivity runs between 70%, but it's not really encouraging because that's what you are actually getting on average from the ECG

itself. Now, one specific technique that was really novel that I want to comment on is a CineECG. So CineECG is based on the same concept of ECG imaging, but they were so smart in their inverse solution. Rather than regenerating just the action potential, they tried to approximate and display the location of the activation on the heart in a pathway. So since the ECG is done in a time series, so we say there are samples per second. So when we see the ECG, it's done at 500 samples per second, which means every one second, we are making 500 measurements. And this is time measurement, which means the signal is propagating in the heart somewhere during each one of these. So are we able to re-engineer and inverse a pathway on the heart to see where this signal starts, where does it propagate and how does it spread in heart? And that's what the CineECG is. They take the 12-lead ECG, they generate an image based on a body torso they give you a 3D heart and they show you where the signal origin is and where does it spread? And based on our simple understanding of the ECG and the conduction pathway, you can start making conversions say, "Wait, look, there is something abnormal here because the pathway's supposed to go to the septum, then it goes to the left and it goes to the apex, and I don't see that here." And to make this technology even more user friendly, what they have done is they used a database of, I think, around 7,000 healthy adults and they collected what a normal pathway should look like. So in addition to seeing in this given patient with this model, now I'm looking at a 3D heart, seeing their actual pathway. It's highlighted... It is overimposed over where a normal pathway is supposed to look like. Now, you can easily start looking at distortions. "Oh, it's now going outside of normal, so this is a diseased heart." And although the technology itself has been validated for things like conduction pathways, which is very intuitive because if there's a conduction abnormality, then this activation pathway will be messed up. But there was a motivation to see, "Can this actually capture ischemia?" Because what happens with ischemic regions, and we know that, we end up with a delayed or a slower repolarization in these areas, and this is one of the mechanisms why we have reentry arrhythmias with ischemia, because due to that altered repolarization, while the heart activates, that area still activates. While the heart is repolarizing, that area might be activating. That's sort of like a distortion. So there was a hypothesis, would something like a CineECG capture ischemia? In other words, it would show you a pathway that eventually leads to the ischemic zone. And the evidence is still emerging. We tested this on couple hundred patients in our data and the results are promising. These were cherry picked patients, so I'm not gonna really exaggerate the finding, but we were really looking at sensitivity of 94%. But again, this is still like cherry picking because it's not like all patients. We were, like, picking examples. But this is sort of like an idea of the field of ECG imaging. All software can be installed on any laptop, any computer, EHR system, 12-lead ECG just reads it and plot it for you on a 3D heart.

Dr. Kashou: That's really amazing, honestly, translating the ECG and using that to see where... Not only conduction defects, but also areas of ischemia. It's really fascinating and I've seen some of your work that you've shared with me; it's really fabulous. And I can't wait to see a little more of what you have in store. The final and probably the exciting area that I know you do a lot of work in is artificial intelligence. And we see this really growing in the field of electrocardiology. How do you see us using this technology to almost harnessing the strengths of it, realizing that there are some limitations, but how do we use its strength to improve the diagnostic yield to detect ischemia?

Dr. Al-Zaiti:- Mm-hmm. Okay, so AI; this is the elephant in the room. So I agree with you. Now, I wanna approach this topic from an understandable or interpretable fashion for clinicians because I'm not one of the big fans of saying, "Oh, just give it to the AI and let the machine do it. Somehow it's gonna pick it up." No, we really need to understand the mechanism and go into the weeds of, how does the AI do it? So we just had a discussion about what happens with ischemia and we said, rule-based systems, look at ST input. If it's above a threshold, ischemia, not above the threshold, no ischemia and end of the story. Now, when you compare that to how a cardiologist reads an ECG, we mentioned that no, it's more of a comprehensive approach. Start looking at QRS morphology, shape, T wave, amplitude, inversions. Is the ST segment concave or is it convex? You start looking at all these things, you took them all into account before you make a determination as a cardiologist to say, "Is there ischemia or no?" Now, you think about that, this is really intriguing. We want the machine to do it this way, but we run into what we call highly multidimensional space problem because now you are not dealing with a simple rule-based system where it says, "Measure ST. Is it above a threshold? Yes. No. What ischemia is out there?" No, you are really talking about training a machine to go into an ECG and start making evaluations of waveforms. So if you think about it, you look at the Q wave, how wide, how deep, its area. You move to the QRS, look at R amplitude, its area. You look at the same thing in the S. Then you go into the ST segment. It's not only the amplitude. You look at overall morphology. Is it upsloping? Is it downsloping? It's concave, convex, you go to the T wave. You look at its duration, its amplitude, its area, and you do that for every single lead, but you also do that for all leads together. So if you think about it, you are simply harvesting features from every lead, the Q area, Q amplitude, Q duration. You move to the heart, you do the same thing for the ST, for the T area, T wave, T amplitude, T symmetry. These are all things that can be quantified from every single lead, then across all leads. And if you get all of these features, and we have done that, you get around 554 features from the 12-lead. How would a rule-based system actually take that into account? Because now... No, you can't do that. And that's the power of the AI. The AI was designed, which is the simple sense, mathematical representations. AI, at the end of the day, is math. So these mathematical representations, their power is, they are heavily geared towards high dimensionality, in other words, you look at hundreds of features at the same time, take into account all features together in the same lead, across different leads and along with all of this multi-dimensionality, the relationships are nonlinear. If you think about the ST amplitude, that was a linear relationship. Goes up, goes down and you make a determination. But taking all these features together, it's a non-linear. So now, if I want to put all of these features together in a mathematical representation that's multi-dimensional space and it's non-linear, simply what you are doing here is AI. So you started out running things like support vector machine, which is a completely non-linear complex mathematical presentation. Random First, Another Algorithm, the Neural Network, they all are multidimensional, you can feed them all these features and they can account for the complexity of non-linear trends and interactions in the multidimensionality. This is the most intuitive way of running AI on the ECG. It combines the power of domain expertise because we have more than a 100 plus years of experience with ECG. It has been there more than a hundred years. It's not like a new field. We know the ECG. So if you featurize all of the things we know as domain experts from the ECG, just feed them in the Neural Network or Random First, technically you are doing the simplest form of AI and this is what we have done on our data. I'm in love with this technique because it keeps the integrity of the human component because all the human engineer features fit into the AI and it has been shown to boost the performance compared to rule-based systems by 50% gain in sensitivity, which is a huge,

gigantic value when you say 50% gain in sensitivity. Now, when you think about you say, "Well, this makes sense because a cardiologist will always beat the rule-based because a cardiologist... Well, that's what humans do." They are good in pattern recognition. So can you compare AI against human interpreters? We have done that. There is still a 37% gain sensitivity, which means AI was using all the same features that a cardiologist is processing in their brain by looking at the ECG, also capturing things that a human eye couldn't, in terms of patterns, and was still able to boost performance beyond what the human imitator is able to do. And that's sort of like how you think about the AI in its simple, most intuitive form to address the problem of interpreting the ECG to detect ischemia.

Dr. Kashou: That's really... I think that's important, what you mentioned, of that domain expertise and using that human component, which we see that there is something there beyond what the rule-based systems can add and almost harnessing that to improve it. I agree, it's amazing and I think that's probably what we need, and really capturing some of those... Which, maybe they are novel signatures or signatures that we know, but we're not just applying very well. You've listed four areas and I would say they're all areas of future opportunities, but where do we...

Dr. Al-Zaiti: So...

Dr. Kashou: Go ahead.

Dr. Al-Zaiti: Let me make one more comment before...

Dr. Kashou: Sure.

Dr. Al-Zaiti: ... we leave the AI approach.

Dr. Kashou: Please.

Dr. Al-Zaiti: Because a lot of people would say, "What about deep learning?" This is the other gorilla in the room. And although I may close with that, I'm not really a big fan of just letting the machine do all the featurization because that's what deep learning is. You feed waveforms to the machine and let the machine do all the work. Now in concept, this makes sense, given that you have millions of training samples. And if you do that, I think deep learning would be able to pick up on a lot of the features, so you can bypass the step of feature engineering or the human crafted features, but again, we need millions of data points. Now, if you wanna ask me about what would be the ideal approach? And I know this might have to do with going into the future direction, but I will jump into this now, since I'm talking about it. It would be great if we have hybrid models. And hybrid in terms of, you extract human engineered features that we know, the machine should look at these things, but at the same time, you feed the raw signal. That's what we call hybrid models. And these are usually multi-layered neural networks, because you really need the neural networks here, where you are feeding both engineered features plus waveform. So you make the task of the neural network easier and at the same time, you make sure there are no false discoveries, so no false positive, no false negative, you minimize these as much as possible in these hybrid neural networks to actually give your assessment because I do believe

that there might be things in the ECG that we don't know about. So if we just wanna limit ourselves to human crafted features, we might be missing something. But the solution would not be abandoning human crafted features altogether and going to deep learning. It should be a hybrid model between both to eventually give the highest accuracy that's possible for the ECG to detect ischemia.

Dr. Kashou: Yeah. The deep learning, like you said, it does have currently some limitations, especially with the whole ischemia detection. Not only using that, but the patients you select... There's a lot of limitations that I know you're very well aware of. And I think you're right, there has to be a little bit of... Maybe it has to be the hybrid. Realizing that there's things that we... Probably a lot we don't know, but there's things that we do know. And can we use the things we know and then maybe find things we don't know to improve this? Is that where you think the focus of the field should be? What are your thoughts?

Dr. Al-Zaiti: So I think... Yes, I think the focus moving forward would be... When I use AI... Again, this sort of encapsulates, it's an overarching theme over the first group of approaches, which is novel signatures of ischemia. And that's where we will have defined that. But AI is sort of an inclusive, overarching thing. So I think yeah, moving into that direction, automated ECG interpretation is one of the big things out there; one of the first applications of computer into medicine, it's just the automated interpretation of the 12-lead ECG. And I think it would benefit a lot from AI. I think the direction should be there, looking at hybrid models, human crafted features, features that are data driven, in addition to raw waveform, feed these together to detect ischemia. And it's not as simple as that, because again, you really need large amounts of data. And I know that in Mayo Clinic you have access to more than 2.5 million ECGs, which is like... Really, that's what you need for deep learning. We're really talking about millions of ECGs. But the other thing is, these ECGs need to be labeled with the right outcome. And that's one of the biggest sources of self-fulfilling prophecies. So when you think about what I mentioned earlier about STEMI, non-STEMI, a lot of people have these deep learning paper in the literature; they are so ubiquitous out there. But when you go into the weeds, they are trying to predict MI defined as a STEMI. Now, when you think about it... And they report an AUC area under the curve for 99.99999% and you think about it, you say that's sort of like, "It's common sense. It's self-fulfilling prophecy." The STEMIs on the ECG, if you put a rule-based system, you're gonna pick it up. So of course, deep learning is gonna pick it up; it's a STEMI. The question is, can we actually have outcomes that are more or broader than STEMI? Things defined by lesions on angiograms because that's the sense. It's not the STEMI, non-STEMI data to know. We really wanna go after occlusion. So are we able to use, like, TIMI flow criteria as our training endpoints? So these large databases need to be labeled with something like a solid endpoint, not things like troponin or things like STEMI. So as we have these two combinations, I think we should be able to build such model. And the last thing, but not least, even if we build such model, this is gonna be based on historical data. And before you incorporate things into the clinical workflow, you need prospective evaluation and real time deployment. And that's, I think, where the field really needs to go. A lot of papers are academic exercises, going through source databases, putting a lot of deep learning or AI out there and they say it works and end of the story. No, we need someone to take the work, move it down the field where you really move into prospective testing. And this is part of the things that we are doing right now at UPMC when I mentioned earlier that we are deploying... We have NIH funding to deploy some of these tools,

which I think it's where the field needs to go. We really need to deploy and test it prospectively, not only deploy it and develop these things on historical data.

Dr. Kashou: Yeah. Dr. Al-Zaiti, it really is the case, right? I mean, you mentioned kind of a model... First off, this is one of the most important questions we have to address, right? I mean, we have all these AI models that are built and I think this is one of the most important ones to detect, is the ischemia, because we know that outcomes improved if we detect them. And it is clear that some of these NSTEMI patients have been well documented to have worse outcomes because maybe the treatment or management's delayed a bit. And so, we have to do better at detecting them. And so, like you mentioned, building a model that detects STEMI only, well that that's not helping our cause because there there's still that other group that needs some help. And I think it's those features you've mentioned, maybe even using some of the ECG imaging, and that hybrid model... And, you know, you heard it here first. The hybrid model, I think that could be the future of using some of these things and then, finally deploying that. And what you're doing now in a prospective fashion is the most important because we need to see that these models are not just academic things that we're building, but they also translate to the care we deliver. And so, I'm glad that you're leading... You're clearly a leader in the field in this. Now, the ECG remains an essential aspect to the evaluation of myocardial ischemia. However, what we saw today with Dr. Al-Zaiti is that it's not perfect and there's room for improvement. New approaches to enhance the ECG's sensitivity to detect acute myocardial ischemia might expedite the care we deliver our patients and even improve their outcomes. And we stand at the edge of exciting developments and promise in the field that are taking place here, at Mayo Clinic, but even in Pittsburgh and throughout the world. Dr. Al-Zaiti, thank you so much for sharing your insights into ischemia ECG detection. I'm so excited and glad, and can't wait for others to hear more about this. It's clear, you're a leader in the field, and we're so excited to learn more about your work in the future that you hold. On behalf of our team, thank you for taking time to join us. It's really been a true pleasure.

Dr. Al-Zaiti: Thank you so much, Anthony. It was a great pleasure as well. And I hope we can continue to work together. The work that you're doing in Mayo Clinic with AI is also very impressive and there's always room for improvement. So it's... Again, it was a pleasure to be here today and we should stay in touch.

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