Physiological Underpinnings of Myocardial Ischemia

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're so glad you chose to join us. Today, we have a fascinating episode as we look at the physiological underpinnings of myocardial ischemia. We have an expert joining us who will help us better understand this topic. Inadequate perfusion of cardiac tissue results in myocardial ischemia. The ECG remains one of the most fundamental diagnostic tools for detecting and monitoring for myocardial injury. The translation of a perfusion defect to detect ECG findings begins at the cellular level. The consequent regional differences in transmembrane potentials, as well as both the local intracellular and extracellular injury currents contribute to the electrocardiographic features during myocardial ischemia. Linking often subtle cardiac current and voltage changes to the corresponding perfusion defects can be challenging. Today, we're going to look at some new methods that have been able to do just that, as well as some of the discoveries that have contradicted the prevailing understanding of ischemia. And we have our expert here, Rob MacLeod, to discuss this difficult, yet critically important topic with us further. Dr. MacLeod was trained in Canada and Austria in physics, electrical engineering, and physiology and biophysics. He has been on the faculty at the University of Utah since 1991. He now is a full professor of biomedical engineering and cardiovascular medicine at the University of Utah. Dr. MacLeod is co-founder and associate director of the Scientific Computing and Imaging Institute, and has held a similar position at the Nora Eccles Treadwell Cardiovascular Research and Training Institute. He also co-founded the Consortium for ECG Imaging, and is the president of the Computing and Cardiology Society, which are both international groups dedicated to using computing approaches to explore all aspects of cardiac function, diagnosis, and care. Dr. MacLeod has a deep commitment to education, training, and mentorship, and for the past 16 years, has been vice chair and director of the undergraduate program in biomedical engineering. He serves on numerous committees around the practice of teaching and learning. His research interests include computational electrocardiology, with a special interest in both simulating and measuring bioelectric fields in the heart and body. He uses both experimental investigation and clinical approaches to improve management of atrial and ventricular arrhythmias, as well as to explore the mechanisms and indicators of acute myocardial ischemia. The broad range of techniques he and his teams use include scientific computing, imaging, image and signal processing, data science, visualization, and high-resolution capturing of bioelectric signals. Dr. MacLeod, what an honor to have you join us today to discuss your work. Thank you for taking time.

Dr. MacLeod: My pleasure.

Dr. Kashou: So, you know, looking at your work, and there's a lot that you've done, but there's a clear emphasis on, you know, myocardial ischemia. And perhaps you can start by sharing, you know, what made you take this direction in your career.

Dr. MacLeod: Yeah, the origins of my interest really go back to my time as a graduate student when we were recording ECGs, high-resolution ECGs called body surface potential mapping. So this is ECGs with 120 electrodes. We were recording body surface potentials during episodes of controlled ischemia in the setting of angioplasty. So during angioplasty, of course, there's a coronary artery balloon that's inflated that blocks the coronary blood flow and creates brief episodes of ischemia. And our mission then was to characterize these ischemic responses and ultimately to use them to feed into a computer model that would allow us to reconstruct the potentials on the surface of the heart from the recordings on the body surface. That's now called ECG imaging, or ECGI. What surprised me at the time when we started these studies was that, unlike what the theory would suggest, the changes were quite abrupt and did not reflect a transient behavior. I always pictured ischemia as being something that, because it's related to perfusion and metabolism, that would slowly spread across the myocardial tissue. And with that, you would expect to see a gradual transition in some of the ECG markers: the ST segments, the T waves. But instead, we saw quite abrupt changes in that context. And that really didn't fit with the underlying theory, at least as I understood it at the time. And so at that point, I decided it was time to understand this at a more fundamental level, a more mechanistic level. And that's really what brought me to Utah. So at that time, and still today, the Cardiovascular Research and Training Institute, or the CVRTI, is really known worldwide for the advanced ability to perform research in various animal models from rodents to large animals, pigs, canines. And in that context, I connected with a fantastic mentor who had preceded me coming here by a few years, a man named Dr. Bruno Taccardi. And Dr. Taccardi a well-known expert in body surface potential mapping, but also an expert in animal surgery and all the animal techniques needed to instrument a heart and really record on the surface of exposed hearts and even within the heart itself. Eventually, we got to the point of collecting 1,000 independent channels of information. So we've gone from the 12-lead ECG suddenly to 1,000 channels. Not something I would ever propose as a clinical intervention, but it does allow us to capture the behavior in the heart on the surface of the heart and really try and fundamentally understand what the response is to, in this case, ischemic episodes. So it's really the arc, been the arc, or one of the arcs of my career and what keeps me here, what keeps me doing experiments, as we continue to evolve both our instrumentation and the underlying notions of the reasons why we ultimately see changes in the ECG.

Dr. Kashou: It's so fascinating. And, you know, you mentioned 12, and that's what we use. And then there's 1,000. You know, yes, it's a lot, but that's kind of what we need to really get it down so that the 12, you know, are valuable. I guess, would you say, or maybe there's something else, what is really the clinical motivation for this relatively basic science research behind all you do?

Dr. MacLeod: Exactly. So the clinical motivation really remains in part tied to these original observations that I made, but became even more focused when I started to discuss with clinicians how they used the ECG to record, and how they used it to detect ischemic episodes. For example, in the exercise lab, this is sort of one of our main targets, is how can we improve the diagnostic ability of the exercise or stress ECG? And I was quite surprised to learn that even today, the sensitivity, specificity, accuracy of this method is remarkably low in the area of 70 to 80%, depending on the particular case in hand. Another example is in the emergency room. As your listeners may know, the number one reason in the Western world for patients coming to the

emergency room is chest pain. And of course, a lot of that chest pain is thought to be related to episodes of infarction or episodes of ischemia leading to infarction. And so there's a lot of motivation to understand this phenomenon better because in the emergency room, this diagnostic success is even worse. There we're looking at 50% errors in diagnosis of acute ischemic episodes. And there are kind of two fundamental ways to look at a problem like this. One is to say, "Let's just keep recording, and then aligning the recordings and features of the signal with outcomes." And that's a very valid way to understand a problem. But being trained in physiology, I wanted to understand what it is we are actually measuring. So what are these injury currents? What are these changes in the ECG? Where do they come from, and how does that relate to the kind of stress that the heart is under? In an acute situation of, let's say, a stress test, whether it's an exercise test or pharmacological dobutamine stress test, what really changes at the cardiac tissue level? With the basic idea that if we understand what we're looking for better than we do now, then we'll understand how to look for it with more accuracy, more precision, and ultimately more useful clinical impact. So it's a big problem clinically that I think we hopefully can improve on by understanding the fundamental sources that we're trying to detect.

Dr. Kashou: You kind of draw me back in. And I know you're an educator yourself and I know finished your last session today. So congratulations on that. But, you know, it's really understanding the why. The why we see what we see on the EKG, right? And I think it's that understanding of why that really makes us curious, but also helps explain, you know, the features we see and allows us to make decisions on that with reason. Maybe you could summarize, you know, the methods that you use, and really what makes them unique in the field.

Dr. MacLeod: Yes, thank you. The body surface potential mapping is still a technique we use. It's the fundamental input to ECGI systems. There are commercial versions of this system. Some of your listeners may have access to them, may be using them even in their clinical practices. So that ability to record from the body surface at high resolution, covering an expansive area of the body surface is certainly one of our tools that we keep using. But we knew that if we wanted to understand the sources, we had to get closer to those sources. And that meant recording on the heart surface initially. And for that, we use epicardial sock electrodes, which have been around in various forums, certainly, for decades. We continued to refine those designs and change the configuration of the electrodes, but we typically record, say, 256 up to maybe 500 individual electrodes just on the epicardial surface of the ventricles, sometimes augmented with atrial patches to capture signals from the surface. But even that was not really enough because a lot of the myocardial activity, especially in the situation of ischemia, plays out within the tissues of, for example, the ventricles. So for that we use intramyocardial needle electrodes. So these are individual, closely spaced electrodes mounted on shafts of flexible needles. We fabricate these. We do 3D printing of the scaffolds. We feed individual, very fine silver wires into these scaffolds. We externalize the tips of these needles, coat them to make them compatible. So they get a silver/silver chloride coating. And then we insert these into the beating heart of animals to which we've exposed through some sort of certain economy, either a central opening through the chest, or sometimes through a lateral incision. So we get access to the heart. We can put needles within the tissue itself, epicardial surface electrodes, and then the body surface electrodes. We're actually able to re-close the chest of these animals and record from all three domains at the same time using, as I mentioned, recording systems that are capable of 1,000 channels of individual recording. So we're capturing lots of data in the signal space. To actually solve the problems or

really come up with a spatial perspective, which of course is essential to ECG, we also have to reconstruct geometry. So we complete the experiments by performing imaging. And we will sometimes record a whole body MRI scanner. We have wonderful scanning facilities here at the University of Utah. We can move the animal to a scanner and record high-resolution images of the entire thorax. We can explant the heart, of course, at the end of the studies or acute studies. So we explant the heart. And we can do high-resolution scanning, both MR and CT, of the individual hearts. And so with that, we get information on the structure, we get information on the electrode locations, and then we combine all that together. And that is in itself a bit of a computational hurdle just to bring all those individual pieces recorded on different systems and different coordinate systems all back together into the same space. And at that point, we have then sort of our complete data set where we have the geometry, we know the electrodes, we know the anatomy of the heart, and we have the electrical signals from all these situations or all these locations. And then on top of that, of course, we have to create interventions. So we've gravitated through a number of different approaches to controlling blood flow in the coronary arteries and now most typically use a hydraulic occluder. So a calibrated device that allows us, once we can access a segment of the coronary artery, to control the blood flow through that segment and into the perfusion bed of whichever artery that we've occluded. So we have a controlled ischemia in which we can determine the blood flow. It's not an infarct situation of a complete closure. We can actually create scenarios that look more like coronary artery disease, a partial occlusion. We can also increase the stress on the heart, that's the other piece of the intervention, by pacing it more rapidly. It's not a perfect surrogate for exercise, but it increases the metabolic demand and increases the requirements of that coronary artery. And so by balancing between the demands placed on the heart metabolically and the blood flow we apply through the coronary artery, we can create a really variable profile of ischemia that, again, we think reflects what happens in an exercise or in a pharmacological stress test. And so we have both the control, we have acquisition, we have all the information. And then we can assemble it, we can make computer models. We can analyze it in a whole variety of ways.

Dr. Kashou: This is just so cool. I mean, you know, I listened to, you know, your lecture back at a conference, and I was blown away by this. But I feel like I continue to be blown away just of how much data, and then trying to synthesize all of this. And I know you've done a lot, but what would you say are some of the most meaningful discoveries your group has kind of led and has contradicted our, you know, current prevailing understanding of myocardial ischemia?

Dr. MacLeod: Yeah, exactly. One of the initial really dogma, ultimately, of myocardial ischemia, especially in this scenario of graded ischemia, of an ischemia that's going through an onset motivated or driven by exercise, is that early ischemia is limited to the subendocardial region. This is what you'll find in lots of great literature. There are many studies in the '70s and '80s that identified these subendocardial regions. The basis for these studies, however, was some wonderful research done by a group of investigators at Duke University, but it was based on scar and it was based on postmortem evaluations of human hearts. So these were results of infarcts. These were not really documented episodes of transient or early-onset ischemia. These were not acute events. These were the result of infarct creating scar. And that scar typically was limited to the subendocardial region. And it was natural to extrapolate from that, at least that was one sort of finding that was extrapolated from those results, that suggested that, oh, ischemia probably arises initially in the subendocardium. There are also metabolic arguments why the

subendocardium is more demanding metabolically. The nature of contraction suggests that that region of the heart is more early, or affected more dramatically and earlier in the ischemic period. There's also even some perfusion arguments. That because the perfusion starts in the epicardium, penetrates through the wall, that under duress, it is the terminal ends of those vessels that would most likely be affected. And so we would see this combination of a metabolic demand that's highest in the subendocardium combined with a perfusion that's limited, especially in the subendocardial region. So it was a natural conclusion that ischemia would start there. And as hopefully all good scientists, we wanted to question that assumption, and we wanted to evaluate that assumption. And so we did it by measuring the electrical changes in the heart with our intramural electrodes throughout the 3D volume. So we record not just from the surface, but inside the tissue itself. And so we could follow the progression of ischemic signs, ischemic changes in the electrograms, we call them, the signals recorded from the heart. We saw changes in the electrograms that were localized, as one would expect in early acute ischemia, but they weren't localized to the subendocardium. This was the big surprise. In fact, we went through literally hundreds of experiments in which we recorded, statistically evaluated where early ischemia would start, would first originate, and we found it distributed throughout the ventricle, throughout the myocardium. So we had subendocardial episodes, we had mid-myocardial episodes. We even had subepicardial episodes. And as the ischemic stress increased, which again, we can control in these experiments, the ischemic zones certainly spread. They merged. They eventually became transmural. They became what we know now as, you know, a STEMI type infarct. We saw those same type of behaviors if we applied enough ischemia and waited long enough, but we didn't see this early ischemia originating exclusively in the subendocardium. And of course, at first you think our experiments are wrong, we've done something wrong, our data analysis is incorrect. We have to repeat this. And so we kept repeating it and repeating it. And then I started to take these findings to conferences, and I would describe them to really expert clinicians who use the ECG on a daily basis, the real people who study the ECG in a way that's really remarkable. And I would describe these findings to them and their eyes would light up, and they would say, "Oh my goodness, that actually explains a case I had last month. The notion of subendocardial ischemia and the injury potentials and the injury currents that would result from that just didn't make sense with the ECG findings I was getting. And you've liberated me with this notion of acute ischemia to think about it in a fundamentally different way, think about the source in a different way, and that's helped me resolve some of these cases that were so perplexing at the time." So I took this as both confirmation that we really might be on to something that's robust and real, and that it has clinical impact. And of course, that's the big gratification when we do basic science research, is we see it can have an impact on patients and on the clinical tools that we use to monitor them, evaluate, diagnose them, and evaluate the influence of therapeutics.

Dr. Kashou: I'm just glad we have people like you that are questioning the prevailing thought, you know, and how we're actually coming up with a lot of the things we look at. Some of the patterns we're still, and even the treatments, that, you know we've gained a lot of insight over the years. That, you know, what were the standards? What were the therapeutics? How are we basing what we know on? And so thank you, you know, for doing that because I would say, even going through medical training, that's still something I commonly see, is the subendocardium is often that first area and for the two reasons, you know, you mentioned. I know there's a lot you

have, and I want to keep kind of learning more, but where do you see your goals of the future for you and your team?

Dr. MacLeod: Yeah, there're a couple of major directions. There are still mysteries that we haven't solved in terms of the mechanism, in terms of how we represent these sources. So how do we capture them in a way that we can eventually quantify? So the cardiac dipole is a wonderful tool to help us understand where activity is coming from, what the meaning of that activity is. It's how we interpret the ECG still in lots of situations. But there're, of course, more sophisticated, more elaborate models. And we're still trying to develop those in a way that will allow us ultimately to create patient-specific models that can drive this technique, this ECG imaging technique. The ECG imaging has wonderful capacity, wonderful potential. When it works, it truly is impressive. There are many situations in which it doesn't work as effectively. And we think that part of the problem may be some of the underlying models, these, what we call, source models. You know, the equivalent of the heart dipole in a more elaborate form. And so we wanna continue to refine those to, again, understand more fundamentally what is the electricity that we're trying to detect. So we think that's one thread that will be useful. Then, of course, with the advent of all these amazing machine learning techniques, we have to look at the signals and identify additional features that we might be able to use to improve clinical diagnosis. To take this, again, this notion of using information that we know is in the signals and trying to capture that to use that to improve diagnostic capabilities. So we're able to take those same machine learning techniques and apply them to our experimentally recorded data where we have an exceeding amount of control, we have an almost infinite ability to generate data. So we can create the large, very controlled, very carefully measured data sets that one simply needs for machine learning approaches. So we're very interested in applying a range of different techniques that are, again, emerging almost as we speak and seeing if one of those might lead to ultimately a clinical utility and improve, you know, diagnosis of these acute ischemic events, which, as I say, are tenacious and difficult and confounding, and yet have an enormous clinical impact. Because so many patients have ischemic episodes where clinicians need to manage. And so ultimately our goal is certainly to have a clinical impact through both of these major directions.

Dr. Kashou: From clinical discovery to the bedside, the ECG is critical for the detection of acute myocardial ischemia. Management decisions, sometimes lifesaving, are made simply based on recognition of ischemic ECG features. However, we are quickly realizing that there is so much work left to do, and we saw that here and heard it live today. Dr. MacLeod, what incredible work you and your team have done and continue to carry out. It is just truly amazing and encouraging to me for someone that loves to learn more about this. And probably the most important topic in our field is better detection of these ischemic features for our patients. I look forward to watching you, your future, your team's future unfold in front of us. And on behalf of our team, thank you for taking time to join us today.

Dr. MacLeod: Well, thank you very much for having me. It's been a pleasure.

Announcer: Thank you for joining us today. We invite you to share your thoughts and suggestions about the podcast at cveducation.mayo.edu. Be sure to subscribe to a Mayo Clinic Cardiovascular CME podcast on your favorite platform. And tune in every other week to explore today's most pressing electrocardiography topics with your colleagues at Mayo Clinic.