Personalized Computational Heart Models to Predict Sudden Death Risk in Hypertrophic Cardiomyopathy

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 could join us. Today we have an exciting episode planned for you as we look at the personalized computational heart models used to predict sudden death in patients with hypertrophic cardiomyopathy. We have a budding expert here with us that will help us better understand this topic. Hypertrophic cardiomyopathy is a disease state characterized by unexplained left ventricular hypertrophy associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that could produce such findings. It is reported to effect between one in 200 to one in 500 people in the general population, and it is considered the leading cause of sudden cardiac death in athletes. The condition is thought to be underdiagnosed leaving many at risk. Therefore, timely diagnosis and proper risk stratification of these patients and even their family members is important. In this episode, we will look at hypertrophic cardiomyopathy in further detail, as well as how personalized computational heart models can be used to improve restratification of these patients. We're fortunate to have Ryan O'Hara here with us today to help us tackle this important topic. Ryan is a PhD candidate in biomedical engineering at Johns Hopkins University in Baltimore Maryland. At Johns Hopkins, he is a senior member of the Computational Cardiology lab led by Professor Natalia Trayanova, as well as an instructor for the applied biomedical engineering program. Ryan's research focuses on the electrophysiology of both ischemic and non-ischemic cardiomyopathies. His developed methodologies with personalized virtual heart technology have led to new improvements for predicting cardiac arrest and ventricular catheter ablation therapy. Ryan, what an honor to have you join us today. Thank you so much.

Dr. O'Hara: Thank you so much for having me. It's a pleasure.

Dr. Kashou: Well, I thought that we'd start at the really the basics for our audience in maybe helping us better understand what is HCM or hypertrophic cardiomyopathy and how does it actually affect the heart?

Dr. O'Hara: So you gave a very good description in your introduction. So the disease, it is characterized by ventricular wall thickening that is caused by genetic disorder. And a lot of patients don't realize they have the disease until they have a cardiac event. Now, for patients that are fortunate that are aware of their familial history they can be diagnosed early on in life. So like along with the hypertrophy that occurs in the heart there's a lot of restructuring or remodeling that occurs in the myocardium. So cell hypertrophy, micro ischemia, and progressive diffuse myocardial remodeling which I'll get into a lot more can lead to ventricular arrhythmias and the worst case is cause sudden cardiac death.

Dr. Kashou: And so it seems like the biggest risk and why this is so important is what you mentioned at the end, those ventricular arrhythmias and the risk of sudden cardiac death. The first presentation is this cardiac event, is that what you're saying?

Dr. O'Hara: To some extent, yes. I mean, for a lot of patients they may not understand that they have the disease. It's evident if you see news articles about an athlete that collapses suddenly on the field. There's been a few cases of that in professional sports even.

Dr. Kashou: And so when we look at this disease state how is sudden cardiac death risk clinically stratified, and then once we've stratified that what does the typical treatment look like?

Dr. O'Hara: So there are two major organizations that have put forth guidelines to stratify sudden cardiac death risk into a hypertrophic cardio population, the American Heart Association as well as the European Society of Cardiology. And they base their guidelines on large population studies that take into account factors such as age, sex, familial history, atrial fibrillation, as well as maybe the presence of MRI enhancement. So enhancement on a medical image. And however, the main root of ventricular arrhythmias in hypertrophic cardiomyopathy is this diffuse fibrotic remodeling that causes the electrophysiology of the heart to go into disarray and causing these ventricular arrhythmias. So recently, actually at the European Society of Cardiology Congress this year, they did announce that they're going to incorporate this fibrotic remodeling into their guidelines, although it's binary. So it's the presence of one or the other, and which is good. And I will get into more information as we progress our conversation. But to treat patients with hypertrophic cardiomyopathy there are two typical treatments. One would be a heart transplant for patients at a full stage of the disease where the heart is consistently in a state of arrhythmia, or the heart is so thick that it cannot efficiently pump blood. The standard treatment for most patients with HCM would be implantation of ICD or an implantable cardioverter-defibrillator that can deliver a shock when it senses a patient's heart is experiencing abnormal heart rate, or an arrhythmia.

Dr. Kashou: Really fascinating, and I know we don't have the time to get into all the different variants of it, and how that treatment might look different. What I think is most fascinating is kind of where I consider you the expert apart from the disease state, but it's this computational heart or this virtual heart, you call it. What exactly is that and then how can that actually be translated and used clinically for us?

Dr. O'Hara: So the virtual heart is essentially a digital twin. It's a replica of the patient's heart, but using a computer. So in order to create this digital twin virtual heart we use clinical gadolinium enhanced MRI. So it's a contrast enhanced MRI scan that shows differences between the healthy tissue of the heart as well as the disease or fibrotic tissue of the heart. So using a clinical image of the heart we can basically segment the geometry of a certain patient's heart and reconstruct a finite element model which can contain information about the fibrosis of the patient. And we have developed methods to create cell models that can replicate the actual potential dynamics of the disease. So once we have this 3D model of the heart we're able to simulate rapid pacing as they may in the clinic to see if we can induce ventricular arrhythmia that can lead to sudden cardiac death. So if we're within these models, we pace from multiple locations to try and figure out if the patient's heart has the fibrotic remodeling that is conducive

to ventricular arrhythmia. And if our simulations are able to induce arrhythmia we may identify these patients at risk. Similarly, maybe in the ischemic population we do the same thing but we are also looking to find ablation targets as like another use for these models. So what we've done in our most recent study we took a cohort of patients in a retrospective study, I should say. And we reconstructed these virtual heart models and we were able to better predict the risk sudden cardiac death than the guidelines set forth by both the AHA and the ESC.

Dr. Kashou: That's quite fascinating given how important it is, and we mentioned how many are undiagnosed, or when it presents, and then family members. So you're using a heart that is almost a mimic, a virtual mimic of the patient's heart but you're doing the testing virtually, right? Is that correct how that works?

Dr. O'Hara: Yes.

Dr. Kashou: Okay. It's so fascinating. Now, what benefit, and I think you maybe alluded to this, do these virtual hearts when they're reconstructed with this T1 imaging add to improve our restratification in these patients?

Dr. O'Hara: So we introduced post contrast T1 imaging or T1 mapping to build these virtual heart models because they provide more information than a standard LG-MRI. This is contrast enhanced MRI. So in LG-MRI, the contrast agent is visible within the regions of focal scar, but it's not great at identifying regions of diffuse fibrosis. So there's like no threshold that currently exists in the literature for a threshold for diffuse fibrosis, which is the hallmark of hypertrophic cardiomyopathy. Whereas in T1 imaging, it's a quantitative measure. It's a quantitative image. So we can say based on the relaxation time or the the pixel intensity of the T1 image, which regions of the heart are healthy, which regions of the heart are unhealthy, and which regions are somewhere in between. So we can take this T1 map, they're usually harder to acquire clinically so we only obtain one or two per patient and we can use this information to modify the thresholds of our LG-MRI image to create a personalized threshold for the fibrotic remodeling in a patient's hypertrophy ventricle which is then subjected to our virtual rapid pacing. And we can detect whether or not the patient is susceptible to arrhythmia and as well as sudden cardiac death.

Dr. Kashou: Now this is all non-invasive work you're doing too right?

Dr. O'Hara: Correct. So for a lot of patients with hypertrophic cardiomyopathy, as long as the disease is identified or even suspected patients will follow up with their clinicians every few years, five years, 10 years, depending on the severity of their disease. And part of this routine, at least at Johns Hopkins, part of this routine care involves obtaining these MRI images. And from these MRI images we're able to do our entire workup computationally without any further additional patient intervention.

Dr. Kashou: It's so neat. It's really amazing what you're doing. Now hypertrophic cardiomyopathy is an important yet underdiagnosed diseases, that puts patients at risk of sudden cardiac death. It is exciting to see how personalized heart technology can improve the identification of patients with hypertrophic cardiomyopathy at risk of ventricular arrhythmias and its potential to prevent sudden cardiac death. Ryan, I've learned a lot from our discussion,

this one here, but even our previous ones. Thank you so much for joining. It's really exciting to see the work you're doing, your colleagues and your lab are doing to address this important topic. Thank you again for joining us today.

Dr. O'Hara: Thank you so much for having me. It's been a pleasure.

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