Dr. Kyle Klarich: Good afternoon, morning or evening everybody, depending on when you're listening to this podcast, coming to you from Mayo Clinic in Rochester, Minnesota. I am Kyle Klarich and I'm one of the cardiologists here on staff. And today we have a fascinating topic, genomics and inflammatory cardiomyopathies. And we are honored to have one of the world's experts in this area, Dr. Naveen Pereira, who is a professor of medicine in the Department of Cardiovascular Diseases, associate Professor of Pharmacology in the Department of Molecular Pharmacology and Experimental Therapeutics and chair of clinical trials operations and medical director of clinical trials at Mayo Clinic. But basically, I know Naveen as a phenomenal heart failure transplant physician and clinician with a clinical and research interest in genomics. He's really well versed in this. And if you could see his whole CV which would take our entire podcast to share with you, he's done a ton of research, had many awards in this area. So we are really happy to have you here, Naveen, to discuss with us the genomics of inflammatory cardiomyopathies.

Dr. Naveen Pereira: Thank you Kyle. It's really a pleasure to be here with you and thank you for this opportunity.

Dr. Kyle Klarich: I was wondering, you know, just when I heard the title of what we were gonna talk about today and did a, just a little bit of, of reviewing of some of the things that you've done, it's clear that heart failure and ventricular arrhythmias can have an inflammatory origin in heart disease such as myocarditis and sarco sarcoidosis. So I'm wondering if you could just start, for those of us like me that don't know a lot about this area, how do inflammatory cardiomyopathies typically present?

Dr. Naveen Pereira Right. And so what's really interesting is I believe that we are making a diagnosis more often. If you recall, 20 plus years ago, imaging techniques were not that good. And most of the times when we clinically suspected inflammatory heart disease, we did a biopsy and proved whether a person had inflammatory heart disease or not. And the whole biopsy situation we can talk about in detail, but it really has poor sensitivity and specificity because it depends where you biopsy and there's always a question of sampling error. But when do we start thinking about inflammatory heart disease? So when patients present now with acute onset heart failure with reduced ejection fraction, we always wonder if this is, especially if the diffuse T wave changes on the ECG, sometimes patients may have significant ventricular arrhythmias and when we see a lot of arrhythmic activity, we wonder if there's inflammation because things like giant cell myocarditis presents in a very prominent way. Arrhythmias are hallmark. Patients with sarcoidosis, for example, can have complete heart block, second or third degree heart block. And especially in a younger person having that raises the suspicion for sarcoidosis. So acute onset heart failure marked by conduction tissue disease, whether it's AV block or ventricular arrhythmias including atrial arrhythmias, one suspects the possibility of inflammation. And now most of our practice is moved to doing cardiac MRI and you onset heart failure reduced EF because we wanna make sure we rule out, you know, other secondary causes, especially inflammatory heart disease. So we are also incidentally now picking up and evidence of inflammation by MRI. That's why I really feel that as we

move to more imaging in patients with new onset heart failure reduced ejection fraction, we are increasingly seeing more inflammatory heart disease diagnosed.

Dr. Kyle Klarich: Fascinating. So it sounds like you would suspect it, you'd start to look for this in a patient that has relatively recent, if not acute onset of heart failure with reduced ejection fraction. So typically in my world as an echocardiographer, that would be, you know, patients admitted to the hospital with shortness of breath or chest pain or some combination of those things comes to the ECHO lab, we get a low ejection fraction. And then the next step for you would be some sort of imaging modality. And you said more than likely today's world cardiac MRI.

Dr. Naveen Pereira: Yeah, exactly. Is

Dr. Kyle Klarich: So is there a role at all for biopsy in these, in these patients or Right. Is there, or how, how do you then, so now the the MRI, tell me how the MRI will come back that you would then how would you follow that to either a biopsy or other diagnostic testing that you might order in that situation?

Dr. Naveen Pereira: Right. And so, so you know, the MRI also, by the way is complemented now with pet cardiac imaging studies. So, so we are, you know, now increasingly well done with a well organized protocol and patient preparation PET cardiac imaging also corroborates the MRI findings. So of course when you see increased FDG uptake and you see mismatches, you suspect there's ongoing cardiac inflammation. The MRI, you know, by T two imaging you see edema and then you get lead gadolinium enhancement and sometimes you wonder if that's active inflammation or scar. And so PET imaging compliments those. The problem is with, unless this is diffuse myocarditis, like with sarcoidosis for example, this patchy involvement. And so when you do a biopsy, the bioptomes are geared to going to the really, the right ventricular in right ventricular aspect of the interventricular septum closer towards the apex. And you may miss getting the area of inflammation. And so it's become better with what is known as electro anatomic mapping or intracardiac electrogram a guided biopsy. So sometimes you do biopsies in conjunction with imaging, you kind of map out, you know, by PET CT or cardiac MRI, which areas you want to target. But those become technically challenging, but the diagnostic yield can increase. But, but really, I mean what has happened is people are moved away from biopsies and if you have the MRI and PET imaging studies both positive for inflammation, a diagnosis is made and most of these patients then get diagnosed with isolated cardiac sarcoidosis. And that's where our recent paper in circulation genomics and physician medicine I think is important. Because what we found is 21% of these patients with presumed cardiac sarcoidosis. And it's called presumed because imaging studies suggest inflammation and the clinical presentation of AV block arrhythmias, low EF support the clinical diagnosis. And we found 21% of these patients in our cardiac sarcoidosis clinic actually had a pathogen or likely pathogenic genetic variant in one of the cardiomyopathy genes. And so you wonder then, you know, is this really cardiac sarcoidosis or is this a genetic cardiomyopathy that's

really masquerading as inflammatory heart disease or has aspects of inflammation? And the first paper was published several years ago and it showed that desmoplakin one of the proteins very important for intercellular communication and et cetera. So desmoplakin plaque in cardiomyopathies were classically associated with these inflammatory findings and imaging. And the diagnosis is really, it's a desmoplakin cardiomyopathy. It's a genetic cardiomyopathy, but it has inflamm inflammatory features. So what, yeah, go ahead.

Dr. Kyle Klarich: Yeah, there. So if I get, if I get this whole imaging package that looks like sarcoid and I don't test genetics, I could go down treating this patient for sarcoid, would that be the wrong thing to do? Because, right. Well cardiomyopathy, I mean you tell me that's, to help me understand that because this is 21%, it's not an insignificant number of patients, right?

Dr. Naveen Pereira: No, absolutely Kyle. So it becomes really important, you know, so what we are suggesting with this paper is that we have to do an additional level layer of phenotype. In fact, in that case series of patients, 60% of those patients did get started on immunosuppression before it was known that this was a genetic cardiomyopathy. And so here's the dilemma we have right now. So if there's actual inflammation, whether it's triggered by the gene or whether this is inflammation induced by sarcoidosis or other inflammatory myocarditis, immunosuppression, as you know, is the mainstay therapy for active cardiac sarcoidosis. And so there aren't good trials showing the benefit of immunosuppression. But you know, steroids we use MMF and other drugs, methotrexate, et cetera. And it's more commonly clinically used if we really think this is sarcoidosis. But we don't know what to do with the genetic cardiomyopathy patients who present with inflammation. And so what we have to do is add, after you see inflammation by imaging PET MRI, we suggest adding this layer of genetic testing as part of the phenotyping of the patient. And whether if gene positive whether to do embark on immunosuppression, we have no idea because this is now just newly recognized and it's a relatively rare disease. So as you know, to do doing a cardiac randomized clinical trial is challenging in a small number of patients.

Dr. Kyle Klarich: Just a couple other follow up questions based on that. So 21% of the patients that were originally diagnosed by imaging techniques when you ran the genomics ended up having the desmoplakin gene, which was an inflammatory. Am I right?

Dr. Naveen Pereira: Well, well it, well actually what was unique about a paper was there were multiple genes. Oh, so what originally started off as you know, a description of Desmoplakin presenting as inflammatory cardiomyopathies. It turns out now that in our study and in others have shown that the, any other gene can also present with this inflammatory pattern. So we had L-M-N-A, N-R-A-S and FHL one and things like that. We, which we described in the paper. Yeah. Do we know the, so it could be other genes too,

Dr. Kyle Klarich: Excuse me. But do we know the natural history of some of these genes? We probably don't even really know the natural history, am I right? Well,

Dr. Naveen Pereira: In general, patients who have a genetic cause of cardiomyopathy do worse than those who don't have a identified genetic cause of cardiomyopathy. In general. It doesn't mean, you know, a lot of these patients with a genetic cause of cardiomyopathy. can respond to medical therapy and should be treated, you know, with standard guideline directed medical therapy. But despite therapy in general, patients worse and then within the genes, you know, some have a worse prognosis than others. So titan is very common, but I would say a gene like LMNA, the LAM neuropathies, the course is far more malignant than say someone with a titan gene mutation. So we kind of know the natural history of genetic cardiomyopathy. And I would say the take home would be general, the genetic cardiomyopathies to worse than the non-genetic D to cardiomyopathy.

Dr. Kyle Klarich: So the person that's gonna see these first is the general cardiologist, the heart failure cardiologist. They're gonna go down the path of imaging, they're gonna get back something that suggests that they may have a sarcoid or a myocarditis. If they're the myocarditis pattern, that's a whole different talk discussion. Yeah. But if there's a sarcoid pathway, then we should be thinking, let's get a, let's get a genetic, a cardiomyopathy panel. Right? And then depending on how that comes out, 21%, roughly 21% in your paper, and I guess probably other papers are showing this is something that we then need to think about. Could it be a genetic cardiomyopathy? And then from there, where do I go now I've got this gene package back and it's positive for one of your, one of these genomic cardiomyopathies. What's the next step for the simple cardiologist that's trying to sort through?

Dr. Naveen Pereira: Right? Right now you have this added complexity, right? That now does a gene positive. So number one is it's important to have informed conjoined decision making with the patient and explain to the patient if you would just convince us with sarcoid. I mean you could very clearly tell the patient that patients with sarcoidosis can, you know, respond to immunosuppression. I'm gonna start you on immunosuppressive therapy. And mostly, I mean this is best done in tertiary care centers that deal with immunosuppression because you really have to monitor these patients, you know, with blood work and make sure they don't develop infectious complications if it's steroids, osteoporosis, et cetera. So, so they're well geared systems like within Mayo we have a very comprehensive, well planned follow up for these patients who get put on immunosuppression. But now if you have a gene positive inflammatory heart disease, you really have to discuss with a patient that there is no data, you know, to support giving you immunosuppression. But you do have active inflammation of the heart. You know, we could go down the path of immunosuppression or we may not. Immunosuppression includes, you know, all these side effects and the possibility may or may not get better and not going down the path may not, you know, necessarily attenuate disease 'cause it's a real unknown. And so, so really treating the phenotype, whether it's arrhythmias. So if you have to give amiodarone, VT ablation, ICD, all those rules should be followed by guidelines. If it's a, a reduced EF putting patients on A-C-R-B-R-

N-E beta blockers, you know, all those therapies don't change. So really following guideline directed medical therapy, whether this is an arrhythmia, conduction tissue disease problem or heart failure reduced EF is the way to go. The immunosuppression question, a general cardiologist is best served by referring this patient to a specialized center. Typically centers that do heart transplant are well-versed to the immunosuppression. So they, those type of centers would be catered to dealing with these patients.

Dr. Kyle Klarich: And I'm kind of guessing from what you've told us, that maybe next steps are gonna be some randomized controlled triumphs.

Dr. Naveen Pereira: Right? Or at least starting off with a registry, you know, where people have these patients characterized and then the outcomes tracked.

Dr. Kyle Klarich: Fantastic. Well I've learned a lot the fact that, you know, you have to go down the imaging path first and then classify, if you have this, it looks like an inflammatory cardiomyopathy, make sure you get genetic testing

Dr. Naveen Pereira: Right. That's something

Dr. Kyle Klarich: That's commercially available that I can just order for my patient through Epic or some other medical record system. Whereas how do we, how do we order the genetic test?

Dr. Naveen Pereira: Yeah. So it's best now within Mayo we've developed a system where we have an intervention actually where patients are shown a video which is recorded by the genetic counselor. So they undergo counseling. And the advantage of the video is we don't have to make a separate appointment with the genetic counselor, which we found a lot of patients who wanna come back for. So, so we do have that. And then we can, and the heart failure nurses actually fill out all the paperwork for the genetic testing. But for the average practitioner, really referring them to a genetic counselor and their web pages, you can do a search, find a genetic counselor, and within the area that you live, you can identify a genetic counselor and refer them to a genetic counselor and they'll take care of it. They'll counsel the patient and they'll order the genetic testing, get the results back and from the patient to physician. And it can go from there.

Dr. Kyle Klarich: One other question that just popped into my head and that is age of these patients, are they typically, is there a a certain age range that would be more classically associated with the genetic cardiomyopathies?

Dr. Naveen Pereira: Yeah, it's really a, a good question. I mean, generally speaking a couple of things that increase the yield of genetic testing, if you may, of it being positive. So one is a familial history. So there's a familial history, you know, one or more relatives who also have cardiomyopathy or arrhythmias, then the yield of genetic testing can go up to 40%. So you know, up to 40% chance that there may be a positive finding by genetic testing. Wow. But there's no familial history. And this is really important because people refer people for genetic testing with this family history, but there's no fam familial history or family history up to 20% can still have a gene abnormality. So, so that's kind of, and generally people think when you're young and you have arrhythmias or cardiomyopathy, I think the yield is higher in younger patients with severe cardiac disease. But again, just like family history present on that, the yield is not as high in older patients, but it's still there. So we don't necessarily use an age discrimination to do genetic testing. 'cause for example, a lot of the titan, you know, the most common abnormality that causes cardiomyopathy is titan older patients can present even in their seventies with a tighten genetic cardiomyopathy.

Dr. Kyle Klarich: That's very interesting. It's sort of the similar thing to one of my areas of interest in that hypertrophic cardiomyopathy. We used to always think it was a young person's disease. And over time we've realized that many of them don't show up in sixth, seventh, and even an or I've diagnosed it in an 80-year-old, 86-year-old. So I think these are fascinating areas and the more we know about genetics, the more we're finding how many things are associated with a genetic origin. And so that's a really fast, is there anything else you'd like to clarify or anything else you'd like to leave the audience with? Take home points?

Dr. Naveen Pereira: Yeah, I mean if you have a patient, you onset heart failure or significant ventricular arrhythmias or AV block, obviously you know PET MRI imaging studies that you do to rule out inflammatory heart disease. And if you find inflammatory heart disease supported by imaging, then obtaining genetic testing I think is an important next step. So then we understand even if patients immunosuppressed, whether the gene positive, gene negative, what the outcomes of these patients are. And we hope absolutely. To build a registry to track these outcomes,

Dr. Kyle Klarich: We need more information. Exactly. So, wow, very interesting. But from my, my take home as a humble clinician, you know, you're still gonna treat them with guideline directed medical therapy, phenotypic guideline directed medical therapy with, if they're low ejection fraction arrhythmias and, and these types of things, you would then jump in with those and then hopefully if it's an inflammatory cardiomyopathy sarcoid or a genetic cardiomyopathy, refer to a center that has transplant capability, still usually be tuned into this.

Dr. Naveen Pereira: Absolutely.

Dr. Kyle Klarich: Would that be a good summary, you think?

Dr. Naveen Pereira: Or That's a beautiful summary. Thank you. Thank you.

Dr. Kyle Klarich: Well, thank you for your expertise and for all the cutting edge research you're doing in this area to help us better understand these, this complex group of patients. Thank you so much.

Dr. Naveen Pereira: Thanks Kyle. It was a pleasure.