Bileaflet MVP Syndrome

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Dr. Friedman: Hello, my name is Paul A. Freedman, M.D. I'm chair of the Department of Cardiovascular Medicine. And today I have the great pleasure of being joined by my colleague, Michael J. Ackerman, M.D., Ph.D., who heads the Windland Smith Rice Genetic Heart Rhythm Clinic. And we're going to talk about a very interesting and more common than we think syndrome. And that is arrhythmogenic bileaflet mitral valve prolapse syndrome. So Mike, welcome.

Dr. Ackerman: Thanks a lot, Paul. It's great to be with you.

Dr. Friedman: Let's start with the basics. Mitral valve prolapse has been around for a long time. There's been questions for decades. Is there an increased risk of sudden death or not? Tell us a little bit about, first of all, what is the difference between mitral valve prolapse, and the mitral valve prolapse, or bileaflet mitral valve prolapse, arrhythmia syndrome.

Dr. Ackerman: Yeah. You're right. It's been around forever. And in fact, the sliver of mitral valve prolapse that may be associated with sudden death was actually first published here, I think from Mayo Clinic. Our colleague, Dr. Rick Nishimura published that. But that was in the setting of a mitral valve that's not only prolapsed, but that is performing poorly. It's leaking badly. So it's a hemodynamic sequela that lead to sudden death, and we're not talking about that at all. We're really talking about prolapsed mitral valve leaflets and a valve that's otherwise working fine. So, the amount of leak or regurgitation is minimal. And you're right. Mitral valve prolapse is kind of like fainting, right? It's incredibly common and almost always it's incredibly benign. So it's something like one to two percent of the planet has a prolapse of one or both of the leaflets, probably a half a percent have bileaflet mitral valve prolapse. So one out of 200 of us have both mitral valve leaflets that prolapse. But we sort of stumbled upon what we call the syndrome, or arrhythmogenic bileaflet mitral valve prolapse syndrome, about eight years ago. And that came out of our Genetic Heart Rhythm Clinic, where we were seeing out-of-hospital cardiac arrest survivors, that it seemed like we were noting bileaflet prolapse too often. And we said, let's do what we do at Mayo. Let's look at our data. And we looked at a 10-year experience of 1,200 patients who came to the Windland Smith Rice Genetic Heart Rhythm Clinic, and as you know, most of them come with physicians querying: Rule out long QT syndrome. And I think that becomes a key part of the equation where, of those 1,200 patients, there were 24 out-of-hospital cardiac arrest survivors. And just like my impression was, 10 out of those 24 had bileaflet prolapse, that's 42 percent. We thought that's way too high of a signal. If it was a nothing, we should see it in a half a percent having both leaflets prolapse and that's where the ah ha came, where we sort of then identified the features of what we called arrhythmogenic bileaflet mitral valve prolapse syndrome. And that was bileaflet mitral valve prolapse, almost always women, but since then not exclusively women, funny T waves. And then you can see the funny T waves is why they got tagged as maybe they're long QT in some way. But then when you do a Holter on them, they have too much ectopy. Long QT patients don't have ambulatory ectopy. But then the

ectopy, the ventricular ectopy is kind of unique. They sort of have a complex ectopy that when they show you couplets, it's almost always an outflow tract focus coupled with a papillary muscle or a Purkinje or a vesicular PVC. And that really became the tetrad of arrhythmogenic bileaflet mitral valve prolapse syndrome.

Dr. Friedman: So just to drill in, so first of all, fascinating and I mean really an important insight. And these are the kinds of cases that keep us all up at night because we all see mitral valve prolapse, right? Two millimeters of prolapse of the leaflets into the atrium during systole, maybe thickened leaflets for usually young, healthy people. And you don't want to alarm people, but devastating things can happen when you miss this syndrome. So first the resting ECG, you mentioned T wave abnormalities, especially in the inferior leads. Do you want to expand on that? What sorts of things make you think, oh, this is not just mitral valve prolapse.

Dr. Ackerman: Yeah. The T waves were, I would say, funky looking. And so we have that FLK funky looking T waves. And they're kind of low amplitude and undulating. And in the inferior lateral leads sometimes T wave inversion, but it kind of gives you a mixed look of, you're not sure is that at TU configuration? Or is that a low amplitude bifid T wave? And so it's just, I would say, most people with just normal prolapse, sort of just one to two percent of us, they have normal T waves. And when they start looking wonky or low amplitude or bifid appearing or sort of a TU look throughout the inferior and the lateral leaves, then maybe you start to say to yourself, maybe this isn't quite the normal-normal, who cares prolapse.

Dr. Friedman: So key point, mitral valve prolapse with bifid T waves, inverted T waves think twice. So then you mentioned the complex ectopy. Now that's coming mostly from the left ventricle. So we would have certain characteristic findings as well. And you want to maybe dig into that a little bit. You know, that's something people need to beware of also.

Dr. Ackerman: Yeah. And so I think there, what we noted was one of the PVC sites looks to be perhaps related to that prolapse in leaflet mechanical mechanism itself, where maybe it's agitating or irritating the papillary muscle or is coming from the vesicular system, like you said, somewhere in the LV, and so the T waves or the PVC profile looks different than the ordinary, vanilla version outflow tract PVC. And you know, as you know, you're way better than I am at PVC pattern detail. And so, I really rely on you and our colleagues to say, that PVC is coming from the papillary muscle and maybe you can tell them what's the papillary muscle. I could try but I'd be nowhere as good as you.

Dr. Friedman: I don't know that I'm any better, but I think the take-home message is, it will have a right bundle branch block morphology. So it'll be mostly positive in lead V1. And that's the key lead coming from the left ventricle. And then depending on whether it's the papillary muscle of the outflow tract we'd look at the inferior leads to positive or negative. So you have somebody and they have these findings. What's the work-up? What are the next steps?

Dr. Ackerman: Well, I think that's really the challenge, isn't it? Because we have to remember, how did we discover the syndrome. It came from, I already tried to die suddenly. So almost all of these patients who we tagged with this syndrome label, their cardiac arrest out of hospital was their first event. That's a very different starting point than somebody coming in and they get an

echo for whatever reason and, oh, by the way, one or both leaflets are prolapsing. Or the young woman who comes in with, I'm basically healthy, but I'm going to tell you and me about palpitations. And now part of that work-up, we get an echo and now we have a prolapse of the leaflets and we have to be really, really careful to not oversubscribe this entity, because I think this entity is going to probably be about a one in 10,000 to a one in 20,000 person entity. It's going to probably fall under ultimately an arrhythmogenic cardiomyopathy, in terms of how we think about this substrate. And that's very different than the one out of 200 of us who have both of our mitral valve leaflets prolapse. And so I don't know that we know exactly, what should we do when we find somebody at the starting point is, I'm alive and well, I've never really had a symptom except maybe palpitations and now you're telling me I have mitral valve prolapse, should I freak out? And I think the answer is going to be no, almost never, but let's perhaps do some systematic electrical testing that we've never really done before. I would say routinely, in mitral valve prolapse or bileaflet mitral valve prolapse in particular, that's: Get an ECG. Are the T waves normal looking? If so, this isn't going to be this entity. Get a Holter. What does the ectopy look like on Holter? Do we see these couplets where you and I and maybe even a 12-lead Holter. And do we see these couplets pattern? And if so, does it look like this pattern of the syndrome of a papillary muscle, a PVC coupled next to it with an outflow tract PVC. And then if the answer to those are yes and yes, then we really scratch our heads and say, yeah, but they're asymptomatic. Now what do we do?

Dr. Friedman: To that end, what about an MRI scan?

Dr. Ackerman: I think now the MRI is becoming really important actually. And that's from some newer work since we first described the syndrome is there's been two features that I think are probably telling us that the bileaflet mitral valve prolapse is maybe just an endophenotype. It's not the critical observation. It's just heralding the presence of potential. It gets the ball rolling. And what accelerates the ball rolling is an MRI with late gadolinium enhancement of the papillary muscle or the mitral valve architecture itself that says, there might be papillary muscle fibrosis. I think that's going to turn out to be a really important marker and then an echo or an MRI marker of the valve leaflet architecture in terms of mitral annulus disjunction, is that mitral valve leaflet hinge point displaced, yes or no? And I think they will be two really important markers. But both of those markers, I would say, have a lot of slop, or noise in the system, in terms of its measurement.

Dr. Friedman: Now you just described something that's different. That is mitral annular disjunction, a relatively new syndrome. Is it part of mitral valve prolapse? Is it separate? And maybe just take a second to describe what it is and how we identify it.

Dr. Ackerman: Yeah. So, mitral annulus disjunction is, in a way I think of it as a congenital heart disease doctor as the inverse or the opposite of a syndrome we've known about for a long time, Epstein anomaly, where there on the Epstein anomaly there is septal leaflet displacement into the ventricle of the right valve, the tricuspid valve. But in mitral annulus disjunction, or MAD, there is actually atrial displacement of the mitral valve leaflet. Most often we measure it in the posterior leaflet, not the anterior, but it could be both. Where both of the hinge points or one or the other is atrially displaced. That's a measurement that could, that atrial displacement of the hinge point of the leaflet, can occur in a valve leaflet that is not prolapsing. So you don't have to

have a prolapse to have MAD. And in fact, in JACC, three years ago, one of our former trainees who studied here with her post-doc, Kristina Hougaa, from Norway, they published mitral annulus disjunction, arrhythmic syndrome. And most of those patients with MADAS or mad ass, I guess you have to be careful there, they didn't have mitral valve. And so I think the challenge with that measurement though, is that measurement doesn't have very good quality metrics to it yet, I would say. There's tremendous interobserver variability. It hasn't yet been standardized as to make that a confident measurement. And so I think we're seeing probably some over-labeling of MAD in echos now, kind of like you and I are seeing over-labeling of trabeculations and things like that. So we're in this messy phase, I would say, where there's just a lot of, you know, the signal-to-noise we need to improve.

Dr. Friedman: You know, it strikes me that we're actually seeing is that there are all these variations on the mitral valve that lead to stretch or a slapping of redundant tissue against the left ventricular wall that leads to fibrosis. And it's the fibrosis in the bileaflet mitral valve prolapse that's associated with arrhythmias in the papillary muscle or where the chordae are hitting the wall. And similarly with mitral annular disjunction, it's that fibrosis at that annulus that may be causing those ventricular arrhythmias. But that leads to the next question. I'm focusing on the bileaflet, arrhythmogenic bileaflet mitral valve prolapse. How do you treat it? Let's say somebody has palpitations, syncope. ECG shows inverted inferior T waves. Holter monitor shows lots of right bundle branch, couplets, triplets, and you're worried about them. They've had pre-syncope. MRI shows fibrosis. What are treatment options?

Dr. Ackerman: Yeah. I think in that patient we're still challenged. I was hoping you'd give me the easy one of, they're already a cardiac arrest survivor, but maybe we'll come back to them. The hard one is the one you just described. And I think there, what I have done is, I think beta blocker therapy there's a role. Some of the patients with nadolol, for example, the palpitations just vanish, the ectopy is suppressed. Some of us have wondered about nadolol and flecainide, some of the papillary muscle and the Purkinje system and the vesicular origin PVC seem to be very flecainide sensitive. There may, if we're more concerned than pharmacotherapy, we have even started to ask you to do an EP study and see if there is ease of inducibility with a nonaggressive ventricular fibrillation inducibility protocol. And if yes, go so far as to do a prophylactic ICD. And then watch and wait and see evolution. But this is not for prolapse. This is for where you think you found a pre-cardiac arrest person who fully satisfies the full tetrad or all of the features of the full-fledged syndrome. They've got annular disjunction, they've got fibrosis on MRI. You don't like the complex ectopy, ventricular ectopy, you think you have found the pre-cardiac arrest person who really is this syndrome, then I think it deserves that approach right now because there's a few too many unknowns yet. When we think we're starting to identify the denominator of the pre-cardiac arrest person with the syndrome, and we have no idea if they're going to stay pre-cardiac arrest indefinitely, or if they're going to join those who have a cardiac arrest as the sentinel event.

Dr. Friedman: You've really nicely outlined just the challenges of a risk stratification in this new and emerging syndrome. Let's take what I'll call the easier case: Out-of-hospital cardiac arrest survivors. No-brainer, they did an implantable defibrillator. Is there a role for ablation?

Dr. Ackerman: Yeah, I think so and we think so. And in fact, Mayo Clinic was the first to publish the series of our experience with ablation for arrhythmogenic bileaflet mitral valve prolapse syndrome. Published it in 2016, in Circulation Arrhythmia and Electrophysiology and our colleague and partner Peter Noseworthy was senior author. And there we took 14 consecutive.

Dr. Friedman: So this was early.

Dr. Ackerman: We follow now about a hundred patients with this syndrome. And so this was 14 consecutive patients that we would call arrhythmogenic bileaflet mitral valve prolapse syndrome that went to the EP lab. Why did they go to the EP lab for ablation? They already started the story with their own cardiac arrest. That brought them in. They get their defibrillator and they're having frequent recurrences of VT or VF episodes requiring shock. So they've declared their natural history. And in them, we've offered PVC ablation, and what we found was that most of those had Purkinje origin ventricular arrhythmias. And in that small series, small — it's actually much larger than when we first published it — but we've demonstrated that the targeted PVC ablation of one or both of the primary foci had a dramatic reduction in symptoms and more importantly, a significant reduction in ICD therapies, appropriate ICD therapies. So I think ablation may bend the natural history of those who are fully declaring themselves as expressive of this syndrome. But we need more numbers and we need more time horizon. But I think the early word is, I think for those with recurrences and certainly one or more ICD shock should cause people to start to ask the question, should we be trying and doing a PVC ablation for them?

Dr. Friedman: It is remarkable and perhaps in some patients where it's harder to know what the right answer is, ablation and observation before ICD may maybe an appropriate option as well. One last question for you before we wrap this topic up. And that is, is this a genetic condition?

Dr. Ackerman: You know, even though we will probably have this thing labeled as an arrhythmogenic cardiomyopathy as a place holder for where does it best fit, it's not genetic like the conditions that you and I take care of, of ARVC, for example, or long QT syndrome, where we have 50 percent of ARVC is a monogenetic insult, 80% of long QT syndrome is a monogenetic insult. That's not going to be the case for this entity. But there are some examples of familiality, where we've seen it run in the family. We've started to do genetic testing for the known cardiomyopathy genes for this. And I would say we're still in single-digit yield, where we find an ARVC mutation or we find a truncation mutation in titin, which starts to make us wonder, that may not truly be a autosomal-dominant monogenetic insult, but this might be part of the, I don't know, kaleidoscope of this syndrome where you need to have this, this, this, and maybe a genetic nudge where your myocardium isn't perfect, that sets up the ultimate, you know, perfect storm for it to happen. So it's not going to be genetic, like most of our monogenetic disorders that we see in the Genetic Heart Rhythm Clinic. But I think we're in the early days of sort of exposing, what is the level of genetic contribution, mono-, oligo-, polygenetic kind of substrate that adds to fuel to the fire, if you will.

Dr. Friedman: Well, Mike, thank you very much. I always learn a lot when we have these conversations. And I think maybe to summarize, I would say vast majority of people, it's reassurance. But to really work-up the ones that have the concerning signs, inverted or bifid T

waves, funny-looking T waves, complex ectopy, typically right bundle and morphology, symptoms that are concerning and then if necessary an MRI that shows fibrosis. Multidisciplinary approach that includes geneticists, electrocardiographers, electrophysiologists, imagers, as we learn more about this uncommon but potentially dangerous syndrome in young people. Then again, thank you for joining us. Great discussion.

Dr. Ackerman: Pleasure.

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