Applications of Autonomic Modulation in Arrythmias

Announcer: Welcome to the Mayo Clinic Cardiovascular Continuing Medical Education podcast. Join us each week to discuss the most pressing topics in cardiology and gain valuable insights that can be directly applied to your practice.

Dr. Friedman - Hello, my name is Paul Friedman, I'm chair of the Department of Cardiovascular Medicine at Mayo Clinic, and it is my great pleasure to be joined by my colleague, Dr. Guru Kowlgi, Assistant Professor of Medicine, heart rhythm expert, who has a special interest and expertise in the autonomic nerves and cardiac arrhythmias. Guru, thank you for joining me.

Dr. Kowlgi - Thank you so much for that kind introduction, Dr. Friedman. I'm very happy to be here.

Dr. Friedman - So, why don't we start with the basics? First, what is the autonomic system, why is it important, and what is autonomic modulation?

Dr. Kowlgi - Yeah, so that's an important question. So, the autonomic nervous system performs an integral role in cardiac innervation. So, it is responsible for pretty much all of the cardiac activity. So, there are two limbs of the autonomic nervous system, we have the sympathetic nervous system, and the parasympathetic nervous system. The sympathetic nervous system is responsible for the fight-or-flight response. So, when we are either physically stressed, or emotionally stressed, that's when the sympathetic nervous system kicks in. It is responsible for causing an increase in the heart rate and blood pressure, and thus preparing the body to handle these circumstances. The parasympathetic nervous system, on the other hand, is responsible for reducing the heart rate, reducing the blood pressure, more active when we are sleeping and when we are resting. So, again, as you can guess, the balance between the sympathetic and the parasympathetic nervous system is what keeps the heartbeat regulated. So, if there is an imbalance, that can lead to cardiac arrhythmias.

Dr. Friedman - And, how is the autonomic nervous system modulated?

Dr. Kowlgi - So, there's an intricate balance that exists naturally. And, then from our standpoint, when we see cardiac arrhythmias that we feel are arising either due to a sympathetic overactivity, or parasympathetic overactivity, we can then attempt to modulate these. Now, we've been doing this for a long time with pharmacotherapeutic agents, such as beta blockers, which can cause a decrease in the sympathetic tone. But, more recently, we've become more familiar with techniques, with catheters, with nerve stimulation, that can help us achieve this in a more direct fashion. For example, we can perform a cardioneural ablation, or target the vagal innervation of the heart, to treat diseases such as neurocardiogenic syncope, refractory vasovagal syncope, and also atrial fibrillation. On the other hand, some of our listeners may be familiar with performing sympathetic modulation for patients with ventricular arrhythmias. These are patients that are a

factor. They do the medical... Standard medical therapy and then catheter ablation. And, when they get admitted with ventricular electrical storm, we can target the stellate ganglia, the cervical thoracic vertebral chain, to reduce the incidence and recurrence of ventricular arrhythmias in these patients.

Dr. Friedman - It's fair to say then that it's fairly well established for some patients with long QT, as you just, by surgically modifying the sympathetic nerves and decreasing sympathetic drive to the heart, there's a significant reduction of ventricular arrhythmias, but now there appears to be an expanded role in atrial arrhythmias, and I'd wanna ask you about that. And, the other thing of interest is the nervous system and its anatomy is complex. So, I really have a two-part question. The first one is, is there a role for atrial arrhythmias? And, the second one is, where would we access the nervous system, from the brainstem, to the thorax, to the epicardium, to the heart? What are the targets?

Dr. Kowlgi - That's an excellent question, and I start with the second part first, because that forms the premise for the first question. So, in terms of the anatomy, there are some key fundamental differences in the way the heart is innervated by the sympathetic and the parasympathetic system. So, while all of these nerves eventually make their way to the heart, the places where they synapse are different. So, for example, the sympathetic nervous system is really housed within the cervical thoracic vertebral chain in the stellate ganglia, and the superior and middle cervical ganglia. So, these are nerve bodies that are going from C-7, cervical seven, to about a thoracic two and three vertebrae, and then they send out efferent neurons that innervate the heart. The parasympathetic nervous system on the other hand has long pre-ganglionic fibers that actually synapse on the epicardial surface of the heart where we have these cardiac ganglionated plexi. So, the way we can approach targeting these is actually directly via catheter ablation, where we all know that we have tools and techniques that can perform transmural ablation in the atria. So, we can target the vagal system from the heart with catheters and the sympathetic nervous system usually in the neck at the level of the stellate ganglia.

Dr. Friedman - So, first talking about the ganglionated plexi, the parasympathetic nerves that are on the outside surface of the heart. Just for clarity for all our listeners, when you're talking about treating them, you would use a standard ablation catheter inside of the heart, and the therapy, the energy would go through the full thickness of the atrium to hit the nerves on the outside of the heart surface?

Dr. Kowlgi - Oh, yeah. So, that's exactly what I was getting to, that in the past we felt that we needed to get epicardial access to be able to target these ganglia effectively. And, that makes intuitive sense. But, the problem is for some of these patients getting epicardial access may be challenging. It does increase the risks of the procedure. So, we now know that with some of our techniques with radiofrequency ablation, irrigated radiofrequency ablation, and pulse field ablation, which is on the horizon, we can get effective transmural lesions. And, there's data to show that endocardial ablations can lead to effective denigration that lasts many years to decades. So, it is certainly a tool that we can use.

Dr. Friedman - Got it. And, now going back to the first part of the question, the expanded role for atrial arrhythmias, tell us about that.

Dr. Kowlgi - Yes. And, I think for that, it's important to understand the pathophysiology of some of these arrhythmias. It makes intuitive sense that if you have high sympathetic tone, then that'll lead to increased heart rate and then abnormal automaticity as a mechanism can become a player. So, patients who have frequent PACs, premature atrial contractions, or premature ventricular contractions, or atrial tachycardia, can be purely because of high sympathetic tone. But, when it comes to complex arrhythmia, such as atrial fibrillation, it's an interplay of factors. So, you can have a lot of triggers, because of high sympathetic tone, but in these patients. having a high vagal tone can also be a problem, because that shortens the action potential duration, and makes the patient more likely to go into atrial fibrillation. From a ventricular arrhythmia standpoint, having a ton of PVCs can be a problem, even in structurally normal hearts. But, in those that have scar, these PVCs can trigger ventricular arrhythmias from a reentering mechanism as well. So, essentially, there's a complex interplay of factors and a sympathetic nervous system modulation certainly can help with arrhythmias as well. There is data in the... On the catecholaminergic polymorphic VT population where the primary arrhythmia is usually ventricular, but sympathetic modulation has been shown to reduce arrhythmias in these patients. So, that is something that we can use and sort of extend to the other patients as well.

Dr. Friedman - It really is striking that we're shifting in a way from treating the end organ in the heart to the higher level control system to potentially address arrhythmia. So, it really is a fundamental paradigm shift and there'll be a lot that we learn as we approach this. Who are the best candidates for these kinds of treatments? And, if you're an internist or cardiologist seeing a patient who might have atrial fibrillation or PACs, or other arrhythmias, are there clues to suggest that this individual may benefit from an autonomic intervention as part of an arrhythmia management approach?

Dr. Kowlgi - Yeah, that is a fantastic question, and a million dollar question, because we are still figuring out as a field the patients that would benefit from these interventions. I think, for a starting point, it makes sense to consider these interventions in patients who have failed the standard techniques, such as medical management and the standard catheter ablation techniques. There are certain arrhythmias where really we don't have any other way of managing them. For example, refractory vasovagal syncope patients, these are young patients that are having recurrent syncope episodes. There really isn't any medical therapy that can help them. We can educate them, we can tell them about certain counter pressure maneuvers, but, beyond that, we are really looking at things such as pacemakers to treat some subset of these patients. So, if they're having refractory symptoms from vasovagal syncope, I think that is a reasonable patient to refer to cardiology and to cardiac electrophysiology. But, for atrial fibrillation and ventral arrhythmias, I think when they've failed the standard treatment options, we should consider them. For Afib, we have had some clinical trials done in Europe in the between 2014 to 2017 that have shown some promise of doing cardioneural ablation in addition to pulmonary vein isolation. And, we are planning on starting a clinical trial here at Mayo Rochester in the summer and fall, where we try to enroll patients, randomize them to one arm that receives the standard of

pulmonary vein isolation, and the other, I guess, PVI plus ganglia ablation to see this difference in outcomes.

Dr. Friedman - So, for patients with atrial fibrillation who failed the standard ablation, which is pulmonary vein isolation to isolate the triggers coming from the veins, there's early signals that it's promising and may help improve outcomes. Now, you briefly touched on vasovagal syncope. One is a fast heartbeat, atrial fibrillation, the other one is a slow heartbeat. So, intuitively, there's a lot to think about. Tell us a little bit more about the mechanism of vasovagal syncope, why ablation in the heart or other autonomic interventions may help, and what's the clinical experience there to support those observations?

Dr. Kowlgi - Great questions. So, essentially, vasovagal syncope, try to think of these patients as patients that have high vagal tone at baseline. So, all of us have our intrinsic sympathetic tone and intrinsic vagal tone. These are the patients when we do hold to monitor and look for certain trends in the heart rate variability, we'll see that they're... The signals that show that they have high parasympathetic tone are already elevated at baseline. These are the patients that have certain triggers. Sometimes, they know what their triggers are, like they could be visualizing something unpleasant like the sight of blood, it could be an emotional trigger, but then sometimes they don't know what their triggers are, and then they have these syncope episodes. They do get some kind of an aura. They'll have some sensation for a few seconds before they pass out. But, again, this can be benign. But, in certain situations, like if they're driving, can be life-threatening. So, for these patients, the way to treat them, beyond lifestyle measures, is to target the ganglionated plexi on the epicardial surface of the heart via endocardial ablation. There have been studies done dating back to 2005, the most prominent group has been the group from Brazil. Dr. Pachon and his team have published a lot of articles on this. They've had long-term follow up for over 200, 250 patients, over 11 years of follow up, and have shown reduction in episodes by about 85 to 90%. So, that's promising data out of there. We do have a US National Registry of about 75 patients or so. The data was presented at Heart Rhythm Sessions last year in 2022 and has been growing since then. And, that looks very promising as well.

Dr. Friedman - So, bottom line for this approach then is, often young people, recurrent vasovagal syncope, meaning they're not having structural bradycardias, they're not having tachycardias, they have that sort of typical vasovagal faint, but it happens a lot. And, so ablation in the heart is stunning, or rather injuring, or modifying, I should say, the autonomic vagal inputs to the heart, which tend to slow it. And, by peeling those back with ablation, there's this huge response rate.

Dr. Kowlgi - Yes, absolutely. And, as people may sort of intuitively guess that these patients do experience an increase in heart rate. So, for example, some athletes may not find that very appealing, because the heart rate, resting heart rate would go from 40 to 65, 70, but from a disease control standpoint, it works really well for vasovagal patients.

Dr. Friedman - What are future directions for autonomic modulation?

Dr. Kowlgi - Yeah, I think the first step, I'll try to divide that into three parts. I think the first step is really getting better at patient selection. I think that's where we need to leverage all the tools we have at our disposal, including artificial intelligence, trying to identify patients, for example, for vasovagal population, the patients that have a high vagal tone to begin with. Can we use ECG and Holter data to identify those patients better? Then, can we use the wealth of data we have to identify patients that have a response at five years, at 10 years, and then sort of select patients better that way? From an inter procedural standpoint, I think it's important to realize that there's anatomic variations. So, if we set out to do cardioneural ablation, ablation in my case would be different than ablation in your case, because your innovation would be different. So, can we identify that based on the signals that we acquire during electro anatomic mapping and figure out where these sites are located, so we can target them better? I think the third step would be just ablation technology. As we get more facile with newer technologies, such as pulse field ablation, can we get better at performing these epicardial ablation via an endocardial route, and get this done more effectively, and sort of more reproducible. I think those are the big things. And, then sort of another big area of interest would be to see if we can perform sympathetic modulation, not just via the stellate ganglia or sympathetic veneration, but with catheter approaches in the vertebral vein. Can we target the stellate ganglion, for example, with catheters, and help our patient population with inappropriate sinus tachycardia? I think there's a lot to be learned there, we're still doing some animal studies, but more to follow in the next few years, I think, and we'll get smarter in this field.

Dr. Friedman - Yeah, no, very exciting area, really paradigm shifting. And, it's interesting you brought up inappropriate sinus tachycardia as well as POTS, sort of related overlapping syndromes, underscoring how much we have to learn in this space, and how, by understanding control mechanisms, we'll be that much better taking care of arrhythmias. Really look forward to seeing the study take off here. And, Dr. Guru Kowlgi, thank you for joining me. It's been a fascinating discussion.

Dr. Kowlgi - Thank you so much. It's been a pleasure.