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Advances in Electrophysiology (EP) Procedures

Narrator:
Welcome to “Medical Breakthroughs” from Penn Medicine, Advancing Medicine Through Precision Diagnostics and Novel Therapies. Your host is Dr. Lee Freedman.

Dr. Freedman:
Great strides have taken place in the field of cardiac electrophysiology enabling the treatment of many cardiac conditions with more effective and less invasive strategies. What are some of the latest developments in this exciting field? I'm your host, Dr. Lee Freedman, and with me today is Dr. Francis Marchlinski, Director of Electrophysiology and Professor of Medicine at the Hospital of the University of Pennsylvania. Dr. Marchlinski, thank you for being with us today.

Dr. Marchlinski:
Thanks for having me, Dr. Freedman.

Dr. Freedman:
We are excited to hear about the things that you're doing, and perhaps we'll start simply. I'm an internist. I often will do a cardiac exam and hear some extra beats, do the EKG and see some premature ventricular contractions. When is that something that I should pay attention to, and how do we proceed with those?

Dr. Marchlinski:
It's a good question, good place to start. I think that the important thing to recognize is the fact that most PVCs are indeed benign. We start out by determining first whether there's associated structural heart disease, so if a person is having frequent PVCs with or without palpitations, we step back and say: Is there structural heart disease? Has the patient had a prior infarction? Is the left ventricular function depressed? If it's not, then, in all likelihood, we have an extremely benign condition. We then take the next step, which is to determine the degree of symptoms. So patients who are very symptomatic, then they warrant treatment. And it's interesting—patients develop symptoms from PVCs because of the irregularity of their pulse. Patients also occasionally experience an effective halving of the heart rate when they develop sudden bigeminy, so the PVCs are not perfused; they occur early in the cardiac cycle and actually result in a nonperfused QRS complex. So the effective heart rate suddenly drops, so some patients actually can experience some dizziness. Many patients, of course, the PVCs are asymptomatic. Their heart condition, if their heart is structurally normal, we don't treat. If patients are symptomatic with either palpitations, or as I said, occasionally they can get dizziness when they sudden develop bigeminy, then we're more likely to recommend some form of treatment to allay symptoms.

Dr. Freedman:
Very interesting. So, if I have somebody who has rather frequent PVCs, start with an echo to make that structural determination?

Dr. Marchlinski:
Absolutely, that's the first step.

Dr. Freedman:
Okay. And then do we assess magnitude or frequency with an event monitor or some other cardiac monitoring?

Dr. Marchlinski:
Yes, there are 2 pieces of additional information that are important. First, there's an entity called PVC-induced cardiomyopathy. So, in some patients the PVCs occur with a sufficient frequency that they actually can cause a cardiomyopathy. We're still working out the

exact mechanism. We don't know whether it represents a variation of cardiac dyssynchrony or whether it's the disadvantaged energetics related to just the coupling of the PVCs, but in some patients a cardiomyopathy can actually develop as a result of the PVCs. So in the patient who has depressed function, who gets an echo and has depressed function, we worry about things like coronary artery disease or other fixed forms of cardiomyopathy, but we also need to recognize that in some patients frequent PVCs can cause the cardiomyopathy. So the question is: What PVC burden causes the cardiomyopathy? And as you pointed out, the Holter can provide that information with respect to the degree of burden. The rule of thumb is PVC burden less than 10,000 in 24 hours is not likely to cause or be associated with a cardiomyopathy, so there seems to be a minimum above which is critical for the potential risk of developing a cardiomyopathy. And one can think about 10,000 PVCs to represent about 1 beat out of every 10 being a premature beat, so if it's less than that, it's not likely to be associated with a cardiomyopathy. But if people have quadrigeminy or trigeminy or bigeminy where their PVC burden may be as high as 25 to 50%, then it can cause the cardiomyopathy. You need to, 1) make sure it's not present and follow these patients a little more closely for the development of the cardiomyopathy even if they don't have symptoms.

Dr. Freedman:
That is very interesting, so even if, as you just said, in the absence of symptoms, assessing the burden can have a great importance in terms of future problems with the cardiomyopathy.

Dr. Marchlinski:
And the degree of follow-up. So again, a frequent PVC or a high burden will necessitate a little bit closer follow-up, echos every 6 months initially or every year to make sure you're not in the early stages of this abnormality and the myopathy is not getting ready to develop.

Dr. Freedman:
So, if there is a substantial burden or if the PVCs are symptomatic, then we move forward with treatment?

Dr. Marchlinski:
That's correct. And there are 2 forms of treatment that needs to be considered. One is the option of pharmacologic treatment and the second is the option of ablative therapy. Let's first start with pharmacologic treatment. We usually start with a fairly safe, benign form of therapy that's beta blocker therapy, recognizing that only about 25-50% of patients will respond to beta blockers, but it's the initial form of treatment; it's relatively benign; we start with a low dose and can titrate it up based on symptom control and control of arrhythmia burden. That's the initial treatment. If patients don't respond to beta blockers, then we'll frequently try calcium channel blockers, again a low yield, probably not quite as effective as even beta blockers are in terms of depression of PVC burden but a fairly benign form of treatment. After that we then move on to other more potent antiarrhythmic agents, membrane activating drugs. There's a whole list of them. We usually consider drugs like flecainide or propafenone. As long as the cardiac function is not depressed, other drugs like sotalol can be utilized in selected patients. There's a long list of antiarrhythmic drugs. Always being careful to consider risks versus the benefits, the proarrhythmic effects of some of these antiarrhythmic drugs need to be considered. And I frequently would recommend that if we're moving on to use one of these more potent drugs, we sometimes need the expertise of the electrophysiologist who has a lot of experience obviously treating and recognizing some of the risks and side effects.

Dr. Freedman:
I can relate to that very much. As I think of those heavy-hitter drugs, I know that the potential for side effects, and particularly, as you mentioned, the proarrhythmic effects come into play. So those are not to be entered into lightly.

Dr. Marchlinski:
Yes, I agree. The second form of treatment is ablative therapy, and it's been pretty exciting in terms of the development of this form of therapy. We basically began doing this in the late 1990s, and it's evolved so it now has become standard of care and recommended therapy for many patients who remain symptomatic after a trial of beta blockers. We've now become very expert at looking at the 12-lead EKG of the ventricular ectopy and being able to pinpoint the site of origin in the heart of these arrhythmias.

Dr. Freedman:
That's amazing.

Dr. Marchlinski:
Most of them come from very predictable sites. There are only a dozen sites that are typical sites of origin, the most common of which are the outflow tract areas, the area where the blood leaves the heart. The right ventricle is the most common region and/or the left ventricle, and we can look at the pattern on the EKG and predict these sites fairly reliably.

Dr. Freedman:
And then when you do go in and ablate these areas, how successful and sustainable are the results?

Dr. Marchlinski:
It's been very exciting because we use now a radar-like system for tracking down the extra beats; especially if they're firing frequently, it's fairly easy to use a catheter-based technique that allows us to pinpoint the focus with incredible precision and then apply high frequency radio waves, radio frequency energy to eliminate the arrhythmia. The success rate now has been over 90%. It's been just growing more consistent and reliable in terms of the technique, and more importantly, the patient who experiences this acute success then goes on with 95% certainty to maintain an arrhythmia-free state. So it's a more reliable sort of guaranteed way of permanently getting rid of these arrhythmias. And I think it's been really exciting because the patient who has a PVC cardiomyopathy, it's reversible. Get rid of the PVCs and control the arrhythmia burden; you eliminate and reverse the cardiomyopathy. So you see the function improve rather dramatically over the course of 3 to 6 months.

Dr. Freedman:
That is remarkable.

Dr. Marchlinski:
It is. I must admit I still get excited when I see that echo result in follow-up and get a big smile on my face when I see the ejection fraction normalize.

Dr. Freedman:
That is great. Well, let's move on, if we may, to what is very, very common arrhythmia, atrial fibrillation, and we encounter it all the time. We can slow the ventricular rate; we anticoagulate, but then there's debate about putting somebody back into sinus rhythm. When is that appropriate, and when is that done by the electrophysiologist?

Dr. Marchlinski:
Sure. I think that, again, this is a work in progress. Back in the 1990s and beginning of 2000, the standard of care was a more conservative approach. It was based on the results of the AFFIRM trial and then the RACE trial. These were studies that randomized patients to rate versus rhythm control with pharmacology. And as it turns out, rhythm control with pharmacologic agents is rather poor. So when the comparison was made and long-term outcome was looked at, the rate control arm did basically as well as the rhythm control arm. In fact, there was less proarrhythmic effects because the patients weren't taking these sometimes toxic antiarrhythmic drugs. So the emphasis based on these studies was on conservative management. And then in the late 1990s we saw this evolution, this gradual development of catheter ablative therapy to isolate the triggers that were initiating pulmonary veins... excuse me, initiating atrial fibrillation that originated in the pulmonary vein region of the left atrium, and by creating effectively a moat around the opening of these pulmonary veins, you isolate the triggers that cause atrial fibrillation; and if that barrier remains effective, the therapy can be pretty dramatic in eliminating atrial fibrillation. So we've launched the strategies used in the development of ablative therapy to improve the techniques that can produce permanent pulmonary vein isolation, and that has produced improved results in terms of atrial fib rhythm control. So there have been a couple of systematic, randomized, prospective studies now that compared pharmacologic therapy with ablative therapy, and ablative therapy has been dramatically more effective to the tune of 70-80% long-term efficacy compared to pharmacologic management where efficacy turned out to be about 20-30% long-term. It was pretty impressive. And we were able to do that without a lot of complications. Initially, we were worried about some of the complications that could occur with the procedure, but they seemed to be minimized now by a lot of the technological advances. So as a result, now we have another choice. We have now instead of just rhythm rate control, we have rhythm control not so much with pharmacology—it's still considered in selected patients and in some patients it's still first-line therapy—but we have a lower threshold for moving towards ablative therapy because of the improved efficacy without a high complication rate.

Dr. Freedman:
That's very impressive. And the efficacy, I imagine, is maintenance of sinus rhythm. Were symptoms also looked at?

Dr. Marchlinski:
Yes. So the indication for doing the procedure in patients with a-fib are the presence of symptoms, and in selected patients the cardiac function again can get depressed—left ventricular function can get depressed—if the heart rate is poorly controlled, and in some patients the heart rate control is very difficult. So in those 2 situations, we've moved to earlier consideration of pharmacologic intervention, and in those patients a trial of drug therapy may be frequently appropriate, but we've moved with a lower threshold. In fact, the latest guidelines suggested that one gives the option of ablative therapy simultaneously with giving the option of pharmacologic management for rhythm control or rhythm maintenance in these patients.

In the studies that have looked at outcome, symptom control has been dramatic, so we've eliminated symptoms as well as, with extensive monitoring now, improved or eliminated a-fib events. So it's been, again, not perfect because we still have room for improvement, but so dramatically better than pharmacologic management. And whenever you have treatment that appears to be

effective over the intermediate term and now long term with reasonably high degree of success in the 70-80% range, we begin to get more optimistic about that form of treatment in many of our patients.

Dr. Freedman:
That's wonderful. And may I ask, are there certain people with atrial fibrillation who are not candidates? Are there age cutoffs? Do we still look at left atrial size, things of that nature?

Dr. Marchlinski:
Well again, we always risk stratify. And it is interesting, as we've increased the experience, we now recognize that there are selected patients who will have a worse outcome with ablative therapy, and those are the patients who have been in atrial fibrillation for many years. Those are the patients with an extremely dilated atria. We usually talk about atria that are bigger than 6 cm as a cutoff where then patients are not likely to respond to ablative therapy. Normal size, of course, is 4 cm diameter for the left atrium, and once it gets above 6 cm, those patients are not likely to do well. So, what is interesting is that we initially thought that patients who were elderly would have a poor prognosis with ablation, and there's been an increasing experience that shows the outcome is quite good. Now again, that has been in a selected patient population where patients first chosen for ablative therapy are elderly, tend to be the fittest of the fit. In fact, I remember one young woman who happened to be 87 years old told me that she was chopping down the tree limbs the day before she came in for a procedure. This is rather a selected group. But they did incredibly well. We now know the fact is that when we do procedures on patients after the age of 80, there will be a modestly higher, but significantly higher procedurally related complication rate. So typically, we advise patients that instead of the typical 2-3% risk of the procedure, it will be increased to 3-4% in an elderly patient population, and that's important to advise patients before they undertake the procedure.

Dr. Freedman:
If you are just tuning in, you're listening to “Medical Breakthroughs” from Penn Medicine on ReachMD. I'm your host, Dr. Lee Freedman, and I'm speaking with Dr. Francis Marchlinski, Director of Electrophysiology at the University of Pennsylvania Health System.

Dr. Marchlinski, maybe we can move on to some of the innovative techniques that you are pioneering at Penn. For instance, what is epicardial ablation and when is it used?

Dr. Marchlinski:
Epicardial ablation is a recently developed technique that is used specifically in patients who have ventricular arrhythmia. So, life-threatening arrhythmias frequently that originate from the ventricle, particularly in the setting of a nonischemic cardiomyopathy, so both right ventricular cardiomyopathies, patients with arrhythmogenic right ventricular cardiomyopathy or dysplasia, and left ventricular cardiomyopathies. It has been discovered mainly initially by pathologists that disease process frequently originates on the epicardium, and the scarring that occurs that serves as the substrate for ventricular arrhythmias sits on the outside surface of the heart rather than the inside. In coronary disease, the arrhythmia substrate is on the inside, so we target those anatomic endocardium for ablative therapy when we're trying to get rid of ventricular tachycardia in the setting of coronary disease. But in the patients with nonischemic cardiomyopathy, we know that the disease is located on the epicardium, and we needed an approach to get access to the epicardium. In the past we started considering surgical options, but that would mean open heart surgery or large incisions to gain access to the epicardium, and the technique was initially pioneered by the group from São Paulo, Brazil, Souza and colleagues. They had to deal with the disease process called Chagas disease. It's a parasitic infection that causes nonischemic cardiomyopathy and lots of ventricular arrhythmias. And they started this technique of epicardial ablation for that specific disease process. The approach that's used is to take a spinal needle, an epidural needle, and to go very cautiously and slowly under the ribcage near the subxiphoid area and very, very cautiously approach the epicardium and enter the pericardial space with that needle. Now, this is done in the absence of pericardial effusion, so there's a virtual* 18:37 space. It's like the epidural space around the spinal cord. And this is obviously complicated by the fact that the heart is moving, so there's very little leeway or forgiveness and one has to be incredibly precise. So if one is precise, one gets into that space; and then once you get into the space, with the needle you can pass the guide wire. From there you're home free because usually once a guide wire gets inside the pericardial space, you can pass sheaths and then ultimately your catheters. And once that happens, you can move the catheter around freely in the pericardial space and map the entire outside of the heart, and we could localize arrhythmias that only exist on the outside of the heart using a total percutaneous approach. It's been very incredibly exciting because we've got to apply it to a number of patients with different nonischemic cardiomyopathies, and the results have really been dramatic, game changing, because these are patients frequently who would get an implantable defibrillator and have multiple ICD shocks and didn't respond to pharmacologic treatment and now we've been able to eliminate their ventricular arrhythmias very reliably.

There are some challenges, of course. Now, the anatomy is the challenge on the outside of the heart. The inside you don't have coronary arteries. On the outside there are coronary arteries; you have to be careful not to damage any with the cauterization that we perform with the ablative therapy. The phrenic nerve also runs in the pericardium, and you need to be able to identify the location of the phrenic nerve and not injury it or move it out of the way so you can apply the energy effectively. But we've overcome a lot of the

challenges, and now it's done in selective manner, but quite routinely in patients with nonischemic cardiomyopathy. As I said, I'm so excited about the result. Probably the most exciting results are those in arrhythmogenic right ventricular cardiomyopathy. It used to be a disease that was thought to be progressive and ultimately ablative therapy wouldn't work, and indeed, ablative therapy from the inside, the endocardium, was not quite as effective as we'd like. And once we moved to the epicardium, we now see success rates in over 80% of patients with long-term complete arrhythmia free, being arrhythmia free, without any drug therapy. And this is a disease process that occurs in young patients, so you can imagine our excitement about a young patient who doesn't need to be on antiarrhythmic drugs, leading a full and active life, not having to worry about ICD shocks. That's a game changer.

Dr. Freedman:
It certainly is. And as I think about this, the idea of putting a spinal needle into a pericardium that does not have fluid in it, do you ever injure the myocardium? How delicate a technique do you need to use?

Dr. Marchlinski:
Very delicate, it has to be incredibly precise. There is some forgiveness. A minor puncture as long as you don't put bigger tubes inside the heart doesn't result in significant bleeding, but the key is to be able to be very cautious, so you don't create a laceration and get the guide wire in. Once the guide wire is in, the risk is eliminated, so that's the key.

Dr. Freedman:
Very interesting. And what's new with device therapy for arrhythmias and intracardiac defibrillators? Can they be placed subcutaneously now?

Dr. Marchlinski:
Yes, that's another advance. You know, we always struggled with the concept, especially in young patients, putting in devices that have leads larger than pacemaker leads obviously to provide effective defibrillator therapy, and there's always the risk in selected patients of lead breakage or lead infection when they're endovascular, so we are very excited about the possibility of a totally subcutaneous device system where the lead is placed only subcutaneously combined with the energy-delivering capability of the can* 22:30—that's the implantable defibrillator that's also placed subcutaneously—and you combine these 2 subcutaneous energy delivering systems and you can effectively terminate ventricular arrhythmias of all type and have something that is not endovascular, so it's all subcutaneous. It's been very effective. And the nice thing, especially in young patients, selected young patients that may have low arrhythmia risk need a device; but over the long-term when we used to implant these intervascular leads, you could anticipate that 10 or 15 years from now we would have a certain number of leads that were failing and leads that had to be extracted or small, but significant, percentage of patients who would have endovascular infection, those risks eliminated. And the reliability seems to be fairly sound, quite an extensive experience now both in Europe and around the world and the US, and people are pleased with the technology and it's a step forward.

Dr. Freedman:
It certainly sounds like it. And I'm trying to picture this. Is the device implanted just under the skin of the chest wall?

Dr. Marchlinski:
Yes, it's usually implanted in the left lateral low subaxillary area in terms of the device subcutaneously, and then the lead is placed like an L along the extending thumb, the device in that lateral pocket to the peristernal region on the left side, and the lead runs up peristernal region subcutaneously. Nothing is inside the vascular system. And it provides an effective energy-delivering system for ventricular arrhythmia termination.

Dr. Freedman:
Now in heart failure I've seen some articles about the use of biventricular pacing as a way to treat heart failure in addition to medications. Do you do any of that?

Dr. Marchlinski:
Yes. So again, it's become the mainstay of management of heart failure, especially if there are conditions that can be improved by pacing both ventricular chambers. So we see the development of what's referred to as ventricular dyssynchrony with the presence of left bundle branch block that can actually make the left ventricle squeeze in a dyssynchronous fashion decreasing its function. And the placement of a lead, the lateral border of the left ventricle towards the base of the left ventricle can provide the potential to pace simultaneously the left ventricle with the second lead placed at the right ventricular apex and improve the contractility of the heart, and that's been pretty dramatic. And we've been working to try to identify the optimum site for lead placement to improve the outcome. We're also working on considering the possibility of epicardial placement. As we development this epicardial puncture technique that becomes more and more reliable—again, this is a future development so it's not ready for primetime yet—but as you can imagine, placing leads with a lot more accessibility in that epicardial space may be the way to go. It is the future, so I don't want to get people too excited until it

goes through the appropriate vetting to make sure it's going to be effective, but I'm excited about the potential.

Dr. Freedman:
Absolutely, and I think of this as coming in toward the end of our treatment algorithm for heart failure. Is that correct? Or is it even before endstage heart failure?

Dr. Marchlinski:
So again, it's not first-line treatment, but you could imagine that, as we begin to lower the threshold for using this technology as we begin to show more and more effectiveness. So now we have patients who, for example, will need a pacemaker for a number of reasons for bradyarrhythmias, and if the pacing produces a left bundle branch block in the setting of mild dysfunction, we can anticipate in selected patients we'll move earlier in their course to treating them with a biventricular device to improve biventricular function before the dysfunction becomes really severe. So again, that's the strategy that's being developed. And in addition, lots of new pharmacologic agents coupling with this, we're working on a variety of other considerations to figure out how to get rid of PVCs, control the atrial fibrillation in patients with heart failure, being a lot more proactive and doing everything we can to inch up that ejection fraction. We are paying more attention essentially to the electrical problems that can make cardiac dysfunction worse, and I think with a great deal of success.

Dr. Freedman:
Well, that is certainly fascinating. I very much want to thank Dr. Francis Marchlinski, Director of Electrophysiology and Professor of Medicine at the Hospital of the University of Pennsylvania for being with us today and for outlining some very exciting techniques that are available to treat many cardiac conditions stemming from PVCs and atrial fibrillation all the way to congestive heart failure. Dr. Marchlinski, thank you again for being with us.

Dr. Marchlinski:
Dr. Freedman, my pleasure, thank you.

Narrator:
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