Overview of Cardiac Arrhythmias and Treatment Options

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DR. WILLIAM SAUER: Okay, thank you. My name is William Sauer. I'm the Section Chief for the Cardiac Arrhythmia Service at Brigham and Women's Hospital, and today I'll be speaking to you about an overview of cardiac arrhythmias and treatment options.

Here is a road map of what we'll be discussing. I'll specifically talk about antiarrhythmic medications and review some clinical trials related to this treatment. We'll speak about implantable cardiac devices. I'll talk about the SCD-HeFT trial from 15 years ago, and then we'll talk about catheter ablation with more recent trials like CABANA and PAUSE-SCD.

So, to introduce you to cardiac arrhythmias, what we're talking about are abnormal heart rhythms that may be too fast, that's the tachyarrhythmias, and the most common is atrial fibrillation and atrial flutter. But there's also supraventricular tachycardia, and then, of course, ventricular tachycardia and ventricular fibrillation. We also treat heart rhythms that are too slow, like sinus node dysfunction, or a heart block, or conduction system disease.

Sometimes you can have premature ventricular contractions that interfere with a pulse rate, so you can see here this is the pulse rate with a PVC interfering with that pulse rate, and it is kind of a pseudo-bradyarrhythmia. By treating the PVC with ablation or medication we're able to improve symptoms related to this type of bradycardia.

Going back to the beginning, we've come a long way. This is about 100 years ago. The Nobel Prize was given to William Einthoven for discovering the recording of cardiac electricity, and in those days you had to place your hands and a foot in saltwater baths that were then connected to electrodes that then recorded the millivolts recordings of the atrial and ventricular recordings.

Nowadays with a smartphone and a simple device we can accomplish the same thing, and in fact, you can have a watch that records your electrocardiogram by just touching the crown of the device, completing the electrical circuit from your left wrist to your right index finger.

We've also made advances with outpatient laboratory monitoring. This is Normal Holter. This is the original Holter outpatient telemetry monitor. It's strapped to his back and it records the electrocardiographic signals over 24 hours. Now we can do pulse checks with our own smartphones, or we can have very small devices that record the electrical activity as an outpatient.

So, we've come a long way, so far that electrical physiology has really taken the lead in telehealth and telemedicine, and it's not uncommon for my patients to send me an email with an electrographic tracing and a question.

Apple has performed a study looking at irregular pulse notifications, and seeing whether or not you can pick up an arrhythmia. Now, keep in mind, this is not using the ECG feature, this is just a pulse feature. If it notifies you of an irregular heart rhythm, it's possible that you have atrial fibrillation, so it's another form of screening. When we look by age, we're able to see that about 3% of the population that didn't know they had atrial fibrillation can receive this notification.

This is important, and there'll be other talks on this, but this is important to try to prevent stroke in patients. The Apple Watch actually has a very high fidelity recording. This is a patient of mine who reported this tracing on an Apple Watch, and the tracing showed supraventricular tachycardia. It was

critical for the diagnosis for an atrioventricular reciprocating tachycardia that we couldn't find on other monitoring.

So, we've really moved - the field has moved - forward with these outpatient sensors, and over the last 100 years the field has really blossomed because of improved detection of arrhythmias, as well as treatment options. Let's discuss those. So, I'm going to be talking about medical therapy, devices like pacemakers, ICDs, and then I'll round everything off with catheter ablation.

The overview of arrhythmias and treatment options begins with antiarrhythmic medications. I want to start with a trial called AFFIRM, and this was a trial that randomized patients with atrial fibrillation to two different treatment strategies: rate control with anticoagulation, or rhythm control with or without anticoagulation.

Now, this is an important point because the trial was performed more than 20 years ago, and back then when we assumed that we controlled atrial fibrillation with an antiarrhythmic medication, some physicians would stop the anticoagulation because the patient was no longer in a-fib. Based in part on the results of this trial, and I'll discuss that, we no longer do that. We recommend lifelong anticoagulation for patients even with apparent successful rhythm control with a medication.

Patients didn't have symptoms, but they did have risk factors for stroke, and the enrollment occurred between 1995 and 1999, so quite a long time ago. I want to discuss this study not just for its results, but historical context, because many physicians still look to this trial inappropriately, in my opinion, about how to manage atrial fibrillation, when really we should be looking at a more recent trial called EAST-AF, and I'll discuss that in a moment.

So, looking at the AFFIRM trial, these were relatively older patients. Some had abnormal left ventricular ejection fraction. Most had hypertension. The rate control arm included digoxin, beta blockers, and calcium channel blockers. The rhythm control arm was mostly amiodarone and Sotalol. There were some other agents like propafenone and flecainide, however, most were amio and Sotalol.

The primary endpoint was all cause mortality, and you can see here that the rhythm control arm actually had a higher mortality compared to the rate control arm. This didn't achieve statistical significance, but this was a little bit of a surprising finding, and a little bit of a change in practice came about because of this finding.

Most people who presented with atrial fibrillation, even if they didn't have symptoms, were pursuing a rhythm control strategy. But based on this trial we then decided to move towards a rate control strategy, especially in those patients without symptoms. When we looked at death, disabling stroke, major bleed, cardiac arrest, or encephalopathy, there really was no difference. The whole idea here was maybe with rhythm control we could prevent strokes, but that didn't occur.

One thing we need to point out is that our rhythm control strategies are not very effective, in fact, only about 60% - oh, I need to go back, I'm sorry. I meant to say before this slide that our rhythm control strategies were not very effective. This slide I wanted to show that the use of anticoagulation was less in the rhythm control arm than it was in the rate control arm. I think that this alone could explain the increase in mortality.

So, the limitations of this trial are, first, it's really historical and I don't think it's applicable to modern practice. We didn't even have catheter ablation back then. Patients with symptoms weren't enrolled, so if you have a symptomatic patient I don't think that this trial applies to them. The mean follow-up wasn't very long-term. It didn't evaluate low-risk patients, and it really didn't evaluate patients with heart failure. I think there is a case for rhythm control even despite all of the AFFIRM findings.

Rhythm control, and I referenced this a little bit, rhythm control is only successful at sinus rhythm maintenance 60% of the time. That's really not a true comparison of strategies because if we're only successful in one strategy 60% of the time, any effect on that strategy is going to be diluted in any intention-to-treat analysis. In those patients where we did see effective rhythm control there was an apparent survival benefit, but of course, there's the healthy responder bias that can be introduced with that, so we really can't make any decisions based on that result.

Then the apparent increase with stroke and mortality in AFFIRM is entirely explained by the lack of anticoagulation in that group. So, I think that rate control is an acceptable strategy for treatment of asymptomatic atrial fibrillation based on this trial, but we should really consider rhythm control if we think that there is a good chance for long-term maintenance. Anticoagulation should be considered, and patients with any symptoms attributed to a-fib really should be treated for a quality-of-life concern rather than for mortality.

Let's fast forward to the EAST-AF trial 20 years later. EAST-AF is a trial that looked at about 3,000 patients, 2,800, and we had patients who had mild cognitive impairment, a median age of 70, so slightly older. They were presented with a first episode or a recent episode of atrial fibrillation. In order to be enrolled you had to have atrial fibrillation in the past year, so the point of this trial was trying to see whether or not intervening with a rhythm control strategy, early rhythm control strategy, had any effect on outcomes.

Some patients were asymptomatic. Most patients were in sinus rhythm upon enrollment. This was a trial of early intervention, so about 36 days had passed before their first AF diagnosis. The CHA2D-VASc score was 3.4, relatively high, indicating anticoagulation, a requirement for anticoagulation, and about a third had heart failure. Most were anticoagulated, so you can see what a difference that the 20 years made from AFFIRM. Most were on beta blockade.

Now, I want to just focus a little bit on this stratum here, because when you're prescribed rhythm control there's a lot of different ways to approach that, and in this light blue bar here is ablation. So, about 20% of the rhythm control arm were offered ablation by the second year in the trial. Most were treated by antiarrhythmic drugs, and about 35% opted not to be on any medication or have an ablation; that's a big change from the 5%. This likely represents the asymptomatic group that decided not to take a drug or have an ablation.

Here are the results of the trial. Enrollment was stopped early after a median follow-up of five years. The rhythm control arm had a significant reduction in the primary outcome, and that achieved statistical significance with a hazard ratio of 0.79, p-value of less than 0.01. That was for a composite endpoint looking at mortality and hospitalization for heart failure and cardioembolic, cardiovascular events.

I want to focus on the primary outcome here where we had a 3.9% first primary outcome; that was the main result, that was the Kaplan-Meier curve I just showed you earlier. But what I want to focus on is

that most of this result was really from the hospitalization of heart failure, death from cardiovascular causes, and stroke. Of note, they also looked at secondary outcomes with mental status score and quality of life, and they also looked at proportion achieving sinus rhythm, and so that was an 82% success rate versus 60% having sinus rhythm at the end of the study.

So, AFFIRM did not show superiority for rhythm control, but there was inconsistent anticoagulation, and there was a low efficacy of antiarrhythmic medications. EAST-AF is kind of a correction of that because we had ablation. We had improved anticoagulation adherence, and we had improved medical therapy for non-arrhythmic therapy, and that is use of beta blockers, ACE inhibitors, and so forth. So, I think EAST-AF kind of corrects AFFIRM and allows us to pursue a rhythm control strategy and consider it even for patients who are asymptomatic with atrial fibrillation.

Now I'll talk about implanted devices. We've come a long with the treatment of implanted devices, even in something as simple as pacing. Now we have options for treatment of bradyarrhythmias with a pacemaker using a standard dual-chamber pacemaker. A pacemaker is an electronic device that's implanted under the skin and is attached to two insulated wires, one going to the top chamber, one going to the bottom chamber, atrium and ventricle. And this was sort of our standard approach for a little while.

Biventricular pacers were used to treat patients who had heart failure, or who were dependent upon pacing and were sensitive to the desynchrony caused by right ventricular pacing. More recently we have conduction system pacing where we implant the ventricular lead and stimulate the His bundle, or the left bundle, or the right bundle branch block. Excuse me. We stimulate the His bundle or the left bundle or the right bundle, and that's conduction system pacing. It recruits the natural conduction system and allows for a more efficient pumping function of the heart.

Looking throughout history, this was the first pacemaker that was externalized, and then here is our internal pacemakers that was placed on the epicardium by a cardiac surgeon, and as time has gone by you can see that the generators have changed shape and become smaller, so small that now we can implant a leadless pacemaker. This is a pellet-like device that we place with a catheter into the heart.

So, here is a superior approach where we place this pellet-type pacemaker or leadless pacemaker, and we leave it in the heart. It's not attached to any wires. It stimulates the heart, and we're able to successfully treat heart block in this way.

Cardiac resynchronization therapy was a major advance for the field. We're able to stimulate the heart from the left ventricle using an epicardial coronary vein. We come into the right atrium, cannulate the coronary sinus, and place a pacing lead in a coronary vein overlying the lateral wall of the left ventricle, and when we do that the heart is synchronized again.

When the heart has stimulation from just say the right ventricular pacing lead there is this desynchrony where the septum comes in a little bit right before the lateral wall, and so that desynchrony, sometimes patients are very sensitive to that and they have a reduced ejection fraction. I sometimes explain it like rowing a boat one oar at a time, however, if you rowed the boat with both oars at the same time, or synchronized the heart, the pumping function is much more efficient and we can treat heart failure successfully using this technique.

I mentioned His bundle and left bundle area pacing, and what that is is a way to place the pacemaker in the septum to stimulate the conduction system, and we can reverse bundle branch block. So, here's a patient who has a typical left bundle branch block pattern, and when we pace the His-Purkinje system we're able to narrow that complex, and in a way it's a way of naturally resynchronizing the heart. A study that looked at this was the His-SYNC trial which showed that it worked just as well as cardiac resynchronization therapy using that biventricular pacing method.

Another way of doing this is actually the best of both worlds. We can pace the conduction system and the left ventricle. Here is a left bundle area pacer, and a left bundle area pacing lead, and here is a lateral wall coronary sinus left ventricular lead. In this recent study called LOT-CRT you can see that when we have the BiV-pace complex and the left bundle pace complex, pacing at the same time, we can narrow the QRS complex and get improved cardiac synchronization. This study showed that there was QRS narrowing with this BiV-CRT method, and they had better echocardiographic outcomes.

Another treatment option for ventricular arrhythmias is the defibrillator, and just like the pacemaker has had remarkable progress, the defibrillator has also had remarkable progress, where we now have a very small defibrillator that fits up in the upper chest and is almost pacemaker-like in its size and its ability to use a transvenous system to get adequate defibrillation thresholds.

Here is a chest X-ray of a single-chamber defibrillator that's placed just like the pacemaker is under the skin, attached to insulated lead. This time it has a shocking coil, and just like a portable paramedic that's out there to rescue a patient in cardiac arrest, it stands by and it waits for an abnormal heart rhythm where it detects it and then terminates it with the delivery of a shock using this shocking coil and the canister itself.

The main trial that popularized defibrillator therapy for primary prevention of sudden death was the SCD-HeFT trial that was published in 2005. This trial randomized patients to a single-lead defibrillator that was programmed to just shock if a very fast ventricular arrhythmia was detected, and it randomized patients who had a reduced ejection fraction and heart failure compared to placebo, randomized into a defibrillator placebo or amiodarone, and the thought was that by finding these patients who may be at risk for sudden death before an event happens, we may be able to save the lives of some of these patients.

Sure enough, over a five-year period the patients who received a defibrillator had a much lower event rate. Of note, amiodarone was similar to placebo in terms of the mortality benefit, and so there really is no role for amiodarone to prevent sudden death in patients who were at risk for sudden death.

Looking through the subgroup analysis, there really was nobody who necessarily stood out and benefitted. The patients who had the most severe heart failure, though, appeared to have a little bit more benefit that was just measured with the six-minute walk test.

So, based on this trial and some others that were in support of it, patients who have a reduced ejection fraction who are on a good background drug therapy for heart failure, the defibrillator is indicated for those patients. Amiodarone, we shouldn't use that for prevention of sudden death.

The defibrillator I mentioned was transvenous, and that's what SCD-HeFT looked at, but since then we - now I showed you this X-ray before - we now have an entirely extravascular system where we can detect

and terminate ventricular arrhythmias with a subcutaneous system that doesn't invade the vascular space. This is a very attractive option for some patients who don't require pacing.

Now we'll talk about catheter ablation, and this is an area that has been growing, and an area that offers promise for patients with previously untreatable arrhythmias. When we look at catheter ablation volume over the last 10 years, it really has been growing, and the reason for that growth is because of atrial fibrillation. Atrial fibrillation was previously managed only by medications.

However, it has really taken over in terms of our volume, and a lot of academies and a lot of hospitals have noticed that their volumes have increased because of patients with a-fib requiring ablation. Of course, we still treat VT, atrial flutter, and SVT with catheter ablation, but we think the growth of catheter ablation is really in a-fib.

Why is that? Well, the antiarrhythmic drugs have really not impressed us, and if we look at amiodarone, that's our lowest effective antiarrhythmic drug, it's riddled with side effects, and you can start looking at the fine print of amiodarone.

You can have optic neuritis, goes down to neurologic, photosensitivity, thyroid abnormalities is common in patients on long-term amiodarone. You keep on going and it keeps on talking about up to a third of patients have gastrointestinal side effects, and the really most important thing is that the injury to the liver, lung, and thyroid, as well as the possibility of pro-arrhythmia, really limits the utility of amiodarone tablets.

Catheter ablation, on the other hand, has had remarkable progress with improved technology leading to improved outcomes. We've developed electroanatomical mapping, intracardiac echocardiography, we have catheters that can detect contact and sensing of force, we have automated signal processing, and now we have a variety of energy sources that we can pick from to perform the procedures safely.

Let's go over an atrial fibrillation ablation. This is the principle of this procedure. This is a patient of mine who had sinus rhythm, and you can see this deformation in the ST segment right here. That's an extra heartbeat that was blocked, that same exact extra heartbeat that initiates atrial fibrillation. Michel Hassagara and some researchers from Bordeaux recognized that, well, if we could just stop this extra heartbeat, that triggering event of a-fib, maybe we can prevent a-fib altogether.

That's what this study showed in 1998 where they identified where the triggers were coming from. It turns out most of them, almost all of them, came from the pulmonary veins, and they targeted those triggers. They were able to successfully terminate and treat a-fib by going after these triggers. When this paper came out it was a real advance in understanding atrial fibrillation, and understanding the role of catheter ablation for that.

Now, it's kind of an orchestra that comes together where we have a lot of equipment, a lot of personnel to take care of this patient. We start by coming into the femoral vein using ultrasound. We're able to place catheters in the femoral vein, move them up to the heart. We then have an ultrasound catheter, a mapping catheter, and we perform a transseptal puncture. There's a thin membrane that is dividing the right and left atrium, and we're able to see that tenting. We're able to see it coming across and we can safely get into the left atrium. We need to get there to find those triggers coming from the pulmonary veins.

Once we're over we can use our mapping catheters to identify those triggers in the pulmonary veins, and just like I showed you on the surface with that extra heartbeat, we can get very high-resolution catheters that identify the electrical signals from within the pulmonary veins, and our job is then to isolate those signals. So, here's our sinus rhythm, here's the intracardiac electrocardiographic recordings, and then here's where atrial fibrillation starts.

The pulmonary vein here starts firing first and initiates the atrial fibrillation, so this is just what that New England Journal paper from '98 by Michel Hassagara and his colleagues, it's exactly what they were showing. We're able to then isolate that pulmonary vein using electroanatomical mapping. Electroanatomical mapping, the way to think about this is it's almost like a mini-GPS system that is placed underneath the patient, and we're able to see the catheter moving in three-dimensional space. We can reconstruct the chamber that we're working in without the use of fluoroscopy.

That mapping system allows us to go around and almost like spot-welding build a perimeter fence around the pulmonary vein. We go one by one, ablation lesions going around the pulmonary veins, and we have this encirclement that then contains the electricity within the pulmonary veins, and this is what it looks like when we're done.

Now after ablation you can see that we have sinus rhythm, and that pulmonary vein is in atrial fibrillation but it's completely isolated from the rest of the heart, and so that's how we're able to maintain sinus rhythm and effectively treat atrial fibrillation with this procedure. I mentioned alternate energy sources. That was a spot-welding using radiofrequency ablation; electrocautery uses the same technology.

But we can also freeze the pulmonary vein. So, the vein is a tube that enters the chamber, and right at that junction where the left atrium meets the pulmonary vein, if we place a balloon in there and freeze that junction we can isolate the pulmonary vein using this strategy. More recently, pulsed field ablation and electroporation has been developed, and that's because it appears that myocytes are very sensitive to that pulsed field electroporation. We know about electroporation because scientists use it to introduce gene therapy or small molecules in their attempts to treat cancer, for example.

But if you give enough of that pulsed field ablation you can render the tissue necrotic and make it irreversible so that it no longer has any electrical properties. Same concept. So, here's that pulmonary vein that's firing, or it has electrical conduction within it. After the pulsed field ablation there's no electrical signal, so we've effectively isolated those pulmonary veins, and we're able to see that with repeat mapping and with imaging.

So, how well does ablation work? Well, the best study that looked at this was the CABANA trial, and this randomized 2,204 subjects to either getting an ablation or a drug. One thing I want to point out with this randomization is that there were a fair amount that decided to cross over and become ablated. In fact, about a third of the drug arm crossed over to the ablation arm.

Now, that wreaks havoc on any kind of intention-to-treat analysis, but it does go to show you that patients want another treatment option besides drugs. So, unfortunately this clouded some of the analyses, because about a third were coming over to the ablation arm.

But when we looked at the primary endpoint for ablation, drugs did worse than ablation, and that achieved statistical significance. When we look at how well ablation works versus drugs, ablation did okay. At about a year there was about a 70% or so success rate. I think we've gotten a lot better than

this. This study enrolled people about 10 years ago. Now with newer techniques and newer technology we're achieving around an 85% success rate at about 12 months, and that's generally what I quote my patients for the success rate of catheter ablation.

Now, if you have long-standing persistent atrial fibrillation, that success rate is a little bit lower. Why isn't it 100%? It's not 100% because that perimeter fence that I talked about, all you need is one gap in that perimeter fence and it's like you never did the ablation, so some patients do require a touch-up procedure to seal that perimeter fence again.

Some of our technology that we have, I talked about electroanatomical mapping, and we can see the reconstructed heart, as I have described. I also talked about echocardiography, but it does more than just ensure the safety for catheter ablation. This is a patient with atrial flutter and we're able to see the catheter on the tissue that we're targeting, and we're able to target difficult structures using intracardiac echocardiography.

In this example for treatment of atrial flutter using an electroanatomical mapping system, you can see here when we are ablating we're creating a line of block, it then terminates the tachycardia. The patient is then in sinus rhythm. We're very successful at treating atrial flutter with catheter ablation.

How about ventricular tachycardia? Well, a recent study showed that we can also successfully ablate ventricular tachycardia. This was a randomized study where you could receive a defibrillator plus ablation versus just a defibrillator alone. Keep in mind, back when we were talking about SCD-HeFT you get a defibrillator versus a medication, and it was proven that defibrillators saved lives, and so now the standard of care for this study which was recently presented at a scientific meeting, the standard of care is everyone gets a defibrillator, but half are randomized to ablation.

In those patients who underwent catheter ablation, we were able to use that same electroanatomical mapping and different techniques to safely treat the ventricular tachycardia. The outcomes showed that those patients who received ablation had improved freedom from the composite endpoint. About 70% or so did well with ablation. So, it's something to consider when someone presents with a ventricular arrhythmia or requires a defibrillator, catheter ablation to prevent shocks, and ventricular tachycardia should be considered.

So, I talked a little bit about antiarrhythmic medications, implantable devices, and catheter ablation. It's now time to summarize. Cardiac arrhythmias are increasingly being recognized by patients, and so we're seeing a lot of patients self-referring themselves, or talking to their physician asking to speak to a specialist. The treatment options that we offer, drugs, devices, and ablation, continue to evolve. Catheter ablation is superior to medications for controlling arrhythmias.

Thank you very much for your attention. I want to send a thank you to all the members of the Brigham and Women's Hospital Cardiac Arrhythmia Service, and I hope you enjoyed this presentation.