SUDEP & The Heart
A Multi-System Approach to Understanding Electrical Disturbances
CURE Epilepsy Webinar
(Transcript)

Dr. Laura Lubbers: 00:00 Welcome, everyone to today's webinar. I'm Laura Lubbers and I'm the Chief Scientific Officer of CURE Epilepsy. And I want to thank you for joining us today. Yesterday, as a community, we recognized SUDEP Action Day, a day to raise awareness of SUDEP, or sudden unexpected death in epilepsy and epilepsy deaths worldwide.

Dr. Laura Lubbers: 00:21 Today's webinar, we'll discuss this topic in greater detail, and is entitled SUDEP and The Heart: a Multi-System Approach to Understanding Electrical Disturbances. Last October, we learned that there's a strong evidence of the association between breathing problems and SUDEP. However, there are equally strong data for cardiac abnormalities, particularly cardiac arrhythmias, or irregular heartbeat, playing a role in SUDEP.

Dr. Laura Lubbers: 00:48 In fact, studies have found mutations in genes associated with cardiac arrhythmias in 15% of SUDEP cases. This webinar is a part of CURE Epilepsy's 2021 Leaders in Research Webinar Series, where we highlight some of the critical research that's being done on epilepsy. Today's webinar, like all of our webinars, is being recorded for later viewing on the CURE Epilepsy website. You can also download transcripts of all of our webinars for reading.

Dr. Laura Lubbers: 01:18 For over 20 years, CURE Epilepsy has raised millions of dollars to fund epilepsy research that supports our mission, which is to find a cure for epilepsy by promoting and funding patient-focused research. CURE Epilepsy provides grants that support novel research projects, and that advance the search for cures and more effective treatments.

Dr. Laura Lubbers: 01:39 Today's webinar will help viewers learn how inherited, neuronal, or cardiac diseases may lead to electrical disturbances in both the brain and heart, and how altered cardiac function may lead to SUDEP, and why it's critical for the epilepsy community to take a holistic approach to fully understand biological changes that ultimately caused SUDEP.

Dr. Laura Lubbers: 02:03 This webinar is being presented by Dr. David Auerbach, an Assistant Professor of Pharmacology at SUNY Upstate Medical University in New York. Dr. Auerbach leads a translational research program, and through interactions with the families of patients with severe genetic diseases, he developed the passion and determination to advance the understanding of electrical diseases in both the brain and heart.

Dr. Laura Lubbers: 02:26 He integrates cellular, animal, and clinical recordings to investigate the prevalence, risk factors, and mechanisms for dual neurocardiac electrical disturbances, and ultimately, sudden death. Before Dr. Auerbach begins, I want to encourage everyone to ask questions. You may submit the questions any time during the presentation, by typing them into the Q&A tab located on your Zoom panel, and then click send.

Dr. Laura Lubbers: 02:51 And I know that there's a question or two that's already been submitted in advance. We'll do our best to get to as many questions as we can. We do want this webinar to be as interactive and informative as possible. However, to respect everyone's privacy, we ask that you make your questions general and not specific to a loved one's epilepsy. So with that, I'd like to turn it over to Dr. Auerbach.

Dr. David Auerbach: 03:15 Thank you very much. Thank you for the intro. And it's a pleasure to speak today, particularly surrounding SUDEP Action Day there. And as Dr. Lubbers said, the title of my talk is SUDEP and The Heart. But in my opinion, we need to really take a multi-system approach to understanding electrical disturbances about the brain and the heart, and the contribution of the respiratory system and dysfunction in this unfortunate cascade here.

Dr. David Auerbach: 03:47 So SUDEP, while under reported, under represented, is a leading cause of death in epilepsy. Patients with epilepsy, unfortunately, are at a 24-fold higher risk of sudden death. And, as the name implies, we don't understand the mechanisms for SUDEP. And SUDEP stands for sudden, unexpected, non-traumatic, non-drowning death in an individual with epilepsy, witnessed or unwitnessed, in which the postmortem examination does not reveal an anatomical or toxicological cause for the death.

Dr. David Auerbach: 04:25 Sounds like a mouthful. But basically, it's the unfortunate situation where someone passed away. We don't know what were the conditions surrounding it there. And at an epidemiological level, 7.5 to 17% of all deaths in epilepsy are due to SUDEP. And in the general epilepsy population, about one in 1,000 patients with epilepsy will die each year. And if we restrict that to some of the more severe intractable forms of epilepsy, it gets all the way up to 6.7 per year.

Dr. David Auerbach: 05:04 So we understand that there's too many SUDEP cases occurring. And we need to develop ways to predict who may be at a high risk of sudden death. And presently, some of the clinical risk factors include both non-modifiable ones, such as unclear treatment history, convulsive seizures, high seizure frequency, and long duration of epilepsy. But importantly, there's also numerous modifiable risk factors.

Dr. David Auerbach: 05:40 And this includes your sleep position, nocturnal monitoring, drug compliance, and alcohol use here. So there was recently a study that came out. Look a little deeper into this. So if we look in the lower right corner here, these are people without a history of generalized tonic-clonic seizures, and that they share a bedroom with someone. And we're going to compare the risk in them to others.

Dr. David Auerbach: 06:10 And if you have a history of GTCS, the odds ratio jumps all the way up to 18.65. While if you don't have a history of GTCS, but you don't share a bedroom, it jumps up to 3.31. And the most concerning, of course, is patients with a history of GTCSs and do not have nocturnal monitoring are at a 67-fold increased risk of SUDEP.

Dr. David Auerbach: 06:41 And this really hit home to me, because for so long, the field was saying that, and here's a quote from a paper that said, "It was not that long ago that some believed that there was little point in discussing SUDEP with patients. Why cause anxiety if the risk cannot be influenced?" And this data here really emphasizes that this was incorrect. There are lifestyle decisions and modifications that may influence your risk of SUDEP.

Dr. David Auerbach: 07:13 So those are all risk factors, but they don't explain why. What is the mechanism for SUDEP? So several of the proposed mechanisms include, in the brain, cerebral electrical shutdown, cerebral hypoperfusion, a lack of blood flow to the brain during this. Next, respiratory disturbances. As I understand, there was a more lengthy presentation on respiratory dysfunction surrounding SUDEP last year.

Dr. David Auerbach: 07:46 Additionally, sleep position and failed arousal, the autonomic nervous system, which provides a direct neuro connection between the brain and the heart, and the topic for today's discussion, cardiac arrhythmias. Importantly, I've been at too many meetings where people are saying SUDEP is due to respiratory disturbances, and then someone gets up and says

it's due to cardiac disturbances. Well, I'm going to be focusing on the cardiac abnormalities today.

Dr. David Auerbach: 08:15 I really think it's this very unfortunate cascade of multi-system changes that ultimately lead to SUDEP. There is not one mechanism for SUDEP. We're going to focus on the heart today. But as you can see, my research program integrates in respiratory recordings and autonomic nervous system function as well. So to provide a little more clinical information about the prevalence of cardiac abnormalities in epilepsy and surrounding seizures, oftentimes surrounding a seizure, there's a large increase in the heart rate.

Dr. David Auerbach: 08:52 And 13% of patients develop bradycardia, very slow heart rates, even asystole stop alterations in the spread of this electrical wave throughout the heart. And this is especially seen in a lot of SUDEP cases. Also, the ECG serves as a measure of electrical activity in the heart. Patients with epilepsy have a higher prevalence and a higher risk of ECG abnormalities, particularly patients with intractable forms of epilepsy surrounding seizures. And of course, a very high prevalence in SUDEP cases.

Dr. David Auerbach: 09:33 So we oftentimes think of how that electrical wave is traveling through the heart to activate the heart, but that electrical activity also has to return back to rest. So ECG measures of cardiac re-polarization, returning back down to rest are often altered, or there's dysfunction in epilepsy patients. And if you can think of it like this, a snake moving along, if that snake is too long, the head of the next snake moving along could bite the tail of the previous one.

Dr. David Auerbach: 10:04 So you don't want a prolongation of re-polarization in the heart. Because then that next wave will bite the tail of the previous one, which serves as a mechanism for arrhythmias. Additionally, as I was mentioning, there's many re-polarization abnormalities. In this report here of SUDEP cases, almost half of the seizures in these SUDEP cases included Qt prolongation. And 10% of these actually reached pathological levels. So there's definitely some level of altered cardiac activity surrounding SUDEP.

Dr. David Auerbach: 10:45 Altered cardiac electrical activity provides a substrate for the initiation of these lethal arrhythmias. And is a 2.8-fold higher risk of arrhythmias in people with epilepsy, and it jumps all the way up to 5.8-fold in symptomatic epilepsies. Also, as you've seen this stat many times, 1% of the population has epilepsy.

But really concerning here is, they make up 4.4% of all sudden cardiac deaths in the general population. So there's a much higher risk of sudden cardiac death in the epilepsy population.

Dr. David Auerbach: 11:24 And also, importantly, a portion of the greater than 340,000 SUDEP cases per year, are likely due to arrhythmias. Importantly, it's not the only one, but it definitely makes up a portion of them. And there are many cases that were captured of near SUDEP, that were due to ventricular fibrillation, this chaotic electrical activity in the heart. A couple of years ago, I got contacted by this pediatric cardiologist.

Dr. David Auerbach: 11:54 He said to me, "I've got a child with this really severe genetic form of epilepsy. I understand you researched in the past. What do we do with this child here?" And I said, "First of all, I'm not a clinician. But this is what some of my research showed." And ultimately, what we found in this child here is that he had such severe mutations in many of his sodium channels, that led to not only electrical disturbances in his brain, but also lethal cardiac arrhythmias.

Dr. David Auerbach: 12:24 And unfortunately, these were missed initially. Everyone was thinking they were just seizures that he was having. And he actually was having many lethal cardiac arrhythmias that fortunately, were captured and then the child was defibrillator there. And now, he has an implantable cardiac defibrillator in him. So also, let's focus now in on some of the severe genetic forms of epilepsy.

Dr. David Auerbach: 12:50 Oftentimes, we look at this genetic ion channel mutation, leads to electrical disturbances in the brain in the form of seizures. Or there's other ones that we associate with an increased risk of arrhythmias. But one of the hallmarks of my research program is this ion channel mutation can lead to electrical disturbances in both the brain and the heart there. And this goes in line with some of the work of the group in Australia, Ingrid Scheffer there, where they did exome sequencing of over 61 SUDEP cases.

Dr. David Auerbach: 13:28 And amazingly, 15% of these SUDEP cases included variants in genes that are associated with cardiac arrhythmias, and 7% of them were due to a classically studied cardiac disease called long QT syndrome, especially long QT2, which is due to a mutation in this gene, KCNH2. I highlight this one because I'm going to present them in some of my research of this in a couple

of slides. Additionally, there's numerous case reports of seizures in patients with classically studied cardiac diseases, as listed here.

Dr. David Auerbach: 14:09 And also, classically studied neuronal diseases, like your Dravet syndrome. Yes, SCN8A diseases. And these potassium channel diseases, all of these have been numerous reports of altered cardiac electrical activity. So, long QT syndrome. Presenting some of my research on that over the next couple of slides, let's discuss, what is long QT syndrome? So, long QT syndrome is due to mutations that alter the balance between depolarizing and re-polarizing currents in the heart.

Dr. David Auerbach: 14:48 So here are the ion channels that make up the cardiac electrical activation recovery process. So for example, if we have an increase in this sodium current, or a decrease in these two potassium currents here, it alters this balance between depolarize and re-polarizing currents. And in simple terms, it leads to badness, in the form of prolonged electrical activation recovery period. And if it becomes so prolonged, it can also lead to re-excitation coming off the actual potential plateau.

Dr. David Auerbach: 15:23 And if a region of the heart fires at the wrong time, this can serve as a trigger for lethal arrhythmias. So I have studied long QT syndrome. I was very interested in that. But I had some results that suggested that we need to look outside the classic organ of study. So I was a basic science trained, and I wanted to ask, do patients with long QT syndrome have an increased risk of seizures? So while I was at the University of Rochester, there was a large registry of over 22,000 people that were with Long QT syndrome, and importantly, their family members who may not have the mutation.

Dr. David Auerbach: 16:12 So we compared people who were genotype positive, versus their family members who do not have the long QT mutation. And as you can see, there's a three-fold higher prevalence of a history of seizures in people who had a long QT mutation. There's numerous different types of long QT syndrome. And as I mentioned earlier, I'm going to focus on long QT2, which had the highest prevalence of seizures.

Dr. David Auerbach: 16:40 And as people are not your mice in your nice, regulated facility, there's many different comorbidities: age, sex, different medications they've been on. So we did more advanced analysis, and we still saw that patients with long QT2 were at a

higher risk of a history of seizures, compared to the long QT negative people. Also, I wasn't the only one who showed this here. The group of Michael Ackerman and Greg et al. at the Mayo Clinic, have shown that 11% of patients with long QT syndrome had a history of seizures.

Dr. David Auerbach: 17:24 And then even when they went and did EEG evaluation on these people, 15% of patients with the EEG evaluation exhibited epileptiform discharges. And here's a third example here, where they looked at abnormal EEG findings, as well as actual epileptogenic activity in controls, excuse me, versus people who had long QT mutations. And you can see a higher prevalence of EEG abnormalities in people with this classically study cardiac disease, further emphasizing, we need to look outside the classic organs of study.

Dr. David Auerbach: 18:03 So, as I mentioned earlier, I'm a basic science-trained electrophysiologist here. So I was excited about those results. We said people with long QT syndrome also have seizures. But the big question of, why are we seeing this here? Why are these people at increased risk of seizures? So the first explanation is, this is all misdiagnosis, Dave. You're missing it here.

Dr. David Auerbach: 18:28 And while I can't rule out that I was completely wrong, we need to recognize here that patients who were taking beta blockers, which are the main line of therapy for long QT syndrome, while it reduced the risk of arrhythmias, it had no effect upon the risk of seizures. There was a different age of onset of seizures or arrhythmias.

Dr. David Auerbach: 18:48 And even when we limited our dataset to people who had seizures and epilepsy, and were actively taking anti-seizure medications, all these results held true. The next one is the same mutant channel that's screwing up electrical function in the heart. It's screwing up electrical function in the brain, too. And as you can see here, if you look at the expression patterns in numerous organs of the body, of course, it's expressed in the heart.

Dr. David Auerbach: 19:16 But it's also expressed, as you see in yellow here, numerous different brain regions. So this shouldn't be surprising. A lot of people are surprised when they first see it. But interestingly, this gene was initially cloned from a human brain cDNA library. And drosophilla, when they were in a jar and they had a

mutation, and someone put ether in it to put that fly to sleep, it did what they termed the ether-a-go-go dance.

Dr. David Auerbach: 19:49 And what it was, was they thought it was these seizures, because of these flies having this mutation. Additionally, if you give a drug to block this potassium channel, it leads to neuronal hyperexcitability in the brain. For the sake of time, I'm not going to go over all these results here, but basically you took less of a stimulus to become activated, and they had burst activity there. Next, in my lab here, I wanted to confirm some of these results in rabbits, because I wanted to generate a rabbit model of long QT syndrome.

Dr. David Auerbach: 20:30 Many people would say, "Why don't you just do a mouse? It's much easier. It's much cheaper." Mice, their heart rate and their cardiac electrical activation recovery process is nothing like humans, while rabbits are a better modeler. So as you can see here, we took tissue from numerous different areas of the heart. And of course, we do see this gene is expressed. But interestingly, in blue here, we see numerous brain regions. And that gene is also expressed in the brain, too.

Dr. David Auerbach: 21:00 You can say, "Okay, that's great. That's at the mRNA level." We also saw it at the protein level. Here's in the brainstem. We do see this protein is also expressed in the brainstem and numerous other areas of the cortex and cerebellum as well. So at that point, I said, "I need to generate an animal model to really understand these neurocardiac electrical abnormalities." So went back to the clinical database and said, "Where are the mutations that are conferring the highest risk of seizures?"

Dr. David Auerbach: 21:35 And those were mutations in this poor domain right here. So using CRISPR technology, we knocked in a mutation in the endogenous rabbit gene. We didn't put this gene on top of that normal one. We went into the DNA code of this rabbit and altered it there. And these are different mutations we made. For the sake of time, I'm going to skip over. But basically, some of them expressed the mutant. Other ones, when that mutation is present, it does not make the gene at all. So this animal has half the number of those channels then.

Dr. David Auerbach: 22:13 So now, let's see what happens in the rabbit there. So what I do is, as I emphasized earlier, I do multi-system type recordings. We do video, EEG, ECG, and respiratory recordings from these rabbits. And they're conscious during this. So I put my ECG

electrodes on them, I put the EEG electrodes on, and we hook them up. And we can do multiple animals simultaneously here. And here's an example where we're seeing EGs and ECGs from these rabbits here.

Dr. David Auerbach: 22:45 If I zoom in on this rabbit right here, we can see really a high quality signal. Those of you who see this here, note, basically, the rabbit was nice and comfortable and had nice little sleep spindles there. He was happy in the restrainer that day. Also, we're doing respiratory recordings as well, and monitoring their oxygen saturation. So we can really understand the multi-system cascade that surrounds seizures and sudden death there.

Dr. David Auerbach: 23:16 So, first off, do these rabbits have long QT syndrome? They better have this prolonged electrical activation recovery process, or I didn't make a model of long QT syndrome. So, if we measure from the beginning of electrical activation of ventricles, to the end, re-polarization of this QT interval at both pre pubescent and adult rabbits, we see that it is prolonged. Thank goodness. That was a big relief that I actually generated a model of long QT syndrome.

Dr. David Auerbach: 23:49 Also, looking a little deeper at some of the other ECG findings, we do see that they did have prolongation of this JT interval as well. Third, now, let's look at the brain here. Does this mutation confer an increased risk of seizures? So what we did is we gave a chemical, a drug, as a proconvulsant, to test what was the minimum threshold for initiation of seizures in these rabbits here? Are there differences in a rabbit with the mutation, versus its litter mate wild type control?

Dr. David Auerbach: 24:32 And what we do is we gave incremental doses. And what we do is we would give one milligram per kilogram and then wait 10 minutes, see what happens. Give two, wait 10 minutes and so on, and see what was the first dose that we did see encephalopathy, finds epileptiform discharges and motor seizures. And as you can see here, the minimum dose or the minimum threshold for these epileptiform discharges and motor seizures, was lower in the mutant rabbits versus the wild type, suggesting a decreased threshold for seizures.

Dr. David Auerbach: 25:14 Also, this, showing similar results here for the motor seizures. As you can see, as we move to the right to higher and higher doses, the freedom from a motor seizure, once we hit four

milligram per kilogram, somebody mutants started to have seizures. While in wild types, this curve is right shifted. It took more for them to develop a seizure. Also, while if we look leading up to the first convulsive seizure here, the wild types didn't have any seizures in an awesome bump.

Dr. David Auerbach: 25:51 Once we hit a certain threshold, they would have a convulsive seizure. But as you can see, the mutant rabbits were having lots of smaller seizures at some of the lower doses. Also, oftentimes, after a seizure, you hit this postictal refractory state, somewhat protected. And then the wild types, you didn't see many seizures right at the next doses here. In contrast, the mutant rabbits continue to have seizures, somewhat like seizure clusters, as you may have heard of.

Dr. David Auerbach: 26:21 So not only are they having a decreased threshold for seizures, they're more prone to repeated seizures there. And since this is a SUDEP talk today, were these rabbits surviving this here? And as you can see here, 50% of these rabbits died of SUDEP during the course of the experiment, while only one out of six of my wild type ones died during the course of the experiment. And here are each doses. And you can see, the minimum dose for SUDEP was much lower compared to the wild types there.

Dr. David Auerbach: 27:01 So, how did they die? Since we had all these multi-system recordings, we were able to look at a detailed timeline of all these multi-system changes. So in green, here, we have the neuronal changes. In blue, we have the cardiac changes. And in purple, we have the respiratory changes. And you can see, there's a high level of concordance between each of these. And it's all of them feeding together that ultimately lead to sudden death there.

Dr. David Auerbach: 27:35 In some cases, there was prolonged periods of respiratory dysfunction and apnea, before SUDEP. While in other cases, there'd be a short run and then there would be a cardiac arrhythmia, and unfortunately, sudden death there. And this looks very similar to this clinical on the hallmark, monumental, MORTEMUS study here. And you can see in patients that unfortunately died of SUDEP, we can see this concordance between respiratory and ECG abnormalities that ultimately lead to sudden death.

Dr. David Auerbach: 28:17 This doesn't really exist in long QT1. For the sake of time, I'm going to zip through a couple more examples here, but also long

QT1. Alicia Goldman and Jeff Noble's group looked at in long QT1 mice, and they also saw a high prevalence of arrhythmias and seizures in these mice here, and a high level of temporal concordance between these events. And they would have large pauses, or even conduction disturbances in the heart there.

Dr. David Auerbach: 28:51 Now, when I was in Dr. Laurie [Isen's 00:28:54] lab, basically, that was when I got interested in tacking a neurocardiac approach. And what happened was Luis Lopez Santiago in the lab there, had taken the brain from a mouse and was studying it that day. I had to get my experimental setup up and going. I said, "Let me have the heart." Luck was on my side that day, I got beautiful recordings. And I came to him at the end of day and said, "What was this mouse?" I said, "Cardiac electrical activity was all messed up in it."

Dr. David Auerbach: 29:25 And we came to find that this mouse had one of the most severe genetic forms of epilepsy, Dravet syndrome. And what I came to show was if I take isolated myocytes from the heart there, they have paradoxically, an increase in the sodium current. And this led to hyperexcitability in these cells here. That's great. It's at a single cell level. What happens in the whole heart? Does that hyperexcitability in the heart translate over? And the answer is yes.

Dr. David Auerbach: 30:00 What we do is we stain the heart with a voltage sensitive dye. So what you'll see is, once I play the movie here, you can see this wave travel through the heart, as if you threw a rock into a pond there and you see the elliptical spread. And you can see the upper part of the heart, the left atrium activates, and then the ventricles activate. This happens a couple times, and all of a sudden, you can see this sudden firing there that leads to an arrhythmia.

Dr. David Auerbach: 30:29 So here's a wave coming from outside, and then oh, that's an abnormal one. You can see it all of a sudden start firing there. Wave comes in from the outside, and then these waves collide. And next one, maybe. And then it goes into this reentrant activity there. So we were able to show in these mice, that they had altered ion channel activity that led to hyperexcitability, which provide a substrate for cardiac arrhythmias, which are much faster and longer lasting.

Dr. David Auerbach: 31:09 So then, you're likely going to ask here, so what happens when they die? And we were actually able to capture an example of

SUDEP here, where they went into this lethal fast arrhythmia that ultimately led to sudden death there. But as I said earlier, mice don't really always replicate humans well. Mice are not little humans. So we took, in collaboration with Jack Parent's laboratory, we took induced pluripotent stem cell-derived cardiomyocytes, drove these cells to become cardiac myocytes, from patients with Dravet syndrome.

Dr. David Auerbach: 31:51 And they too, had altered sodium channel activity. And in one of these cases, this child has such a severe alteration in the sodium current that we actually observed alterations in this patient's ECG. Also, it can lead to autonomic disturbances. This is the work from Franck Kalume and Bill Catterall's group here. I'm moving a little quicker because I want to make sure that there's time for questions, but the take home from this here is that there was altered autonomic function here.

Dr. David Auerbach: 32:30 That there was increased parasympathetic hyperexcitability, and they saw this in the Dravet mice, as well as mice that only had the Dravet mutation in the brain. Also, Laura Isen's lab, looking at another sodium channel, has shown increased cardiac electrical abnormalities at the single cell level. In another disease, similar to my previous findings in a different model, they are showing ectopic hyperexcitability, and having arrhythmias. And they again, also captured sudden death in them.

Dr. David Auerbach: 33:14 So in each of these, these are all classically studied neuronal diseases, forms of epilepsy. But they're all showing altered cardiac activity as well. And here's another one from Jeff Noble's group. This was a [Glasscock 00:33:32], showed that when you have this KV1.1 mutation, which really isn't expressed much in the heart, there still was cardiac electrical abnormalities. So to summarize all this for you today, cardiac arrhythmias provide one mechanism for SUDEP. And I showed you that patients with epilepsy have a higher prevalence of ECG abnormalities, such as slow brady or fast tachyarrhythmias.

Dr. David Auerbach: 34:03 Additionally, genetic analysis has shown that there's a high prevalence of mutations in cardiac arrhythmia genes in SUDEP cases, and particularly long QT mutations. And then using numerous different animal models, I've shown you here, or reviewed other people's work, of a high incidence and prevalence of neuro and cardiac electrical abnormalities. And to conclude for you today, it is critical to take a multi-system

approach to examining genetic ion channel diseases of both the brain and the heart.

Dr. David Auerbach: 34:42 Before I conclude for you here today, it really was an honor to present to each of you, because I enjoy presenting to a lot of the foundations that are led by families, people who have such a passion and dire request of us always to advance our understanding of SUDEP, and to develop new detection tools, or identify new therapies. And this is what really is contagious to us, because it drives us to put our work into perspective. And oftentimes, foster us to get back in the lab and make us want to make, hopefully, the next landmark change in SUDEP research.

Dr. David Auerbach: 35:30 And finally, my last two slides for you here is, how can we eradicate SUDEP? No one person is going to be able to do this. So last year, during COVID, actually we had the SUDEP Summit. Numerous investigators, clinicians, basic science research, clinical researchers, medical examiners, advocacy groups, all got together and we tried to prepare a document of, how can we advance the SUDEP field?

Dr. David Auerbach: 36:05 So the major take homes from it, from the clinical working group, was we need to develop new technologies to detect seizures and to detect SUDEP, and set up SUDEP trials, the basic science working group. So we need to establish better models of SUDEP. What is a good model of SUDEP? The awareness and behavior group. So we need to develop ways to better advise clinicians on how to discuss SUDEP with their patients, and for patients and their families to better understand SUDEP, and how to report this.

Dr. David Auerbach: 36:49 Reporting it is not going to save someone from SUDEP. But if we have a better understanding of the prevalence, and who are these patients who unfortunately are dying due to SUDEP, maybe we can in the future, better predict. Public health and epidemiology, improve SUDEP counting, SUDEP screening tools. So all that's great. These are lofty goals. Where are we going with this now? So we're finalizing a draft of this paper, to hopefully be published soon.

Dr. David Auerbach: 37:21 And some of us recently got back together to try to take some of these ideas and champion the SUDEP Summit's priorities, to ensure that our greater community is taking up this work moving forward. And then last, my most important slide here is this was not all done by me. This was done by numerous people

in my laboratory. Kyle Wagner, my lab manager, Lou and Jackson, and Anjlee and Kyle, all have contributed to the study, as well as numerous past members of my lab.

Dr. David Auerbach: 37:59 And of course, none of this can be done without my funding sources. So thank you very much, everyone, for your time. It was a pleasure presenting this to you. I'll take any questions.

Dr. Laura Lubbers: 38:11 Thank you, Dr. Auerbach. That was terrific. I know there are already lots of comments and questions coming in. And so we'll now, start our Q&A period. Just a reminder, if you have questions in the audience, please submit them in the Q&A tab in your Zoom panel and click send.

Dr. Laura Lubbers: 38:27 So, why don't we start with one of the questions that was submitted in advance? Do you know if a condition called early re-polarization could increase the risk of SUDEP? And if so, what treatments or interventions are options to reduce that risk?

Dr. David Auerbach: 38:45 Sure. So early re-polarization syndrome, also is associated with a high prevalence of cardiac arrhythmias as well. That is true, that early re-polarization syndrome can also be pathological as well.

Dr. David Auerbach: 39:07 Actually, a group just 45 minutes down the road from us in Syracuse, spent many decades studying this, in fact. In terms of therapies, that field really requires the expertise of your clinical electrophysiologist, because it's so patient-specific that it would be difficult for me to give a silver bullet therapy right now.

Dr. Laura Lubbers: 39:38 Okay. But great advice. Thank you. Please talk with your physician and see if additional consultations might be helpful. So you've touched on some of the risk factors and some of the things that people can do. And somebody had a question about the interaction between SUDEP and sharing a bedroom. Can you tell us what that's about?

Dr. David Auerbach: 40:00 Sure. So yes, people who have epilepsy, who share a bedroom or have nocturnal monitoring, it's the simple hypothesis that hopefully, someone in the room will wake up when you have that seizure and help put you in a safe position. Turning you on your side, making sure that your face is not buried in the pillow, anything like that. That's the major theory behind that.

Dr. Laura Lubbers: 40:34 Okay. Thank you. You've done a lot of work with the Dravet patient population. Is it recommended that patients with Dravet syndrome receive annual cardiac screening?

Dr. David Auerbach: 40:50 I'm a firm advocate for definitely, Dravet patients getting cardiac screening. The frequency of that? I don't think we know enough right now to say whether one time versus yearly. But I definitely would recommend if it's a child who's going through puberty, basically testing both before and then after puberty. Because we know that sex hormones can alter the expression of ion channels in the heart there. So in that sense, I would say getting frequent testing.

Dr. Laura Lubbers: 41:30 Okay. That's great advice, because that's a piece that we've not talked about, the role of puberty and hormones.

Dr. David Auerbach: 41:37 Yes.

Dr. Laura Lubbers: 41:38 So very important. Is there any connection between AV block and SUDEP?

Dr. David Auerbach: 41:46 Yes. Yes. When I was saying throughout conduction disturbances, AV block is an example of a conduction disturbance. In simple terms, it's either a delay or failure of that electrical wave to travel from the upper part of the heart, the atria, down to the ventricles, the lower part.

Dr. David Auerbach: 42:06 And if that lower part of the heart, the ventricles is not firing and contracting at a sufficient rate, it cannot complete its sole function of pumping blood to meet the metabolic demands of the body. So yes, AV block is associated with SUDEP there.

Dr. Laura Lubbers: 42:30 Okay. Okay. Important. Thank you. So there are a couple of clarifications. I think you've touched on this, but just to reiterate, can mutated ion channels cause seizures?

Dr. David Auerbach: 42:41 Correct. Yes. Numerous gain and loss of function of sodium channel mutations that we classically look at in the epilepsy field, are also leading to electrical disturbances in the heart, and several cardiac ion channel mutations, such as long QT syndrome, Brugada syndrome, CPVT, are all ... Also, there's numerous reports of seizures in them as well. But there's a lot of research that's going on, to really understand the mechanism for this association.

Dr. Laura Lubbers: 43:18 Okay. Great. So more to come?

Dr. David Auerbach: 43:22 Yeah.

Dr. Laura Lubbers: 43:24 What should you ask a cardiologist to screen for? I know that's a medical question, but can you comment on that?

Dr. David Auerbach: 43:32 Sure. So I'm a firm advocate for performing cardiac testing under different physiological states. And what I mean by that is, doing cardiac testing when at rest, when maybe asleep, as well as during times of increased heart rate, such as exercising. Because to me, it's the contribution of numerous forces that ultimately lead to these unfortunate events there. So we need to be getting cardiac testing under different heart rate states there, or autonomic states.

Dr. Laura Lubbers: 44:18 Okay. Great. Great to test these different paradigms.

Dr. David Auerbach: 44:19 Oh, one other thing to add to it. I talked purely about electrical abnormalities today. I could give a whole nother talk on the structural abnormalities in the heart. So when talking about cardiac workup and everything, echocardiograms, looking at wall thickness, contractile function, that's a whole nother topic that there is strong associations in the epilepsy field as well.

Dr. Laura Lubbers: 44:46 Okay. Great to know. Great to get people thinking broadly about this.

Dr. David Auerbach: 44:51 Yeah.

Dr. Laura Lubbers: 44:52 And similarly, would vasovagal events be a concern?

Dr. David Auerbach: 44:57 For SUDEP?

Dr. Laura Lubbers: 44:57 Yes.

Dr. David Auerbach: 45:01 Vasovagal events, to me, that's more of a hemodynamic blood flow type thing where vasovagal, you pass out. But then there's normally this, then surge of adrenaline, sympathetic activity, gets the heart pumping stronger, increases your blood pressure, and then you oftentimes wake up. So I don't really see vasovagal events as much associated with SUDEP, but there's a lot that we don't know yet.

Dr. Laura Lubbers: 45:40 Okay. Right. Do you know, have the VNS and the RNS been included in studies? Do they provide any protection? Do we know?

Dr. David Auerbach: 45:51 Yes. Yes. So Richard Verrier's group at Harvard there, looked in patients with vagal nerve stimulators and showed that those with vagal nerve stimulators, there was actually improvements in the re-polarization, or their cardiac recovery process in those would VNS. In terms of seizure control, of course, there's been a lot of research showing the efficacy of that. So hopefully, did I answer your question?

Dr. Laura Lubbers: 46:29 Yeah, I think so. And there's a related question on whether patients with VNS implants should continue to get cardiac care.

Dr. David Auerbach: 46:39 Yes. Yes. The VNS is firing when there's a sudden change in heart rate. But I was at a cardiac conference during grad school, and this quote was used many times during the conference. He showed a video of this gentleman walking through the airport, and then drop dead suddenly.

Dr. David Auerbach: 47:00 And the question throughout was, why did this patient die today, not tomorrow, not yesterday, not a year ago? So even though things are under control, we still need to be monitoring these patients, and practicing with safe lifestyle habits to cut down on our risks of seizures and SUDEP.

Dr. Laura Lubbers: 47:22 Okay. Yeah, there are lots of related questions here. Someone commented about, should a patient who started with fainting, which lead to seizures, follow up with a cardiologist again? We started with a cardiologist and got okayed for the fainting before the seizure started. Sounds like a connection there.

Dr. David Auerbach: 47:43 Sure. I'm going to give a textbook answer. I'm sorry for saying this, but you need to get the cardiologist and the neurologist and your family practice physician sitting all at the same table to figure out which is causing which there.

Dr. David Auerbach: 48:02 Too oftentimes, our patients push back and forth between specialists. And maybe I say this because I'm not a clinician, but these clinicians all need to sit down at the table together and give better team-based care. My wife's a physician, so I can tell her that.

Dr. Laura Lubbers: 48:23 I would wholeheartedly agree with you. We definitely need to work towards more comprehensive care for these complex disorders. And for many different health issues. But I think especially for epilepsy, we really need as a patient community, to be pushing for that comprehensive, holistic care. And that includes mental health, just my little aside there. Let's see. So we have a question from a researcher. Is brady or tachycardia more common during the seizures leading to SUDEP?

Dr. David Auerbach: 48:58 Okay. So brady, both are reported. Oftentimes, there's been a greater prevalence of reports of bradyarrhythmias, slow heart rates, that can be due to slow firing of the pacemaker in the heart. But also, that includes your conduction disturbances. Because even if that upper part of the heart is firing normally, that wave may not get down to the lower part of the heart. But there are many case reports and even small studies showing tachyarrhythmias as well.

Dr. Laura Lubbers: 49:40 Okay. Okay. Complicated. And here's another related question, of course. If somebody is potentially at high risk, would a pacemaker make a difference? I know that's a medical question and we're not giving medical advice here. But are you aware of anything?

Dr. David Auerbach: 49:59 Sure. So, depends what the electrical disturbance is. A pacemaker is there as a backup. If that pacemaker in the heart, the SA node, doesn't fire at the rate that it's supposed to be firing, that pacemaker jumps in. Or if that electrical connection between the atria and the ventricles is not functioning properly, you can pace the lower part of the heart, the ventricles.

Dr. David Auerbach: 50:29 So it contracts. It excites and then contracts at the appropriate rate. But if the electrical disturbances are not due to a rate, but due to a rhythm abnormality, the pacemaker is not the right thing. That, you need to really consult with your cardiologist to understand, what is the electrical abnormality taking place in my heart?

Dr. Laura Lubbers: 50:56 Okay. Okay. So this comes from a family who is concerned about SUDEP in their child. Are there any over-the-counter heart monitors that could be used? I know the Apple Watch is being developed as a system. There's the Embrace. But that doesn't have a heart piece to it.

Dr. David Auerbach: 51:20 Right.

Dr. Laura Lubbers: 51:22 I know you interact a lot with families.

Dr. David Auerbach: 51:25 Yep. So unfortunately, right now, there's no alarming device. The Apple Watch will report if it detected any atrial electrical activity, abnormal atrial electrical activity. But it does not presently alarm at all, unfortunately. And the challenge with that is, as some parents could sympathize with some of these seizure-detecting watches here, the high false positive alarming is a big issue.

Dr. David Auerbach: 52:05 And I see that as a big obstacle in the field, because you don't want that Boy Who Cried Wolf scenario there, where alarm's going off every time, it's always been a false alarm. And then you miss that one real one. So I think we really need to have devices that have a high level of sensitivity and specificity there. But not published at all, but my lab is definitely looking into some wearables to try to detect electrical disturbances in the heart.

Dr. Laura Lubbers: 52:47 Great. Great. It's great to know that this is an area of focus, and more to come. And hopefully, we'll have solutions for people. So there are still lots of questions. And there's also, I want to share, there's lots of very positive comments and thank yous coming through. Deep appreciation, people in different parts of the world are listening in right now. And very appreciative of this.

Dr. David Auerbach: 53:08 Wonderful.

Dr. Laura Lubbers: 53:09 Somebody asked that they would like to share your research with their child's epileptologist. Would it be possible to get information? Or even if you know of any reviews or summaries that we might pass along to help people have this conversation with their doctor?

Dr. David Auerbach: 53:26 Definitely. Definitely. Dr. Lubbers, probably the easiest thing, I can send you a PDF version of this talk, as well as a couple papers afterwards that could be made available.

Dr. Laura Lubbers: 53:40 That's great. We can definitely make those available. Absolutely. People can just go to our website and get the synopsis. You'll be able to review this webinar again, get written transcripts if they'd like. And then we can share additional information.

Dr. Laura Lubbers: 53:54 So here's a question that's a little bit more ... It's not biology-based, but policy-based. There is a law called Halyn's law, which was passed in Connecticut, which requires medical examiners to have one hour of training in SUDEP, with the goal of collecting SUDEP patient data. Do you think this would be helpful if it was more broadly applied?

Dr. David Auerbach: 54:21 Absolutely. Absolutely. And during the SUDEP Summit, we had a medical examiner as part of it. And I think whether it's a medical examiner or the coroner system, it's so critical to have them more knowledgeable and trained in identifying SUDEP cases. Because that's the only thing that's going to help us to get that ball rolling in terms of recognizing the prevalence and the risk of sudden death.

Dr. Laura Lubbers: 55:00 Yeah. And it's terribly under reported.

Dr. David Auerbach: 55:02 Yes.

Dr. Laura Lubbers: 55:02 And we're still learning a lot in terms of the research, but we need to be at least thinking about it. Could this be due to, for this person who has epilepsy?

Dr. David Auerbach: 55:10 We see billboards all the time, about the prevalence of cancer, Parkinson's, Alzheimer's, all these things. But really having some hard, accurate numbers about the risk of SUDEP is so needed. It's so needed.

Dr. Laura Lubbers: 55:29 Yeah. Yes. Yes. Yes, there are many, again, very positive comments and appreciation, and people who are listening in who have been impacted by SUDEP. So I want to make sure that you're aware of that.

Dr. David Auerbach: 55:40 Great.

Dr. Laura Lubbers: 55:41 And how valuable this is. So we will post more information on our website. I know there are additional comments, and we'll still sort through them and see if there's anything else that we can address at a later time. But I do want to thank you for this phenomenal presentation, and all the additional information that you've provided. And I also want to thank our audience.

Dr. Laura Lubbers: 56:03 As always, you show up with great questions, great attention. And that's so deeply appreciated, too. We need this exchange back and forth. If you have additional questions about the topic,

or would like to suggest a future webinar topic, or wish to learn about more of CURE Epilepsy's research programs, please visit our website, or email us at research@cureepilepsy.org.

Dr. Laura Lubbers: 56:25 And if you'd like to review our webinar from last year, addressing breathing and SUDEP, visit the CURE Epilepsy YouTube channel, where all of our webinars are archived. And please be sure to register for our next webinar on November 10th, as we recognize Veterans Day, with a webinar addressing post-traumatic epilepsy and cognitive dysfunction, which impacts people with traumatic brain injury, including our military veterans. So again, thank you, Dr. Auerbach. Thank you to our audience. Please, stay safe everyone.