Episode 10 – What ECG can tell us about the events on molecular scale

Guest: Axel Loewe, PhD

Peter Kotanko
Welcome to the Renal Research Institute's Frontiers in Kidney Medicine and Biology, where we share knowledge and advances in kidney research with the world. In today's episode of Frontiers in Kidney Medicine and Biology, we discuss how physiology-based mathematical modeling of the heart can improve clinical care. My guest is Dr. Axel Loewe, Head of Computational Cardiac Modeling at the Karlsruhe Institute of Technology in Germany. Dr. Loewe and his team are developing computational models of the heart to answer questions of clinical relevance, such as cardiac arrhythmias and their treatment.

Axel, welcome for this part of the Frontiers in Kidney Medicine and Biology series.

Axel Loewe Hello, and thank you for having me.

Peter Kotanko
Axel I, when, when I'm looking at your work, which is really dealing with the mathematical modeling of cardiac function, the cardiac electrophysiology, and we'll talk a lot about this, of course, I was really wondering, Axel, what brought you to this kind of esoteric field?

Axel Loewe
I've always had a strong interest in both technical aspects and medicine. And after finishing school, I did a community service at an emergency service. And after that, I was still interested in medicine. But I decided to study electrical engineering and information technology. And then, a few years into my studies, I realized that there is this nice field that really allows to make that connection. And that's biomedical engineering, and computational modeling, in particular. And that's how I, now I ended up there and where my interest and enthusiasm was sparked.

Peter Kotanko
This is really interesting. So, the first thing was, the experience you made in an emergency room apparently, this is part of the story. How can one say that I'm a theoretical physicist, doesn't relate to medical reality? My understanding is, you have a very keen understanding of what's going on the ground, what health care workers, what physicians would need, what the patient's situation is, right?

Axel Loewe
Yeah, I think this is essential, it's so easy to get lost in ideas that that appear interesting and relevant to us as modelers. But when talking to clinicians, one might realize this is not an actual problem. It's solved already. Or it's just irrelevant. So almost all of our projects are in close collaboration with clinicians to really have that link, and have a feeling for their actual needs. And to get a concrete idea, what could in the end really benefit the patient.

Peter Kotanko
In the center of your work is the heart now? And can you just explain in a few words to a general audience, what actually makes the heart beat? What's the underlying electrical mechanisms just in a in a few words.

Axel Loewe
For me, personally, a very fascinating fact about the heart is that it's kind of self-sustained. So if you explant the heart during transplantation, for example, it will keep on beating as long as you make sure that it's sustained with oxygen and nutrients. And that is because the heart has an intrinsic pacemaker. So, some of our listeners might know pacemakers that get implanted as a medical device, but actually the heart has a natural pacemaker. It's the so-called sinus node. And this generates an electrical impulse, which is the origin of every single heartbeat. And from there on, then an electrical propagation wave or excitation wave spreads and propagates throughout the cardiac tissue. We have the two upper chambers of the heart the atria, they are excited first, and there is a little electrical silence when the excitation synchronizes and then in a very specific way activates the two main chambers of the heart, the ventricles, that then do actually also pump the blood into the great vessels and supply the whole body with fresh blood.

Peter Kotanko
It's actually fascinating to see that, as you said, the heart kind of sustains its activation, if provided with oxygen and nutrients. So, but where's now the intersection between the mathematical modeling you are doing and this and the physiology of the heart? Where does this come into? Where does this enter the picture?

Axel Loewe
I think modeling is a very essential part of understanding things. And those models, they can be really simple - just thought experiments. And in some cases, I think whenever we understand something in physiology, we formulate some kind of model. And often, those are models that can be drawn on a piece of paper, or formulated in a few sentences. But sometimes those models can also be formulated in a mathematical way. And once we have that, we have a mathematical formulation. This gives great new opportunities. So often there are variables or parameters in the equations that represent certain physiological properties, like for example, a potassium concentration in the blood. And then we can change this concentration and see what happens to the model. What does the model predict when we change that? And this field of formulating physiological processes mathematically, especially in the field of electrophysiology has a long history. Hodgkin and Huxley were the first ones to describe that back in the 1950s already for a neuron, so the nerve cells, and they have very similar mechanisms. And their fundamental principles or the building blocks they describe for how ion channels open and close. 70 years ago, it's still what we're using today, to a large degree, also in current models of cardiac electrophysiology.

Peter Kotanko
Well, sometimes I would hear, and it's attribute I believe, to Albert Einstein, the saying that all models are wrong, but some are useful. So could you just say a few words about the potential usefulness of your models?

Axel Loewe
I think there is a lot of truth to this quote. And I think models need to be wrong in a certain sense, because they need to be a simplification of the reality. If we wouldn't need to simplify them, we could just study reality. But we want to, in a very focused way, neglect certain aspects of reality that we think are not helpful and might just blur our view on what we want to study. And this is what we are considering in the model. So models need to be a simplification of reality. And then the second aspect that some of them are useful, is true as well. But we need to make sure that the actual model we are using is well suited to study what we want to study. And this is called model validation. So asking ourselves the question, if this is the right tool for this question, and I believe that there are a lot of questions that can actually be answered by computational models, or at least the computational models can contribute a large share to the answer. And we've seen quite some examples in not just the recent years, I would say the last decades. When speaking about my field, cardiac electrophysiology, a lot of the basic fundamental understanding of how cardiac arrhythmias can develop and what are the circumstances that allow to sustain those arrhythmias? What are also mechanisms that can terminate arrhythmia? A lot of this understanding actually comes from computational modeling.

Peter Kotanko
I'm just wondering, I mean, you say it that the modeler like yourself and others they have to decide how angular a model actually should be. And I mean, how do you make these decisions? I mean, there is, I'm always hearing this is not science, it's rather art. So would you agree with that?

Axel Loewe
I would disagree. There's a lot of, I would say, craftsmanship and model building. But I believe that it's really essential to always keep in mind and have clear the scientific question we want to answer. A model is built for a purpose. And we cannot just take one model from the shelf and use it to study whatever we want. Before doing that, we need to ask ourselves, is this model suited to study what we want to study? If yes, great, we can use it. If not, we might need to build a new model, or take an established one and refine it. So to make an example, what we were interested in, in a lot of our collaborations, was the effect of changes in the blood electrolyte concentrations as occurring in dialysis patients. What effect do those changes have on the cardiac electrophysiology and then, in turn also on the ECG that can be measured? And most of the models just assume that those concentrations, the potassium concentration, for example, stay constant. And this is a prime example of how we cannot just take such a model, and then try to study what happens if we change the calcium concentration. Now, we need to make sure that the model considers all the relevant aspects. And for, for this study, of course, the potential to have dynamic changes of all relevant ion concentrations is key.

Peter Kotanko
You referred to Huxley earlier. I mean, they were looking into single cells, right? I think their electrophysiological model was really dealing with single cells now that the heart comprises, of course of millions of cells of very different cell types. I am wondering, how, how do you actually scale? Or how do you actually bridge those scales? I mean, from the single channel in the cell, different thing, different cell types, up to the entire organ? This seems to be a daunting task, or

are you actually modeling each single cell? Are you grouping them together? Can you provide us some more insights around that?

Axel Loewe
This is a very good question. And it comes to the heart of our modeling approach, really. So what we do is called multiscale modeling. So we have different scales that we're looking at. And those are both spatial scales and temporal scales. The example that that can be easiest to follow is probably the spatial scales. So the smallest entity we're looking at, the smallest building block, is an ion channel. And this really is a structure in the membrane of each cell that is just a couple of nanometers big, but it can open and close. And when it's open, it allows ions, charged particles, to migrate from the inside of the cell to the outside, or vice versa. And this transfer of charged particles has an electrical effect. So it changes the electrical voltage between inside and outside the cell. And that's really the essential mechanism of cardiac electrophysiology. And those ion channels, those single building blocks, they can be quite nicely characterized experimentally by, for example, patch clamp experiments. So biologists do electrophysiological studies, in a dish, single cells, and characterize those channels. And then when the modeling comes into play, we first adapt a generic ion channel description to this very specific channel that was measured. And then the really fascinating part is when we take those different ion channels together and integrate them in one common cell model. So a cell has not only a potassium channel, but it also has a calcium channel and when we look closer, it does not only have one type of potassium channel, but a whole series of them. So this is the first step of integration that we do by going from the ion channel level to the integrated cell level. And then as you mentioned, the cells of the heart are not isolated, but they are electrically coupled and make up the cardiac tissue that allows an excitation wave really to propagate. And this is then also reflected in the model. Mathematically speaking, this requires to go from ordinary differential equations to partial differential equations. And that's because at that point, then also the spatial spread comes into play. For the single cells, they are just at one point, but when we look at tissue, we also want to see how the excitation spreads. And that's the next level of integration, then, at that point, as you mentioned, we need to homogenize. Currently, it's not feasible to model every single cell in a heart, and to represent it in the in the model. But we homogenize and we look at how a whole group of cells behave in that tissue. And this allows us to study reentry mechanisms, for example. So reentry doesn't happen in a single cell, it happens on the tissue level. And those reentry phenomena and how they can be stopped by defibrillation, for example, they require tissue models. And then the last step we do is to go from the tissue level to the whole body. And this allows us to also compute virtual ECGs. For the electrical potentials on the body surface, we can derive virtual ECGs. And that's a very good way to link back to measurements because ECG can be easily acquired in a patient. It's noninvasive, it's cheap, it's available everywhere. And now we can really close that gap from the experiments on a single cell level, just a couple of nanometers, up to an ECG measurement on the body surface, so in the range of some centimeters. Bridging those gaps mechanistically is something where I think computer models can play a role

Peter Kotanko
Thank you for walking us through these various scales. I mean, am I mistaken by assuming that one goal of your work would be to create the sort of a mathematical twin of a patient's cardiac electrophysiology. So in other words, that I would have a model eventually that's different from yours, and so on and so forth. Is this one of your goals? This will be the first question. And

second question is kind of what kind of data would be needed from the person whose mathematical twin you're attempting to create? And last but not least, I mean, where do you stand on that pathway?

Axel Loewe
That's a lot of questions. I try to remember all of them. Let's start with the first one, the digital twin. And yes, this is one way that we follow, one route we follow to translate those models into clinical benefit. And it has been shown already, not just by us also by other groups, that for specific diseases, this can really be done. So we build a model that reflects the heart of the individual patient. The rather easy part of that is to reflect the shape of the heart. So hearts have different sizes. Some of them are more symmetric, some are less symmetric, the wall thickness varies. But this can be pretty well characterized by medical imaging modalities, so computed tomography or magnetic resonance imaging. And then those images can be taken, we identify the heart and we built a computational model of that. This is called anatomical twinning. So the digital twin of the individual anatomy. And then there is a second aspect which is often more tricky, and that's the functional twinning. So the excitation wave in your heart might spread a little faster than in my heart. The cells in your heart might need a bit longer to recover from the previous activation than in my heart. So we know that there is quite a bit of interindividual variability. So this comes back to the point I made before that we need to make sure that the model we are using is suited for our context of use, for the question we want to answer. And this means that also a digital twin needs to be personalized differently, depending on the question we want to answer. For example, if we want to terminate atrial fibrillation, which is a very common arrhythmia, and we want to predict where would be the best ablation lesion that the physician could apply, we'll need some functional information from the atria. Another example is to predict whether a patient would benefit from an implanted defibrillator or not. And there have been some proof of concept studies also applied to patients prospectively, that showed that for the latter questions or whether a patient who suffered a myocardial infarction would benefit from an implanted defibrillator can be very well answered with a digital twin, which is only informed by modeling. Sorry, which is only informed by imaging. And why is that? That is because the crucial difference between patients is the shape of the scar that the myocardial infarction left. And this scar can also be imaged with specific imaging protocols. And if we can do that, we can incorporate it into the model. And then we can do very aggressive testing in the computational model, if we can induce this arrhythmia. And this is much easier in the model because it doesn't harm anyone. The patient doesn't need to be in the EP lab during the study. And we can do very aggressive, but also very exhaustive and testing. And then we can see whether this arrhythmia can be induced or not. And if it's not the case, then the patient doesn't require a defibrillator. And if it's the case, then this can aid the decision making of the clinicians to go ahead and actually do the interventional study in the patient.

Peter Kotanko
Axel, I am, I am really wondering if your models could also be used to develop new drugs, new anti-arrhythmic drugs, and then that those drugs or drugs of interest or potential drugs could be tested in your model. So where does science where does the regulations where does medicine stand at this point in time?

Axel Loewe
This is a very, very interesting and also very lively field. And then one advantage is that for characterizing drug action, we often don't need to go to the tissue or to the organ level. But we can we can study those effects in single cells. And one aspect that the models can do is that you can ask the question: What would an ideal drug look like? So which channels should be blocked, to which degree to compensate for a specific genetic mutation, for example? And then the simulation study could tell what an ideal mode of effect should be. And then you would only need to find the drug, or the agent that does exactly that. This is one aspect, but the probably more relevant one is to characterize existing agents. And there is an initiative led by the US FDA, the so called CiPA initiative, and it tries to refine the way that pharmacological agents are assessed before they enter the market. And it consists of different pillars. Some in vitro experiments but one of the pillars is also in silico experiments. And the job of those in silico experiments is to integrate the data that were acquired in cell experiments in stem cell experiments as well, and to see what the effect on the different ion channels is if they are combined, which effect does it have on the cell level? And those interactions are often very complex, highly nonlinear, so it's not trivial to predict what would happen if you only see the data. And those models can help. And they are on a good way to become an essential aspect of the regulatory path for assessing new pharmacological agents and there and ruling out that there is cardiotoxicity. So to rule out that those drugs could cause lethal arrhythmias.

Peter Kotanko
So I have to say as a as a nephrologist, I'm really excited to hear about those developments and one reasons is that in kidney patients on dialysis, sudden cardiac death is the most frequent single cause of death. And I am wondering, if you do you have any insights into sudden cardiac death in dialysis patients, and in maybe even address the question? How could the modeling work you are doing help in in, you know, in reducing this cause of death?

Axel Loewe
I can see two ways here. I'll start with the more controversial one probably. And that is a study we did not so long ago that was inspired by several reports that reported that sudden cardiac death in dialysis patients is often caused by a slowing of the heart rate. So sudden cardiac death in the general population is a tachyarrhythmia, so we have very fast reentrant waves that prevent the heart from pumping blood effectively. But those reports in dialysis patients said that it's very likely that this is rather a constant slowing of the heart rate, until it's so slow that the blood cannot be pumped effectively. And what we did in the model is to look at potential reasons why this happens. And we found evidence that this could be caused by a decrease of the calcium concentration in the blood, which would lower the frequency of the spontaneous excitation that our natural pacemaker, the sinus rhythm, generates. And besides the computational study that derived this hypothesis, we found some empirical evidence by looking at heart rate versus calcium. But what is still lacking is an in vitro confirmation of this hypothesis. This is so challenging because we see a lot of interspecies differences in pace making. So, in normal animal models, they have much higher heart rates. And so that's why this pace making can only be studied to a certain degree in animal models. And it would really require experiments in human sinus node cells. So this is one way where I think models can have an impact on the this field of sudden cardiac death on this huge problem of sudden cardiac death and dialysis patients. And the other one would be to design and develop methods to predict critical situations. And there, we see a lot of potential in the electrocardiogram ECG. This is

because this is acquired so often, nowadays, with wearable devices, it can also be used for home monitoring, point of care monitoring, continuously. And we know that shifts in the electrolyte concentrations do cause changes in ECG. Often, they're not really easy to identify in clinical recordings because there are so many influencing factors. The heart rate might change, the patient might have some physical activity, which also affects the ECG. So this is why we like to use the computational model to generate such data. Because we know the only parameter we've changed in the model was the concentration of potassium, for example. And then, when we observe a change in the simulated ECG, we know exactly the reason for that. And this was because the calcium or potassium concentration was changed. And not because something else happened, because the patient had a bad day or drank more or drank less on that day. So this is a way to design algorithms that from the ECG could either predict situations like hyperkalemia or could be trained to predict critical situations in general. And this is a second way of how computational modeling I think could contribute to fight sudden cardiac death in dialysis patients.

Peter Kotanko
So what you're saying, in essence is that the EKG could be used to derive, say, the concentration of potassium in the blood. Do you think that this is something for, looking years and years ahead, for a consumer product, where people who can do as it's currently already possible to record an EKG say, with their cell phone or with a watch, and then derive potassium concentrations? And do you think that modeling as such, is sufficient to do that, or do you also need some input from the artificial intelligence world to train models in a way based on the patient's characteristics?

Axel Loewe
I think there is a lot of synergy between modeling and artificial intelligence or machine learning. And that is because machine learning requires huge amounts of data. The more data, the better. And the better the ground truth labels or the quality of the data, the easier it is for the machine learning approach. And this is a thing where computational models can contribute by generating those data that can be used to train the machine learning algorithm. And we recently published a paper where we trained a classifier only based on simulated ECGs. And it could predict the acute success of pulmonary vein isolation in atrial fibrillation patients in clinical data. And those clinical data were not seen at all when training this algorithm. So this is a way that this could happen. But of course, in the end, it always requires to show that it works on clinical data. And sometimes also, huge amounts of clinical data are beneficial during training. So either we have very good models that are very representative of the actual mechanisms in the patient, and also of the variability that can occur in the patient. Or we need very big, high quality data sets to train those classifiers. And as a third option, those two approaches can also be merged, so that we have hybrid data sets, both from clinical recordings and generated in silico with a computational model.

Peter Kotanko
What I've learned over the last 30 minutes or so is this is a highly dynamic field where we're looking forward, I guess we can expect really major developments that will benefit patients and maybe in the general population in one way or another. Now, we are coming to the end of our really interesting conversation. And actually what are your points you would want our audience

to take home with just if you just could give us a brief summary of what you think are really the essential points you would want people to remember.

Axel Loewe
I hope I could share my enthusiasm and show how computational models can be a valuable complementary approach to the established experimental settings like single cell experiments, like animal experiments, or clinical studies, and that they provide a way to generate mechanistic insight. A model that was built from first principles of physics and biophysics can provide a very controlled environment to study the effect of specific changes. So we can really test clearly formulated hypothesis in the computational models. So this is one aspect that I wanted to bring across. And then the second one is that I think there is more potential than is currently being used for collaboration between clinical research and modeling, so we need to have a stronger link there. And speaking from my perspective, this is a need for more and better data. So data sharing, open data, well annotated data is really a bottleneck right now. So for example, the prediction of critical events in dialysis patients, what we would need is digital ECGs. But then linked to other measurements, like the blood electrolyte concentrations, but also information like age and sex. And those resources are very limited. You know, they are very limited in the sense that they are not openly available, but these data exist. And if we can make them available to others, I think we can really make much bigger steps forward.

Peter Kotanko
I guess what you are saying is really a call for more collaboration. And, and of course, you and I, and many of our listeners know that it's really this collaboration across fields, this sharing of specific skill sets and an interaction of multiple disciplines is what really advances eventually, our care for patients. So Axel thank you very much. This was a wonderful, interesting conversation, and I wish you all the best for your ongoing research, and I'm looking forward to catch up with you. And then let's see what the future looks like in three, four or five years and to see what those applications will look like then.

Axel Loewe
Thank you, Peter. Thanks for having me.

Peter Kotanko
Thank you for joining the Renal Research Institute for this episode of Frontiers in Kidney Medicine and Biology. We invite you to engage with us on our social media channels. And look forward to seeing you again for the next episode on Frontiers in Kidney Medicine and Biology.

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