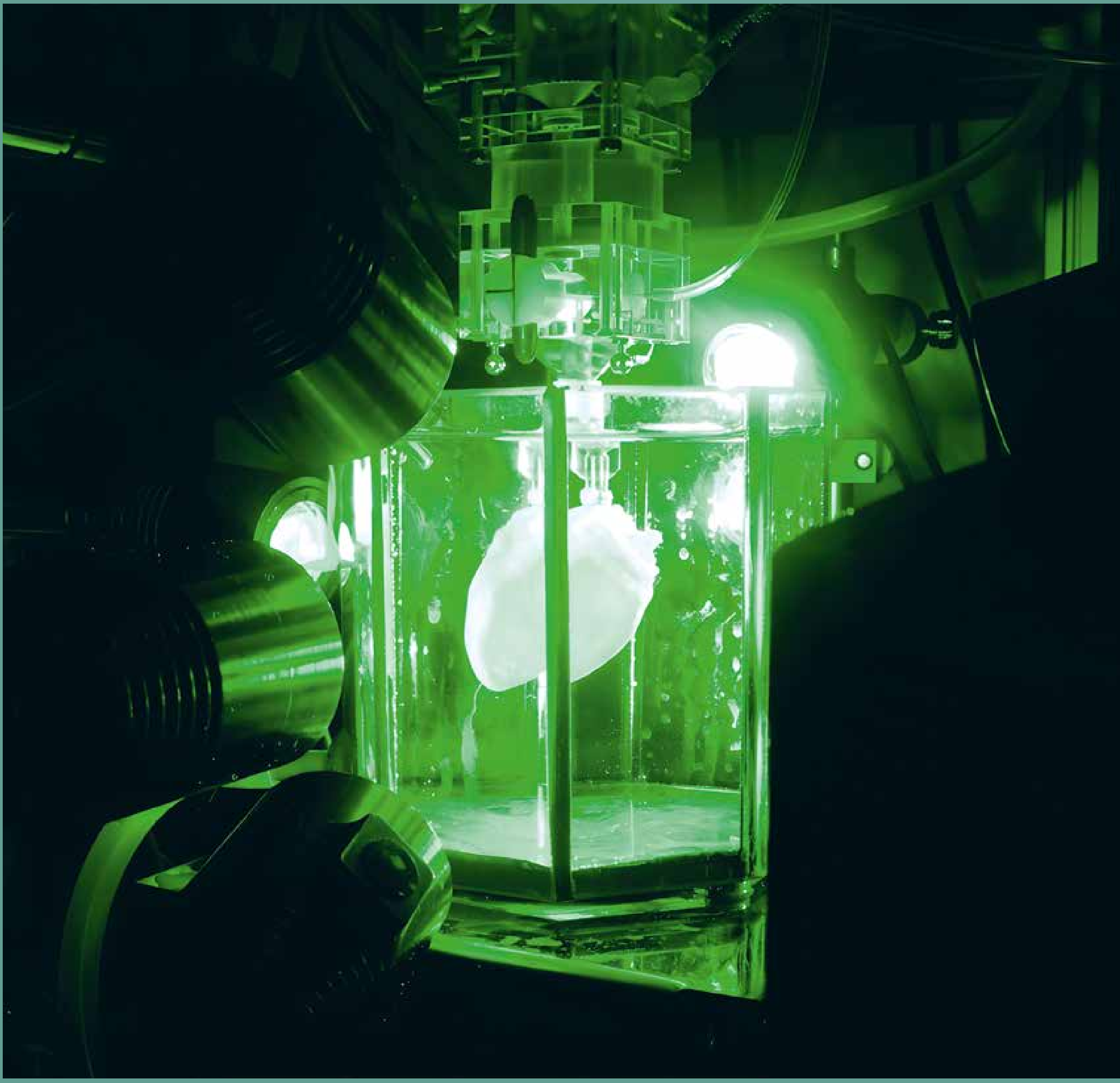
FOCUS

THERAPIES FOR TOMORROW



A ray of light for heart patients: a Göttingen-based team conducted experiments on a rabbit heart floating in a nutrient solution, clarifying what happens in the heart muscle during arrhythmias. Researchers are using this information to develop gentler treatments.

PHOTO: EFIMOV, NIKOLSKI & SALAMA, CIRC. RES. (2004) / CHRISTOPH, SCHRÖDER-SCHETELIG, S.L. (2017)

A METRONOME FOR THE HEART

TEXT: TIM SCHRÖDER

Cardiac irregularities are among the leading causes of death in industrialized countries. They are frequently treated with defibrillators, which deliver painful electric shocks. Physicist Stefan Luther has discovered a gentler way to stop these arrhythmias. Together with partners in industry, he now aims to bring this technology to market.

The heart is a biological marvel. It beats for decades – without pause and without needing maintenance. No technical pump lasts as long. With every beat, it pushes around 80 milliliters of blood into the arteries; that's about five liters per minute, or roughly 7000 liters per day – equivalent to some 38 bathtubs full. Given this workload, it's hardly surprising that something occasionally goes wrong. For example, some people's hearts fall out of rhythm over the course of their lives. They develop an arrhythmia, such as atrial or ventricular fibrillation. In Germany alone, more than 65,000 people die annually from a severe cardiac arrhythmia.

SUMMARY

Until now, cardiac arrhythmias could only be stopped using strong and painful electric shocks.

A Max Planck research group has visualized the vortex-shaped contractions during arrhythmias using ultrasound and other methods.

A detailed understanding of the electromechanical processes involved in arrhythmias makes it possible to stop them via "Adaptive Deceleration Pacing" (ADP), which is a series of weak electrical pulses.

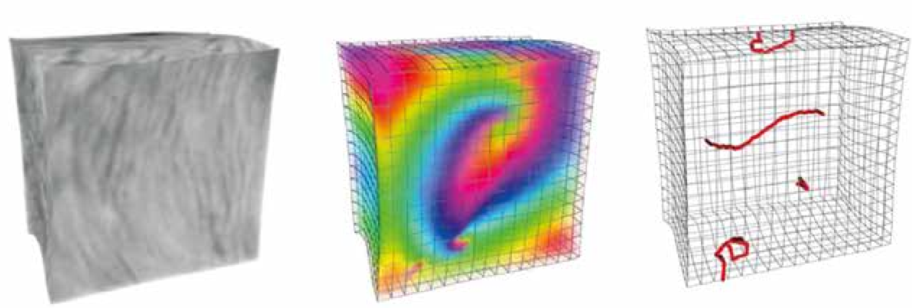
Normally, the heart contracts in a steady, wave-like motion with every beat. First, blood collects in the two atria. From there, it's pushed into the two large ventricles, which press it into the arteries. The wave-like contraction begins in the wall of the right atrium, at the sinoatrial node and spreads from there across the entire organ. In people suffering from a cardiac arrhythmia, however, chaos breaks out. Instead of a regular wave of excitation, the heart moves uncontrollably. Instead of pumping blood, the muscle merely flickers (fibrillates).

To bring the heart back into rhythm, medical professionals have so far relied on a rather forceful method: defibrillation, a powerful electric shock that causes every muscle cell to contract simultaneously, bringing them to a sudden halt. After a short recovery period, they begin to contract again. Often, this helps the heart get its rhythm back. "People who've experienced such an electric shock while fully conscious compare the pain to a horse kicking them in the chest," says Stefan Luther, Research Group Leader at the Max Planck Institute for Dynamics and Self-Organization in Göttingen and professor at the German Centre for Cardiovascular Research. "It's something you wouldn't want to go through again." There is no question that high-energy defibrillation saves lives. However, in addition to the pain, it can also damage tissue, which may lead to further heart problems. That's why Luther wants to develop gentler methods. And it looks as though he'll be bringing these to market in the coming years together with industrial partners.

It's been a long road to get here. For more than ten years, Luther has been studying "stimulus conduction in the heart." Initially, the goal was to understand and visualize the processes within the heart to derive concepts for treating cardiac arrhythmias. "For a long time, the heart was simply regarded as a moving organ," he says. "Of course, it was known that it could be stimulated electrically. But the precise relationships between electrical stimulation and movement were not understood. In contrast, our goal was to understand the heart as an electromechanical unit."

Electricity in the heart? Indeed: muscle cells are controlled via an electrical potential at their cell membrane. To achieve this, the metabolism stores ions inside the cell until an electrical voltage exists between the interior and exterior. Contractions are triggered by the abrupt transport of ions back and forth between the inside and outside, which changes the voltage.

But what goes wrong electrically in the heart when it no longer beats correctly? Luther realized he had to un-



To the core of ventricular fibrillation: from ultrasound images (left), the Max Planck team reconstructs the vortex-shaped muscle contractions during a heart rhythm disorder (center). This also allows the paths of the vortex cores (rotors) through the muscle to be tracked (right).

PHOTO: MPI FOR DYNAMICS AND SELF-ORGANIZATION derstand the entire system, from the entire organ down to the individual cell. One thing known for certain was that arrhythmia causes the heart to shift from an orderly state to a chaotic one. Luther was already familiar with this subject: at the start of his career, he had studied the chaotic movement of bubbles in liquids – a "physically complex, non-linear system." And that is exactly what occurs during an arrhythmia. During atrial fibrillation, for example, the heart muscle stands still except for minor twitching. The blood no longer flows properly, which can result in clots forming. These can cause thrombosis and block blood vessels. But how do you visualize this electromechanical chaos? Luther first ran computer simulations to investigate. These showed how an electrical pulse in the heart tissue triggers both tensile and compressive forces – much like an ocean wave pushes water ahead of it but also pulls it along. That's how the mechanical movement spreads throughout the entire heart.

The simulations also showed that, during an arrhythmia, the steady wave of excitation splits into many small waves. These mini-waves, or wavelets, each rotate around a central point called a rotor. Just as a tornado carves its path through a landscape, these rotors, along with their waves, wander chaotically back and forth across the heart. This is what creates the irregular twitching and flickering. To investigate the interaction between chaotic movement and its electrical excitation, Luther – along with medical researchers from Cornell University in the United States – conducted an extraordinary experiment several years ago. He placed a rabbit heart in a glass vessel filled with a nutrient solution. The solution provided the organ with all the essential nutrients it needed to continue beating outside the body. While the heart moved, it was filmed by cameras. They recorded two different things: first, the movement of the heart, including its contractions. At the same time, the cameras captured electrical information. To do this, the researchers had treated the muscle tissue with a special dye that changes color when the electrical potential at the membranes of the muscle cells changes. This meant that the dye provided a signal exactly where the muscle cells were currently being electrically stimulated.

At the Origin of the Wavelets

On the computer, Stefan Luther and his team linked the two image datasets together. It was fascinating: now it was possible to see exactly where the electrical impulses originated in the rabbit heart, how the electrical excitation circled the rotors, and how the heart muscle moved accordingly. The fusion of electrical and mechanical information was a success. This means that, using his computer models, Luther can now also work in reverse – deducing the electrical stimulation and the location of the rotors →

PHOTO: GETTYIMAGES

Painful lifesaver: currently, cardiac arrhythmias are stopped in emergency situations by delivering strong electric shocks via the two electrodes of a defibrillator.

solely from the movement of a heart muscle, and thus identifying the origin of the chaotic wavelets. “This is the prerequisite for future arrhythmia treatment. Because you can then specifically treat those areas of the heart muscle where the chaotic movements originate.”

Looking at the heart from the outside reveals what’s happening electrically on the inside – this can now be done for humans too. Thanks to a collaboration with the University Medical Center Göttingen, Luther was able to record a beating heart during surgery some time ago. In this case, however, not with a camera, but with an ultrasound machine. The Göttingen team showed that this too can record the movement of the heart muscle in high resolution. When patients are connected to heart-lung machines during cardiac surgery, it’s common for the heart chambers to begin to fibrillate. After the operation, the fibrillation stops. Arrhythmias can be studied effectively in this situation. The ultrasound recordings Luther made showed with millimeter precision how the tissue moves, swinging back and forth in fine waves. The rotors around which the waves circle are also recognizable. “The great thing about the new 4D imaging process is that, in the future, you’ll be able to observe the electromechanical processes in the heart with a device that is standard in every hospital: ultrasound,” says Luther.

Optimized Therapies

Precisely understanding what is going wrong in the heart is crucial because there are many different types of arrhythmias – atrial fibrillation, for example, but also ventricular fibrillation. In other cases, the ventricles beat too quickly. Doctors combat each of these diseases with specific procedures. In atrial fibrillation, the part of the muscle tissue where the arrhythmia originates is destroyed. This procedure is called ablation. The tissue is heated via a catheter or treated with a laser. However, this treatment is currently not very precise. During surgery, doctors use a catheter to insert measurement electrodes into the heart at the exact location in the muscle from which the arrhythmia originates. However, this measurement is relatively inaccurate.

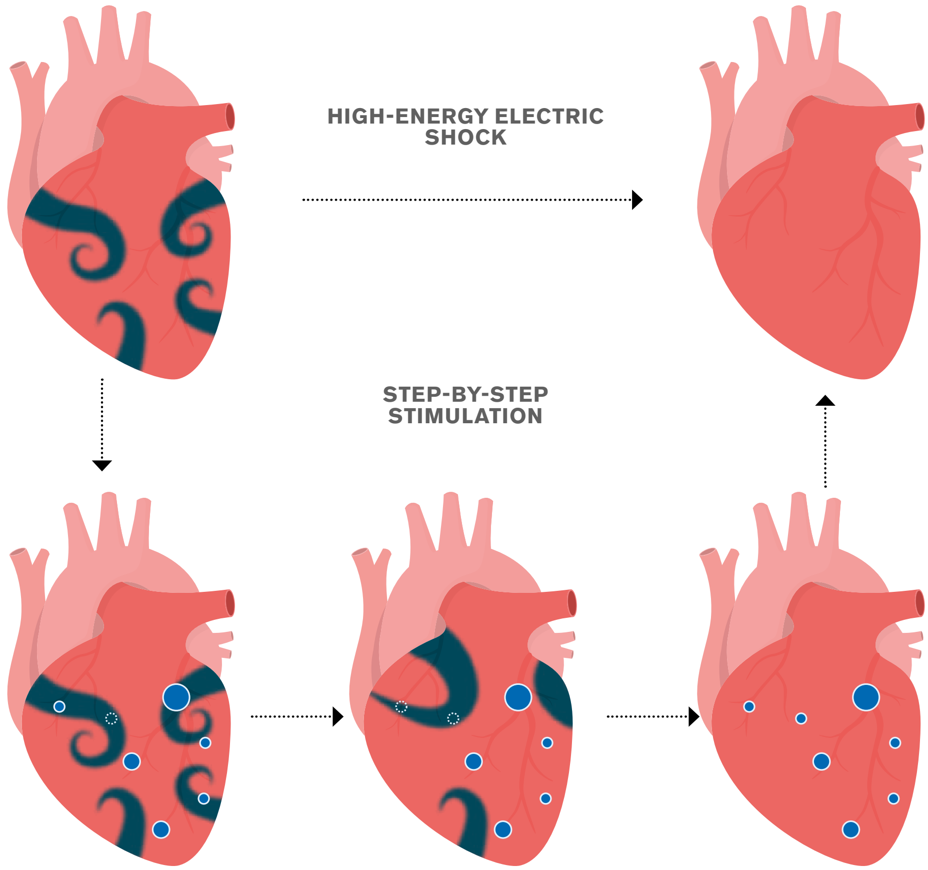
Meanwhile, defibrillators are implanted in patients to treat ventricular fibrillation, among other conditions. Thin electrodes run from this device into the heart. They deliver electric shocks if the heart loses its rhythm. “However, the electric shocks from implanted defibrillators are so painful that many patients have the devices removed,” says Luther. “They would rather take the risk.” Another issue is that the heart tissue often develops scarring at the points where the electrodes are attached, which can also lead to complications.

Luther is tackling the problems of current treatment methods in different ways. He is collaborating with Yale University in the United States on research into ablation. They intend to use the new 4D ultrasound soon to map arrhythmias right down to the rotors, in order to locate and ablate the origin of the rhythm disorder in the heart muscle more accurately than ever before. Luther’s US colleagues are enthusiastic about the Göttingen approach: “Stefan’s lab has done pioneering work,” says Joseph Akar, an expert in cardiac electrophysiology at the Yale School of Medicine. “The new 4D ultrasound technology allows us to examine complex heart function non-invasively for the first time and with a previously unattainable level of detail. We’re convinced that this technology can fundamentally change the diagnosis and treatment of life-threatening cardiac arrhythmias.”

When it comes to defibrillation, Luther’s goal is to reduce the intensity of the electric shocks to the point that they no longer cause any pain. This has already worked in the lab. In the early 2020s, one of his doctoral students first discovered, through a simulation of the rotors and wavelets, that the chaotic behavior can be stabilized by applying a regular sequence of weak electrical pulses rather than a single strong electrical shock. Shortly thereafter, Luther’s team found that the effect is even greater if the pulses are not fired regularly, but specifically at varying time intervals. As experiments on rabbit hearts showed, the chaotic movement of the rotors and wavelets is slowly braked in this way – until the arrhythmia disappears completely. Luther calls this process adaptive deceleration pacing (ADP). With this process, he has succeeded in pushing the stimulation below the pain threshold: the decisive step toward a painless defibrillator.

“The new 4D ultrasound technology allows us to examine complex heart function non-invasively for the first time and with a previously unattainable level of detail.”

JOSEPH AKAR



Gentle treatment: vortex-shaped contractions during an arrhythmia can be stopped with several mild electrical stimulations instead of a single high-energy electric shock.

GRAPHIC: GCO BASED ON WORK BY THE MPI FOR DYNAMICS AND SELF-ORGANIZATION

Together with manufacturers of defibrillator implants, Luther will now further advance the ADP principle. One goal is a defibrillator whose electrodes sit on the surface of the heart muscle. Such extravascular defibrillators have the advantage that the electrode cables are not anchored inside the heart, which avoids scarring and other complications. However, extravascular defibrillators also have a significant disadvantage: since the electrode is placed on the outside of the heart, a considerable amount of energy is required to restore the arrhythmic heart to a normal rhythm. The electric shock is correspondingly painful. This is another reason interest in defibrillation with gentle pulse sequences is so high.

On the journey to bringing this gentle therapy into medical application, Luther must master more than just the biophysics of the heart: “It’s an immense challenge to transfer basic research results into clinical application. In addition to a good idea and an excellent team, you also need a lot of perseverance and plenty of support,” he says. Successful technology transfer, he notes, is rarely as simple as stepping out of the lab; rather, it arises through long-term collaborations between research institutions and industrial companies. It also requires an environment that fosters applied research so that new ideas can be brought to market quickly. The Göttingen-based team has enlisted the support of Max Planck Innovation, the technology transfer subsidiary of the Max Planck Society, to commercialize this know-how with medical technology companies, or possibly through a startup. Luther is confident that it will work out. For him, the idea that correcting arrhythmias requires a single intense shock is outdated. He has made significant steps towards a gentler form of treatment.

GLOSSARY

ARRHYTHMIA
refers to various heart rhythm disorders, such as atrial or ventricular fibrillation.

ROTOR
refers to the central point around which wavelets rotate during an arrhythmia.

WAVELET
is a chaotic wave of excitation in the heart muscle. During an arrhythmia, the uniform excitation wave of a healthy heart breaks apart into several wavelets that travel across the heart muscle.

www.mpg.de/podcasts/medizin-der-zukunft (in German)