Shocking Rhythms

How do jolts of electricity bring people back to life after heart fibrillations?

By LISA SEACHRIST

"Vee-fib!" the doctor cries as the heart monitor squeals an alarm: The small, erratic heartbeats it was registering have diminished into a flat line.

The emergency room nurses, doctors, and technicians tear open the patient's shirt, start cardiopulmonary resuscitation, and roll in the defibrillation machine. A technician applies a jelly to the machine's paddles and hands them to the physician.

"Clear!" yells the physician, and the emergency team steps away.

The lifeless body on the table jerks as the physician applies hundreds of volts of electricity in an attempt to jolt a still heart into beating once more.

Nothing. The flat-line warning continues to scream.

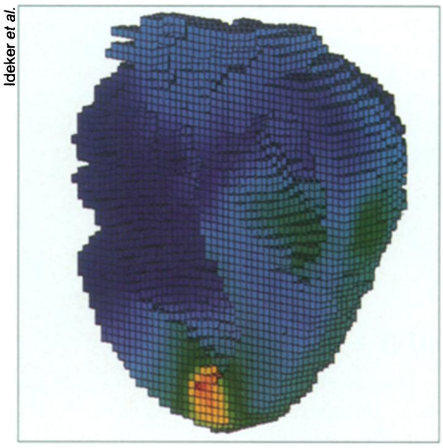
"Clear!" the physician bellows again. The patient jumps. Beep, beep, beep. The monitor sings out success as the gathered medical personnel breathe a collective sigh of relief.

Insert Ross, Green, or Lewis for any of the doctors' names, and the scene could come from an episode of television's *ER*. As familiar as we find the image of a medical team shocking a patient whose heart has stopped, the fact remains that the technique often fails. Physicians and researchers understand little about how those electric shocks can sometimes yank a heart out of impotent quiverings or dead stillness into robust, regular beats.

Much of the mystery lies in the complexity of heart muscle, where each individual cell interconnects in varying degrees with its neighbors. For years, scientists have attempted to understand how electric impulses flow through the heart's maze of cells to establish rhythmic contractions. Now, with the help of new theoretical models of the way electric currents spread in the heart and new methods of visualizing those patterns, researchers are beginning to uncover some of the heart's secrets.

"I find it fascinating that so much of the mechanism for defibrillation is still not understood," says John P. Wikswo of Vanderbilt University in Nashville.

The adult heart, a fist-sized muscle weighing less than a pound, supplies the entire body with oxygenated blood. It has four chambers: two atria—thin-walled receiving chambers capable of low-pressure pumping—and



Ideker *et al.*

This cross section of the heart shows the electric gradient produced when a catheter delivers a defibrillation shock to the bottom of the heart.

two ventricles—thick-walled, high-pressure pumps. Oxygen-poor blood from the body enters the right atrium and cycles to the right ventricle, which pumps the blood into the lungs, where it loads up on oxygen. The blood then enters the left atrium and is forced into the left ventricle, which pumps the blood from the heart throughout the body. In a healthy adult, this cycle occurs typically 72 times a minute.

Each beat of the heart arises from a synchronous contraction of the thousands of small, interwoven muscle fibers that make up the heart wall. Electric currents originating from a node in the right atrium travel along the heart's system of nerves. To stimulate the heart fibers to contract in the appropriate sequence, the impulses must also spread among the muscle cells.

These impulses sometimes fail to reach all areas of the heart in proper sequence. During a heart attack, for example, a part of the heart muscle dies; the dead tissue may impede the flow of those impulses. The muscle fibers then begin to contract independently, creating fast, erratic beats known as fibrillation.

Fibrillation in the atria causes blood to pool there and form clots, increasing the risk of stroke. When fibrillation hits the ventricles, oxygen-laden blood cannot be pumped to the rest of the body. In 4 to 6 minutes, the brain starves from lack of oxygen, and the person dies.

A very recent example is figure skater Sergei Grinkov, who "ultimately died of fibrillation that began after a portion of his heart muscle died during his heart attack," says cardiac researcher Stephen Knisely of the University of Alabama at Birmingham. Despite prompt medical attention, shocks to Grinkov's heart failed to make it beat again.

Emergency medical personnel fail to revive nearly 80 percent of heart attack victims in the United States who enter ventricular fibrillation, or vee-fib. In many cases, medical attention comes too late. In others, the electric shocks generate no response.

Surviving often means suffering repeated life-threatening episodes of fibrillation. Doctors treat those patients by implanting miniature defibrillation devices into their torsos. While those devices save lives, they are far from ideal. The defibrillation shocks themselves sometimes destroy heart muscle.

Researchers don't fully understand why fibrillation begins, much less how outside electric stimulation can restore the normal pulsing of the heart. One theory holds that the fast, erratic heartbeats of fibrillation occur when electric impulses fail to diminish as they spread through the heart. Instead, they find a way back to their starting point. An impulse reentering the same pathway causes the heart to have an extra beat. An additional impulse from a defibrillation paddle or electrode presumably stops the runaway impulse by lengthening the refractory period of the heart's cells, in which they are immune to further stimulation.

The earliest attempts to understand how external electric impulses travel through the heart were predicated on the understanding of how nerves carry electric impulses. Like heart muscle cells, nerve cells propagate electric impulses as a flow of sodium and potassium ions into and out of the cell. Stimulation above a certain threshold causes an area of the nerve cell's membrane to reverse its resting electric charge, or depolarize, as positive sodium ions rush into the negatively charged cell. The rush of sodium propagates along the cell. For all practical purposes, the nerve cell acts as a cable transmitting a signal.

Researchers initially tried to explain impulse propagation in the heart using a cable model. They predicted that wave impulses arising from an electrical shock would spread across the heart in an elliptic pattern from the region initially stimulated by the shock. But the arrangement of cells in heart muscle is very different from that in nerves. Electric waves created by sodium and potassium flowing through a membrane travel not only from cell to cell along the fiber but in three dimensions across fibers. Because the current does not flow with equal ease in all directions, determining the patterns of impulse flow among the cells requires an astronomical number of mathematical calculations.

In 1987, Robert Plonsy and Roger Barr of Duke University in Durham, N.C., suggested a simplified model of the heart that included only intracellular space and extracellular space rather than individual cells. This bidomain model initially predicted the same elliptical wave front as the previous model.

Wikswo and Vanderbilt colleagues Nestor Sepulveda and Bradley Roth speculated that to get a true picture of the heart, the model would have to include the resistances the impulse experienced in three directions—along, across, and through the fiber. "Without taking into effect the differing abilities of the current to flow inside and outside of the cell, the bidomain tells you nothing," says Wikswo.

Working with the bidomain model, Sepulveda began making predictions about the number and volume of cells immediately depolarized by a shock of negative current from an electrode called a cathode. This volume of cells, known as the virtual cathode for that shock, initiates electric stimulation of the rest of the heart. Sepulveda and Roth predicted that the shape of the virtual cathode would be like a dog bone oriented across the fibers rather than an ellipse along them.

At the same time, Wikswo observed such a dog bone pattern in a rabbit's heart by detecting the electric waves as they passed electrodes stationed near the stimulating electrode. The Vanderbilt team published these findings in the February 1991 CIRCULATION RESEARCH.

The researchers' inability to implant enough electrodes to monitor the flow of electric currents from cell to cell in the heart stymied efforts to document the phenomena they predicted. But recently developed optical fluorescent dye techniques reveal the activation of the cells and can show electric changes at many locations in the heart simultaneously.

Using the bidomain model and fluorescent dye methods, the Vanderbilt team predicted that there would be an excessively positive, or hyperpolarized, area on either side of the virtual cathode. This area, which they call the virtual anode, resists electric stimulation and fails to propagate the impulse.

Independently, Knisely also demonstrated a virtual anode. While measuring small currents in heart muscle that were not strong enough to propagate an electric signal across cell membranes, he found an area that couldn't transmit current. It was close to the site where he had applied the small shock.

Initially, he could not interpret the findings, because he "was unaware of Roth and Wikswo's work," he says. Following more precise measurements, Knisely describes his finding and interpretation in the December 1995 CIRCULATION RESEARCH.

Roth has continued his mathematical work with the bidomain model and predicts in the December 1995 IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING not only that the stimulus from a positive or a negative electrode will cause a wave to spread but that removing either stimulus will depolarize cells. Wikswo corroborates Roth's predictions in rabbit hearts in the December 1995 BIOPHYSICAL JOURNAL. "Understanding these effects may help us create better ways to defibrillate," he says.

Many researchers think that defibrillation works by lengthening the period during which the heart cells cannot be stimulated. Knisely says that understanding the virtual cathode and anode may allow researchers to find better ways to lengthen that refractory period.

That goal is still many steps away. Roth points out that "to date, all of our work has been on a single electrode, and implantable defibrillators rely on multiple electrodes."

In addition, the Vanderbilt work has been done entirely on regions of the heart in which the muscle fibers lie fairly straight. Heart muscle fibers spiral around the heart, so the models may not predict how electricity flows through the entire heart, Knisely says. Roth agrees, and both are independently modeling and looking for virtual electrode effects in the more strongly curved areas of the heart.

Knisely is also applying fluorescent dye techniques to map the heart. His current system uses 528 electrodes to monitor the fluorescence, and he hopes to expand soon to more than 1,000 electrodes.

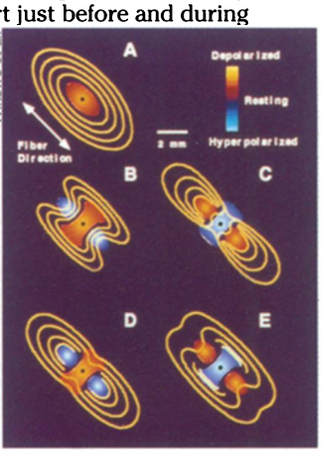
As yet, these types of investigations have provided no new treatments for patients needing implantable defibrillators. Nonetheless, researchers have produced improvements without fully understanding the mechanisms of defibrillation. Raymond E. Ideker and his team, while at Duke, discovered in animal experiments that a biphasic waveform—a lower, safer shock made up of a jolt of electricity followed by a weaker pulse—effectively defibrillates the heart. Implantable defibrillators now in use deliver this kind of shock.

Even so, Ideker notes that "it only takes 50 milliamps of current to throw a healthy beating heart into fibrillation, but to defibrillate you need 10 amps, or 200 times as much current, to bring it back to a normal rhythm."

He says that physicians are now using the equivalent of a stick of dynamite to open a door, when better techniques in the future should be able to provide a key.

Ideker and his colleagues at Alabama are mapping the electric activity of the human heart. They record data during clinical procedures, such as implantation of defibrillators, that require physicians to artificially stimulate a patient's heart.

The team now uses 36 electrodes to record the heart's activity, and the researchers plan to expand to more. By mapping the heart just before and during fibrillation, they hope to gain clues to the electric patterns that trigger the disorganized quivering.



Researchers originally thought that electric shocks would spread depolarization (red) in an elliptical pattern (A). The resulting dog bone pattern differs with negative (B) and positive (C) jolts and when negative (D) or positive (E) current is turned off.

Today, implantable defibrillators detect abnormal heart rhythms that often herald ventricular fibrillation. If gentle attempts fail to interrupt those rhythms before fibrillation begins, the devices send a large defibrillating shock to the heart. Ideker hopes that one day they will deliver instead a precise and foolproof shock that won't damage the heart.

"We are at a much higher level of ignorance today," says Ideker. "But it would be nice to find a way to use the key rather than a stick of dynamite." □