Heart Like a Wheel

A relatively simple model of electrical activity in the heart may help explain sudden coronary deaths

WHEN COLLEGE BASKETBALL STAR HANK GATHERS collapsed during a game and died 2 hours later, it was a shocking reminder that heart attacks can fell even young people and athletes in prime condition. They may not get as much attention in the press as AIDS or cancer, but heart attacks kill more people in this country than any other single cause—more than 500,000 Americans each year.

Many of those deaths are caused by electrical disturbances in a damaged heart that cause it to beat incoherently, or fibrillate. And unfortunately, the mechanisms underlying the disturbances are poorly understood. Partly because of this lack, existing treatments for heart fibrillation are crude. For instance, defibrillation, the application of electrical jolts to the heart to make it start beating normally again, works only about two thirds of the time and often damages the heart in the process of reviving it. (In Gathers' case, the team physician used a defibrillator on him shortly after he collapsed, but the machine did not save him.)

The heart's complexity has been a major stumbling block for researchers who are trying to describe how the electrical signals that control its activity originate and operate. But in the past few years, a small cadre of heart researchers has been working toward a simple, testable theory that can make quantitative predictions about heart activity. Recent experiments have verified several of the model's predictions, giving the workers confidence that they're headed in the right direction. The work should open the way, the researchers say, to better design of defibrillators and pacemakers and more effective treatment of heart patients.

Traditionally, researchers studying heart attacks have focused on how damaged heart muscles trigger irregular patterns of electrical signals. But Arthur Winfree, a mathematical biologist at the University of Arizona, advocates another approach. "From my point of view," he says, "it's hopelessly complicated to study damaged muscle. I'd rather study something simpler—healthy, normal heart muscle—and get a quantitative, testable theory."

The physiology of the normally functioning heart is well known. Its intrinsic pacemaker, a patch of special tissue at the top of the heart, sends out a rhythmic pattern of electrical signals that cause the heart to contract. A signal first moves through the atria, the two small chambers at the top of the heart, and then passes into the ventricles, the main pumping chambers. The electric signal passes from one heart cell to the next because the firing of one cell sets off the firing of adjacent cells. The ventricles also have a system of nerves called the Purkinje fibers that help speed the electrical impulse across the inner surface of the chambers. The electrical signals wash like waves through the heart muscle, and researchers can monitor their progress by inserting electrodes into the heart cells that indicate when a wave is passing.

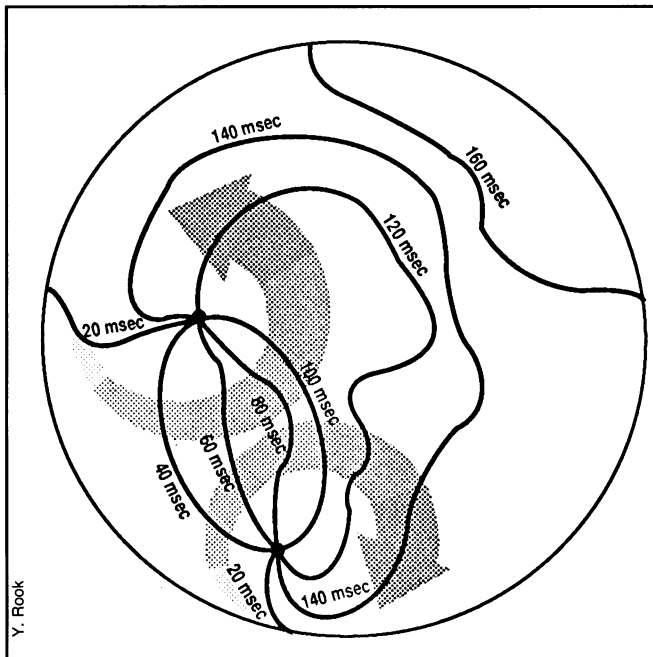
Winfree's idea was to see if he could devise a relatively simple model of the electrical activity in the heart that could predict what electrical stimulus is needed to trigger fibrillation. And, he says, he has done just that.

Winfree's model ignores many details of the heart's cellular structure and instead focuses on what he sees as the defining feature of the heart: that the cells forming the heart muscle are an "excitable medium." In essence, this means that each point in the heart can pass along an electrical signal, but after the signal passes through, the cells must rest for a short while until they recover and can fire again.

Excitable media are familiar in many areas of science, particularly in chemistry. For more than 20 years, chemists have studied the Belousov-Zhabotinsky system, in which traveling waves of chemical activity constantly change the colors of a liquid in a dish. Mathematicians have developed models to study the waves of activity in such systems, and it was Winfree's hypothesis that a similar model could explain much of the heart's electrical activity in a relatively straightforward way.

Winfree points out that waves in an excitable medium have one vital difference from the waves that form, for example, on the surface of a still pond when a pebble is plopped in. On the pond, waves always expand in circles and two waves pass through one another without interfering with each other. But in an excitable medium, once a wave has passed through, a second one cannot traverse the area until it has recovered. This means, for instance, that two converging waves cancel each other out since the areas immediately behind each wave are dead zones. It also implies a behavior that may have vital implications for understanding the heart: the waves in an excitable medium can take the form of a rotating spiral as well as expanding circles. No pond ever saw a rotating spiral wave, but the heart sees such waves.

One of the immediate pluses of Winfree's approach was that it offered a new model for tachycardia, the rapid heartbeat that is often the precursor of heart fibrillation. For many years, cardiologists have associated tachycardia with an injury to the heart in which a small patch of tissue is killed. In this case, an electrical signal cannot pass across the dead area so it must go around. Sometimes a



Double rotor. *Properly timed electrical stimuli set off a double rotating wave of electrical activity in a dog heart, viewed from the bottom. The lines indicate the positions of the waves at various times after the initial stimuli. The illustration is adapted from results obtained at Duke University Medical School.*

signal will circle all the way around the damaged tissue and end up back where it began, starting the cycle all over again, and going around and around and around, several times a second. This creates a rotating cycle of contractions in the heart that resembles fans at a football game doing "the wave." A person whose heart is doing "the wave" will have a very fast heartbeat: tachycardia.

Winfree's model implies that the heart does not need damage for a rotating wave to form. Several recent experiments have confirmed this. Jose Jalife at the State University of New York Health Sciences Center in Syracuse experimented on a 2-centimeter-square layer of sheep heart muscle kept alive in a tissue bath. With collaborators Jorge Davidenko, Paul Kent, Dante Chialvo, and Donald Michaels, Jalife used electrodes on two sides of the heart tissue to apply two stimuli timed according to Winfree's predictions. The result was spiral waves in perfectly healthy tissue, Jalife says.

More striking is a double rotating wave produced in Raymond Ideker's lab at Duke University Medical School in an intact dog heart. Ideker and student Nitaro Shibata applied two timed electrical stimuli in line with Winfree's predictions and produced two separate waves of electrical activity circling two pivot points on the heart (see figure).

What does this have to do with tachycardia in human hearts that don't get two carefully timed electrical stimuli? The connection isn't clear, Winfree admits, but the ability of healthy heart tissue to sustain rotating waves is important for several reasons. One is that it provides a simple model for studying rotating waves—one that doesn't involve damaged tissue. Second, the results indicate that it's possible tachycardia can be triggered in healthy hearts by some stimulus that has a similar effect to the electrical shocks in the lab experiments. "There are mechanisms galore that you can imagine in your armchair," Winfree says. If healthy hearts are vulnerable to tachycardia, cardiologists would want to know.

Perhaps the major implications in Winfree's rotating wave model, however, involve understanding the onset of fibrillation, which in human hearts often starts with a period of rapid heartbeat. And in the laboratory models in which tachycardia is induced by electrical stimulation, exactly the same thing happens. "The first rotating wave takes 140 or 160 milliseconds; the second one takes 120 or 140," Winfree says. "When the period gets down to less than 100 milliseconds, the waves are coming faster than the tissue can respond, and it deteriorates into fibrillation."

Such models as Winfree's provide a base line from which experimental cardiologists can study not only the normal heart but also hearts that have been damaged in a specific way. At the University of Limberg in the Netherlands, for example, Maurits Allessie has tested rabbit hearts in which he mimics the effects of muscle damage by freezing part of the heart. In cases where an entire area is killed except for the top 1 millimeter, Allessie finds that although he can induce tachycardia in the heart, he cannot push it into fibrillation. Discovering why a heart that has been damaged in this way will not fibrillate could provide insight into preventing fibrillation in humans.

At Columbia University in New York City, Andrew Wit studies rotating waves in animal hearts where a major coronary artery has been tied off to imitate the damage caused by a coronary blockage in humans. Just like humans, the animals suffer from ventricular tachycardia in the first week after their "heart attack," and just like in humans the rotating waves of tachycardia can lead to fibrillation. Wit has found that the causes of the later episodes of tachycardia are different from what triggers them right after the heart attack and that the anatomy of the surviving cells is important in determining whether an animal will have problems. He hopes eventually to develop drugs that can prevent the rotating waves from developing.

But his models tell Winfree more than what can cause a potentially fatal bout of fibrillation; they also suggest ways to improve the designs of contemporary pacemakers. Winfree calculates that the best electrodes for pacemakers would be spheres with a radius of about a quarter of a millimeter, much smaller that the size of those now in use. And, he says, current pacemakers probably use more energy than necessary, thus shortening battery life and increasing the risk of damage to heart tissue. "The theoretical calculations imply that if you make the electrode the right shape and size you can reduce the energy needed by a factor of 10," he says.

The potential for improving defibrillators is even greater, Winfree says. "What we do today [with defibrillators] will someday be considered as crude as trepanning," he predicts, referring to the ancient practice of removing a piece of the skull to let evil spirits out. The electrical jolt of a defibrillator damages the heart, often so badly that a patient whose heart starts back up will die of a second fibrillation a few hours later. The energy requirement could probably be reduced by a factor of 10 or even 100, and do the same job with much less damage, Winfree says.

Ultimately, heart researchers would like to build a device that can continuously monitor a heart's electrical activity, decide when the heart is getting dangerously out of its normal pattern, and apply the proper electrical stimulus to set it right. Although there are experimental devices now that try to do such a job, truly effective units will have to wait until researchers have a better quantitative understanding of the electrical rhythms of the heart. But once that happens, the Hank Gatherses of the future should be able to play their games without the fear that their hearts will betray them.

■ ROBERT POOL

Tweaking Molecules with Laser Light

When Keith Nelson talks about his "molecular tweezers" he doesn't mean he has a tiny tool that can physically grip a molecule and move it. But he does have the next best thing. Nelson, a chemist at the Massachusetts Institute of Technology, is part of a group of researchers that has for the first time harnessed sequences of laser pulses to push molecules around. The technique opens the way to studying molecules in configurations other than their equilibrium states, something chemists must do if they are to understand intermediate states in chemical reactions. In the future, precisely controlled laser pulses might even be used to drive chemical reactions or phase transitions in crystals.

The dream of controlling molecules with laser light goes back to the early 1960s, when lasers first became laboratory tools. One early idea was to use lasers as "molecular scissors." Since each chemical bond in a molecule has its own characteristic energies, researchers hoped that by tuning lasers to match those energies, they could put enough energy into the bond to distort it or even break it altogether. Over two decades, researchers spent a great deal of time and money pursuing this Holy Grail, to no avail. "By the mid-1980s," says Herschel Rabitz, a theoretical chemist at Princeton University, "people had decided it was an impossible problem." The difficulty is that molecules tend to redistribute the energy they absorb among many chemical bonds, making the "scissors" too blunt to do the job.

Nelson, along with MIT chemist Gary Wiederrecht and Bell Communications Research laser specialists Andrew Weiner and Dan Leaird, took a different approach in their laser experiments. As they report on page 1317, they were not trying to create a