

BY AMY MAXMEN

In a warm spring day last year, David Weisman left work mid-afternoon to take to the sky above an open field in suburban Washington.

A lifelong model airplane enthusiast, Mr. Weisman, 76, had stowed his planes in his trunk that morning and after work headed out alone to the nearby field. The next time he was seen, long after midnight, he was lying dead on the ground not far from his car, with the airplane controller in-hand and a plane beside him.

"It was completely bizarre," says Matthew Kay, a biomedical engineer at GW and Mr. Weisman's son-in-law. "We were devastated. David's death was just so unexpected."

The circumstances that day likely involved a phenomenon little understood by scientists—and yet altogether common. The death, the family believes, was due to sudden cardiac arrest.

It is not the same as a heart attack, although the terms are sometimes confused and the conditions can be linked. In a heart attack, a blockage prevents blood from reaching part of the heart muscle, killing or damaging the tissue; during this, the heart usually is beating.

In the case of sudden cardiac arrest, the heart stops. The problem here is electrical, often in the form of electrical storms in the heart that throw off the rhythm of its beat. In the chaos of these lethal irregular heartbeats, called arrhythmias, the heart is unable to effectively pump blood and quickly starves the brain and body of oxygen.

Outside of a hospital, sudden cardiac arrest strikes hundreds of thousands of people each year in the United States. For the vast majority of them, like Mr. Weisman, it is fatal in a matter of minutes.

Researchers and clinicians have a variety of ideas about what can trigger these lethal arrhythmias. One of the major risk factors is coronary artery disease, the build-up of artery-clogging plaque. If a piece of plaque becomes too large or ruptures, it can block an artery and prevent blood from reaching part of the heart, suffocating the muscle. In other words, it can cause a heart attack. And that can affect the heart's electrical system.

In the case of Mr. Weisman, the family believes a heart attack sparked a lethal arrhythmia. He had a family history of coronary artery disease and sudden cardiac death.

In a darkened room awash in green light, a preserved rabbit heart (used here as a demonstration) is positioned in Dr. Kay's imaging equipment and is viewed through a magnifying glass. During experiments, the green light is used to illuminate a dye that tracks the heart's electrical activity.

WILLIAM ATKINS

THE NEW STORM CHASERS

Inside the hunt for a trigger behind lethal electrical tornadoes that overwhelm the heart.





“What I want to know is:

Professor Matthew Kay in the lab.

Now, with the help of a recent \$1.65 million grant from the National Institutes of Health, Dr. Kay has begun recreating inside the lab these electrical storms of the heart, and mining the data for answers.

“What I want to know is: What happens in that first few minutes after an artery is blocked?” says Dr. Kay. “What causes some people to have a deadly arrhythmia and other people to only feel pain, call for help, and survive the attack?”

Equal parts biologist and engineer, Dr. Kay’s lab reflects that same powerful marriage of sciences. He holds a primary appointment as an assistant professor in GW’s School of Engineering and Applied Science and a secondary appointment in GW’s School of Medicine and Health Sciences. In his Ross Hall lab, physiology graduate student Luke Swift hails from a biomedical background, while graduate student Huda Asfour is an electrical engineer.

Asked why a machine-minded person would be interested in a lab dealing in the realm of flesh and blood, Ms. Asfour

brushes her dark curls behind her ear. The heart, she replies, is “the ultimate machine.”

The human heart beats roughly 100,000 times a day. Behind each beat is a series of precise electrical pulses that cause a pattern of muscular contractions, driving the circulation of blood and nutrients throughout the body. So mesmerizing is this life-permitting beat, it is little wonder civilizations over the centuries have waxed poetic on the heart’s enduring pulse.

When those electrical pulses are disturbed, the heart’s muscular contractions fall dangerously out of sync. In 1930, cardiologist Carl Wiggers, of then-Western Reserve University, in Ohio, demonstrated the effect when he set out to record an exposed, beating dog heart as it became arrhythmic. He delivered an electric shock to the heart and described the “fluttering, undulatory, convulsive” movements that followed.

Since that time, heart researchers have aimed to look within the heart to understand how arrhythmic electrical pulses begin and race from one section of the heart to the next.

In Dr. Kay’s lab, a fluorescent dye is used to make visible the electrical activity within the heart. Mr. Swift, one of the graduate students, points to a series of images recorded from an animal heart which shows the typical flow of electrical activity for mammals. A heartbeat begins with a burst of activity in the right side of the heart, called the atrium, where “pacemaker” cells reside. The signal spreads through the atria and down through the ventricles before it starts once more.

In an arrhythmic state, the images show a small tornado of electricity twisting in the ventricles, the most common cause of sudden cardiac arrest.

“It’s like the tuba players in a marching band suddenly start doing their own thing,” Mr. Swift explains. “That might

be kind of funny on the playing field, but it's disastrous for the heart."

The pacemaker's beat competes with one of these anomalous tornadoes; when it occurs in the ventricles—known as ventricular fibrillation, or V-fib—tissues push and pull against one another, leaving the heart in a quiver, unable to contract as a single unit to pump blood.

How do these anomalous electrical tornadoes arise? Dr. Kay thinks it may have to do with the return of blood to heart tissue that's been starved by a blocked artery, whether the flow is returned by a surgeon removing the obstruction or by body chemicals that widen blood vessels. Specifically, Dr. Kay thinks the problem could be when a blockage is not completely cleared and blood is only partially restored.

This situation, known as low-flow reperfusion, could be one cause of deadly electrical mishaps, he says.

In simulating this effect, he says, they've seen that when pinched-off arteries are partially reopened, blood trickles back in to the starving heart muscle, and the first cells to receive this nourishment "enter a mode of hyperactivity and beat like crazy."

If low-flow reperfusion is causing the electrical system to misfire, then it could be that the people making it to the hospital and surviving a heart attack are the ones with the worst artery clogs—ones that don't allow any reperfusion until a surgeon goes in and clears the blockage completely.

These chaotic storms are "such a big problem," says Marco Mercader, a clinical electrophysiologist at GW with whom Dr. Kay consults. "We need to understand them better so we can develop ways to treat them. Dr. Kay's work to understand the basic science is extremely important."

Stanley Nattel, a cardiologist and

alive a heart taken from a rat or rabbit, and to keep it operating much the same as if it were still inside a warm body.

"What sold me on this system is that the heart is working under the most physiological conditions possible," says Dr. Kay. "It's now representative of individuals who quite suddenly died as they were just mowing the lawn or flying a model airplane."

In the small room devoted to their imaging system, a rat heart is hanging amid the tubes keeping it alive. Two LED lights and two high-speed cameras are aimed at it, poised to record aspects of the heart's electrical and chemical activity.

With steady hands, Mr. Swift inserts a tube no thicker than a string into one of the heart's main vessels. He then connects the tube to a high-precision pump, which can be used to cut off blood supply and model different rates of reperfusion.

What happens in that first few minutes after an artery is blocked? What causes some people to have a deadly arrhythmia and other people to only feel pain, call for help, and survive the attack?" —Matthew Kay

There is some evidence to suggest this might be the case. Studies on dog hearts indicate that partial restoration of blood flow can be deadly. And in a clinical setting, partial restoration of blood flow—for example, from a partially successful angioplasty—has been shown to lead to an arrhythmia, which doctors can catch quickly enough to shock the heart back into the correct rhythm.

Exactly how low-flow reperfusion might trigger those competing electrical tornadoes, no one is sure. But Dr. Kay's team is poised to find out.

"We've developed a model to reproduce low-flow reperfusion in the lab, and we've developed the instrumentation to study how it may cause little, alternative 'pacemakers' to form," Dr. Kay says. "We're now at the forefront of understanding acute lethal arrhythmias."

director of the electrophysiology research program at the Montreal Heart Institute Research Center, says it's not clear to him how often low-flow reperfusion happens. But he's quick to add that sudden cardiac death remains an important and largely unexplained phenomenon, and that research on little-understood situations like low-flow reperfusion is worth the effort.

"We need to think more deeply into what causes sudden death," says Dr. Nattel, "because even though treatments for heart disease have tremendously improved, people keep getting sick, and many people die."

In January, the team finished assembling the system that it had been building for years.

The set up—a nest of tubing, pumps, and cameras—is uniquely able to keep

"We acquire a lot of data," says Ms. Asfour, the engineering graduate student. And she would know—the complex task of processing and weaving together that data falls to her, which she does using computer code she's written.

Ms. Asfour must pool three sets of data gathered by the imaging system: data from an electrocardiograph that monitors changes in the heart's rhythm (the familiar tracing of peaks and valleys); high-speed images of the heart's electrical activity, visible via injected dye; and high-speed images of a compound called NADH, which indicates where tissue is deprived of oxygen. Both the dye and the NADH are visible because they fluoresce under the right wavelengths of light, provided by the LEDs.

One of her biggest challenges has been to synchronize the camera shutters so each snaps photos at the same time.

To process the data and make it useful to the team, she uses her computer software to properly align images from each camera so they can be stitched together into movies—no small task when tracking a beating heart. The two movies then also need to be synced so that, say, a specific spot on the heart’s ventricle 10 seconds into the NADH movie can be compared to the exact same point at the same moment in the electrical activity movie.

So far, Dr. Kay’s team has found that during low-flow reperfusion blood returns to choked-off areas of the heart, but it happens unevenly, creating what seems to be a patchwork of different oxygen levels across a small area of tissue.

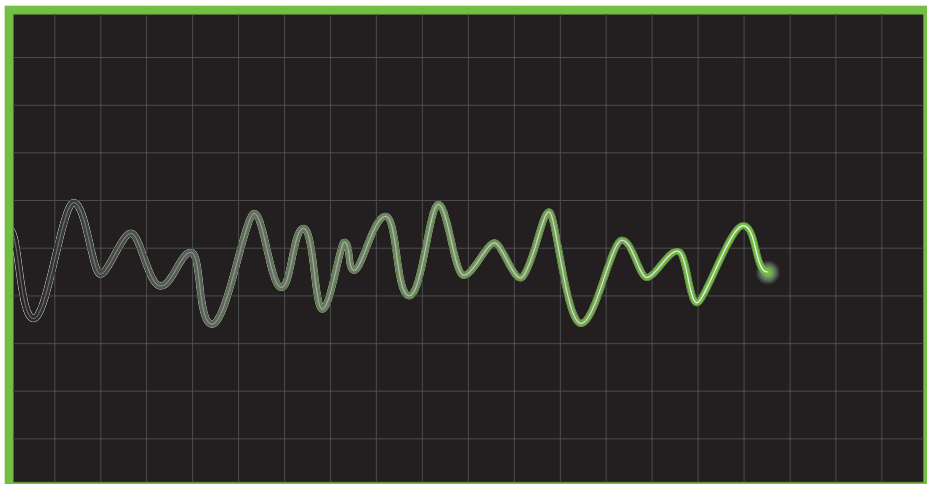
Earlier research by Dr. Kay and collaborators, including GW cardiac physiologist Narine Sarvazyan, had found that it is at the borders of these differentially oxygenated areas where tornadoes of electricity can originate. Those findings agree with other studies showing that erratic beating begins at these borders.

Dr. Kay’s current team also was one of the first to find that arrhythmic beating lasted longer in the low-flow situation, perhaps because the low flow infuses the tissue unevenly and creates many more border zones.

To further explore the team’s hypothesis, Ms. Asfour and engineering undergraduate student Matthew Wilkins are measuring the voltage of small groups of heart cells they’re culturing in Petri dishes the size of a quarter. At the bottom of each dish is a tiny metal grid, consisting of almost invisibly thin electrodes.

Mr. Wilkins and Ms. Asfour can record the effects that different conditions have on the electrical state of the cells by, for example, taking oxygen away from the cells and observing how the flow of electrical charge changes.

“The first time I saw these heart cells beating on their own I got goose bumps,” Ms. Asfour says. “It was a wonderful feeling to see the cells beating in synchrony, just as they do in the heart.”



Sample electrocardiograph tracings show the electrical activity of a normal heartbeat (top) and the chaos of ventricular fibrillation (bottom), which renders the heart out of sync and unable to pump blood.

In March, Dr. Kay’s team began working on another angle of sudden cardiac death. Beyond understanding the arrhythmias that cause it, Dr. Kay’s lab is aiding an effort to prevent them in the first place.

In a collaboration led by GW’s Dr. Sarvazyan, the team is working with Gordana Vunjak-Novakovic, a biomedical engineer at Columbia University, whose lab is growing cardiac muscle fibers from stem cells. Drs. Sarvazyan and Vunjak-Novakovic are testing whether these muscle fibers could be used as a “bandage” over heart tissue that’s been damaged by blood loss from a heart attack.


Dr. Kay’s lab then will use its imaging and perfusion techniques to test how these bandaged hearts respond electrically to a simulated heart attack, chiefly whether they carry any added risk of sparking a deadly arrhythmia.

In the meantime, though, the mysterious tiny storm fronts of arrhythmia

continue to loom for people with coronary artery disease. Dr. Mercader, Dr. Kay’s clinical collaborator, explains: “When people have a heart attack because of a blocked blood vessel, we remove the clot but I don’t think we are always 100 percent effective at removing everything.”

For instance, he says, if plaque buildups exist deeper down in the branches of an artery they may create “sluggish” blood flow that can elevate a person’s risk of ventricular arrhythmias.

For Dr. Kay and his team, the hope is that studying low-flow reperfusion will shine some light on the origin of lethal arrhythmias. “People with advanced, but undiagnosed, coronary artery disease are sometimes called ‘the walking dead,’” Dr. Kay says, “because they probably have a couple of major clots but do not learn about them until it’s too late.

“We’re very excited to be working on this enormous problem,” he says. “And we’re just getting started.” 

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