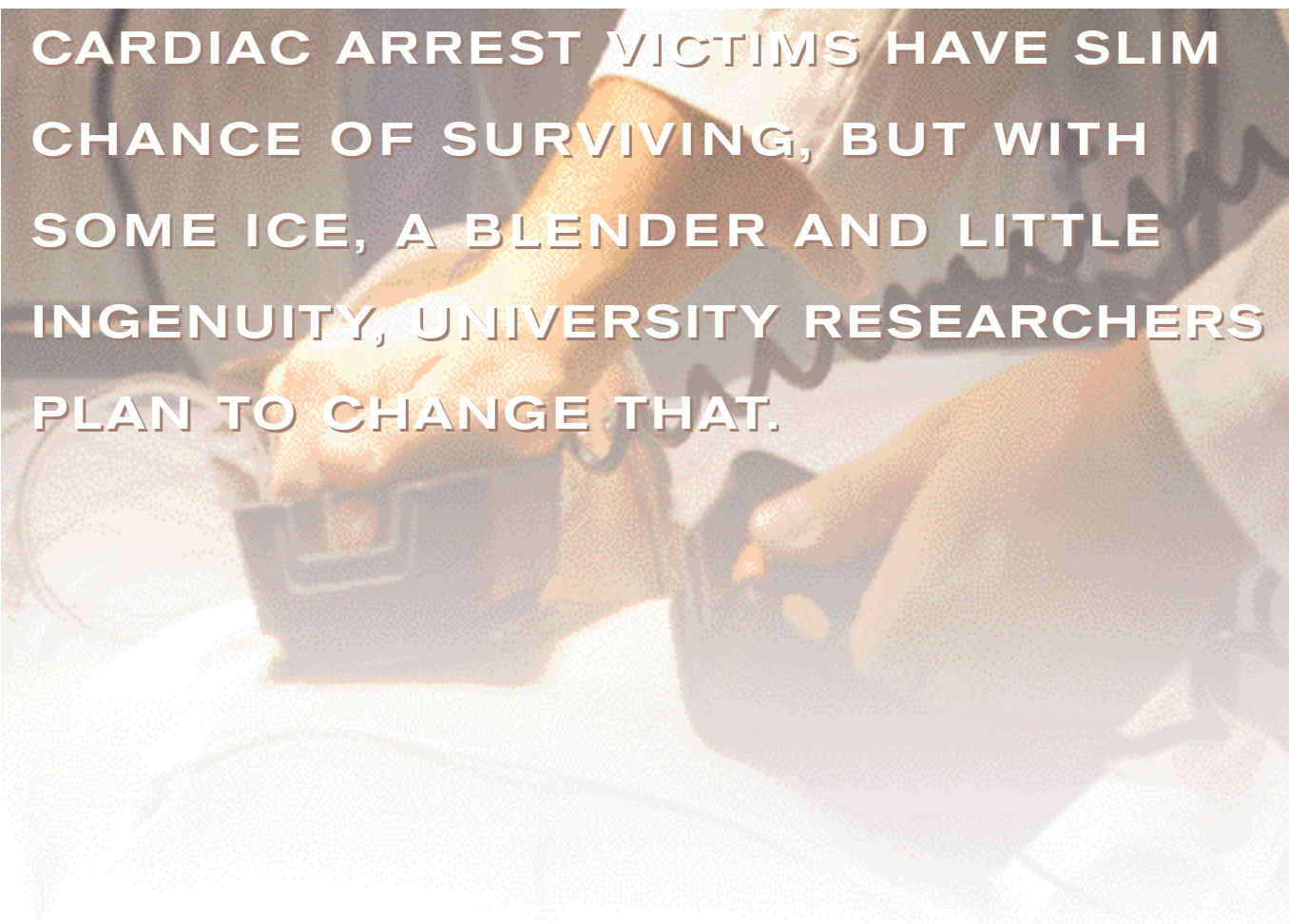


When the heart stops beating

BY YUDHIJIT BHATTACHARJEE



CARDIAC ARREST VICTIMS HAVE SLIM CHANCE OF SURVIVING, BUT WITH SOME ICE, A BLENDER AND LITTLE INGENUITY, UNIVERSITY RESEARCHERS PLAN TO CHANGE THAT.

IN THE COLLECTIVE CONSCIOUSNESS OF HUMANITY, across cultures and time, no event is more emblematic of death than the ceasing of a heartbeat, the sudden conquest of silence over the rhythmic sound of life. When the heart stops beating during cardiac arrest, it no longer pumps blood to the brain or other vital organs. As time ticks by, the body's life-support processes fail one by one, and death marches in.

That fatal sequence of events plays out in more than 450,000 victims of sudden cardiac death in the United States every year. Despite advances in emergency medicine and cardiopulmonary research, the survival rate of patients who suffer cardiac arrest remains less than 5 percent.

Lance Becker and Terry Vanden Hoek dream of erasing those dismal statistics from future handbooks of the American Heart Association, or at least replacing them with less frightening numbers.

The medical professors and their colleagues at the Emergency Resuscitation Center (ERC) at the University of Chicago are developing ways to bring cardiac arrest victims back from the brink of death. The treatments could save more than a fifth of cardiac arrest victims — or an estimated 100,000 American lives a year — and could benefit victims of trauma, heart attack, stroke and brain injury as well.

“If we could find a way to stop or at least slow the cell damage before it becomes irreversible, we could save thousands of lives,” says Becker, the ERC's director and one of the main investigators in the project.

The first challenge turned out to be finding the right people: scientists who could take their research from the test tube to the patient, or from “bench to bedside.” This forced the ERC project to pioneer cross-disciplinary collaborations at the overlapping edges of traditional fields.

In addition to physician-scientists from the ERC, the research team includes engineers at Argonne National Laboratory as well

as university specialists from cardiology, pulmonary critical care, cardiothoracic surgery, plastic surgery, anesthesiology, neurology, pediatrics, radiation/oncology, veterinary medicine, physics and chemistry.

Begun with an initial grant of \$50,000 from a grateful cardiac arrest survivor, the project has garnered more than \$11 million in funding from the National Institutes of Health as well as various foundations and corporations — all focused on the unique biological challenges of cardiac arrest and restoring life.

Within minutes of sudden cardiac arrest, blood stops flowing to the patient's brain. Cells in the brain and the heart begin to suffer; at first, injury, but then as time passes, irreversible damage. Even when blood flow is restored after this stage by pumping the chest or by delivering a shock to the heart, too often the patient fails to recover.

The research team aims to change that with a two-pronged approach. The first strategy involves prolonging the ability of the heart and brain to survive without irreversible cell damage; the second is preventing damage to heart and brain cells when blood flow is restored.

In developing the first strategy, the scientists have taken a clue from Mother Nature. New research indicates that cardiac arrest survival can be improved with hypothermia — the dropping of body temperature. Since cooling seems to offer protection to the heart and the brain, the researchers figured that one way to shield both organs from fatal injury would be to cool them within minutes of cardiac arrest.

To achieve this rapid cooling, ERC researchers along with Argonne engineers have developed a technique that involves pumping cold slurry — a slush of salty ice crystals — into a patient's veins or targeted organs, such as the stomach or lungs, where blood that flows to the brain and heart is cooled rapidly. Their goal is to create a slurry-delivery device that non-medically trained people would be able to use to keep a cardiac arrest



Argonne engineers have created highly fluid ice slurries that can pass through small-diameter tubing for quick delivery to cardiac arrest victims. Normally, the slurry contains small, rough ice particles (far left) that move sluggishly through a funnel. By altering the crystals structures from angular to smooth, globular particles (left), the ice passes quickly and easily through a funnel, a small medical tube or a patient's vein.

Photos courtesy of ANL



Lance Becker (right), professor of emergency medicine, is among the many scientists from a dozen disciplines who are working to increase the survival rate for cardiac arrest victims. Also pictured is research technician Travis Anderson

Photo by David Joel



Argonne engineers Ken Kasza (left) and John Oras prepare to test another batch of ice slurry.

Photo by David Joel

patient in a more viable condition while the patient is being taken to a hospital.

The scientists are not only testing varying slurry mixtures and creating new cooling equipment, but they are also conducting animal studies to test the cooling power of the slurry. In a typical experiment, the slurry is administered into the animal, and researchers measure how quickly the temperature drops in different parts of its body.

A FISTFUL OF SLUSH

Under bright fluorescent lights in a room packed with machines, a team composed of medical doctors, engineers, veterinarians and research technicians prepare to test a new coolant. With nearly a dozen people needed for a single experiment, the scientists — donned in protective gear, white aprons and yellow rubber gloves — scurry to prepare the data collection and sterile instruments. Some check the temperature readings from critical points in a pig's body, while others pour a slush of salty ice crystals into a tube inserted in the animal's stomach.

"Brain temp down 3 degrees centigrade," Becker shouts to Vanden Hoek, the ERC's co-director and another main investigator in the project.

"Feel that," Vanden Hoek says as he scoops up a fistful of slush from a beaker and plops it into the palm of a colleague. The cold penetrates through the glove in a flash. The colleague winces, grins and nods approvingly.

The objective for the afternoon is to cool the brain and interior of the pig and to study how quickly it can be done via the stomach.

This is one in a series of animal experiments that the researchers are conducting to measure the cooling efficiency of their slurry. In human patients, most likely the coolants would be both injected into a vein and delivered by a tube into the stomach. The experiments are designed to provide a more detailed understanding of how the body cools, the differing

rates of cooling in various organs and the mechanism of temperature adaptation.

When the project began in 1999, Becker and Vanden Hoek knew they wanted an efficient cooling technique. The challenge was to find a way to cool rapidly enough to induce hypothermia in the heart and brain within minutes.

"Within moments of a cardiac arrest, the pace of blood flow inside a patient's body drops to a minimal level," Becker explains. "That makes it even harder to bring a temperature down rapidly since blood is what carries heat from one part of the body to another."

The group first considered cooling blankets developed by NASA for its space missions. "The rate of cooling was nowhere near what we needed," Vanden Hoek says. "You could wrap one of those blankets around and be freezing at the skin, but your heart and brain would still be warm."

"We knew the problem we had was really an energy engineering problem," Becker says. "We needed somebody who could move energy around."

That thinking led the researchers to turn their attention to ice slurry developed by Argonne engineers for industrial air conditioning. It consisted of fine ice crystals that could be pumped through tubes like a liquid. Could this substance be injected into the bloodstream of patients to cause quick cooling?

It seemed like a workable idea, certainly one that the ERC doctors thought was worth exploring. "The slush had two things going for it: It was mostly water, which the body can accept without too many problems, and it could pass through standard medical equipment like an intravenous tube," Becker says.

Among the issues foremost in the minds of the ERC researchers were safety and practicality. The slurry had to be completely nontoxic, and when it melted it had to be the same as a typical saline solution — 0.9 percent salt solution.

So the ERC scientists made a trip to Argonne. When they first sat down for discussions with the engineering team, it seemed like a mistake. "We spoke two different languages," Becker recalls. "My fellow researchers from ERC and I were talking cardiac arrest, and the folks from Argonne were talking energy coefficients."

GETTING THE MIXTURE JUST RIGHT

In another corner of the lab, Ken Kasza, John Oras and Jeff Franklin — all Argonne engineers — are churning a concoction of ice, salt and water in a blender. Their equipment looks unimpressive — an icebox, bottles of chemical salts and saline solution, calibrated jars and a blending machine. From a distance, the engineers seem like three apron-clad chefs whipping up a smoothie.

Oras takes a scoop of coarse ice out of the freezer, dumps it into a jar and adds measured amounts of salt and water. While Kasza stirs the mix, Oras has his gaze fixed on a stopwatch dial. "Now," he says, after about 50 seconds, and Kasza brings his stirring to a halt.

The mix is transferred to the blender. After half a minute of blending, the men inspect the slush. "More chemical," Kasza says. Oras switches the blender on for a second time. The duration is shorter than the first.

"We don't want to crush the ice any further," Kasza explains. "We just want to melt the edges to smooth out the ice crystals."

During the past decade, Kasza and his colleagues at Argonne have churned out gallons and gallons of this stuff — mainly with the goal of cooling large buildings efficiently. The slush they produce this afternoon will end up in the pig. Sometime in the future, the same kind of slush may course through the veins of a cardiac arrest victim, offering a fresh lease on life.

The Argonne team is developing its slurry-making paraphernalia into a portable device. "It'll be a black box. You press a button and the machine will pump out slurry," Kasza says.

Lifesaving Access

Scientists from Argonne National Laboratory and University of Chicago's Emergency Resuscitation Center (ERC) say their ice slurry-producing appliance that rapidly cools a patient's body could become indispensable equipment not only in hospitals and health care centers but also in ambulances and the battlefield. The cooling device they envision would be simple enough for paramedics or emergency medical technicians with limited medical training to use in emergencies to save lives.

Researchers already are studying whether public access to resuscitation equipment improves the speed of treatment and odds of survival for victims of sudden cardiac arrest.

The Public Access Defibrillation project, sponsored by the National Institutes of Health, is underway in 25 U.S. and Canadian cities. Begun two years ago, the project examines whether convenient access to defibrillating machines at public places such as malls, airports and theaters significantly increases survival in cardiac arrest victims.

As part of the study, ERC has trained more than 1700 volunteers around Chicago to use an automatic external defibrillator (AED), a machine capable of reviving a failing heart by delivering a mild shock. A similar number of volunteers has been trained to perform cardiopulmonary resuscitation (CPR), the traditional method used by medical personnel to save heart attack victims.

"We know that rapid use of an AED can save lives," says Lance Becker, who is principal investigator of the study in Chicago. "The question is whether having these devices readily available at different locations — apartment buildings, conference centers, train stations and so on — can save more lives than cardiopulmonary resuscitation."

The study is scheduled to end in September, after which data from all cities will be sent to the research headquarters. Analysis will compare survival rates at sites where volunteers were trained to perform CPR but lacked defibrillator access with rates at sites equipped with AEDs and volunteers trained to use them.

The research will help frame "informed public policy regarding the use of defibrillators by non-medical volunteers," says Anne Barry, a registered nurse at the University of Chicago Hospitals and a study coordinator.



Physician-scientist Terry Vanden Hoek applies lab research findings to ongoing ERC experiments on animal models. Such experimental treatments may one day benefit victims of sudden cardiac arrest, as well as other traumas.

Photo by David Joel

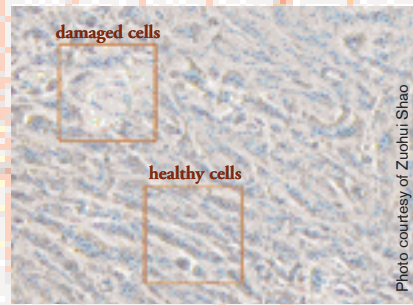
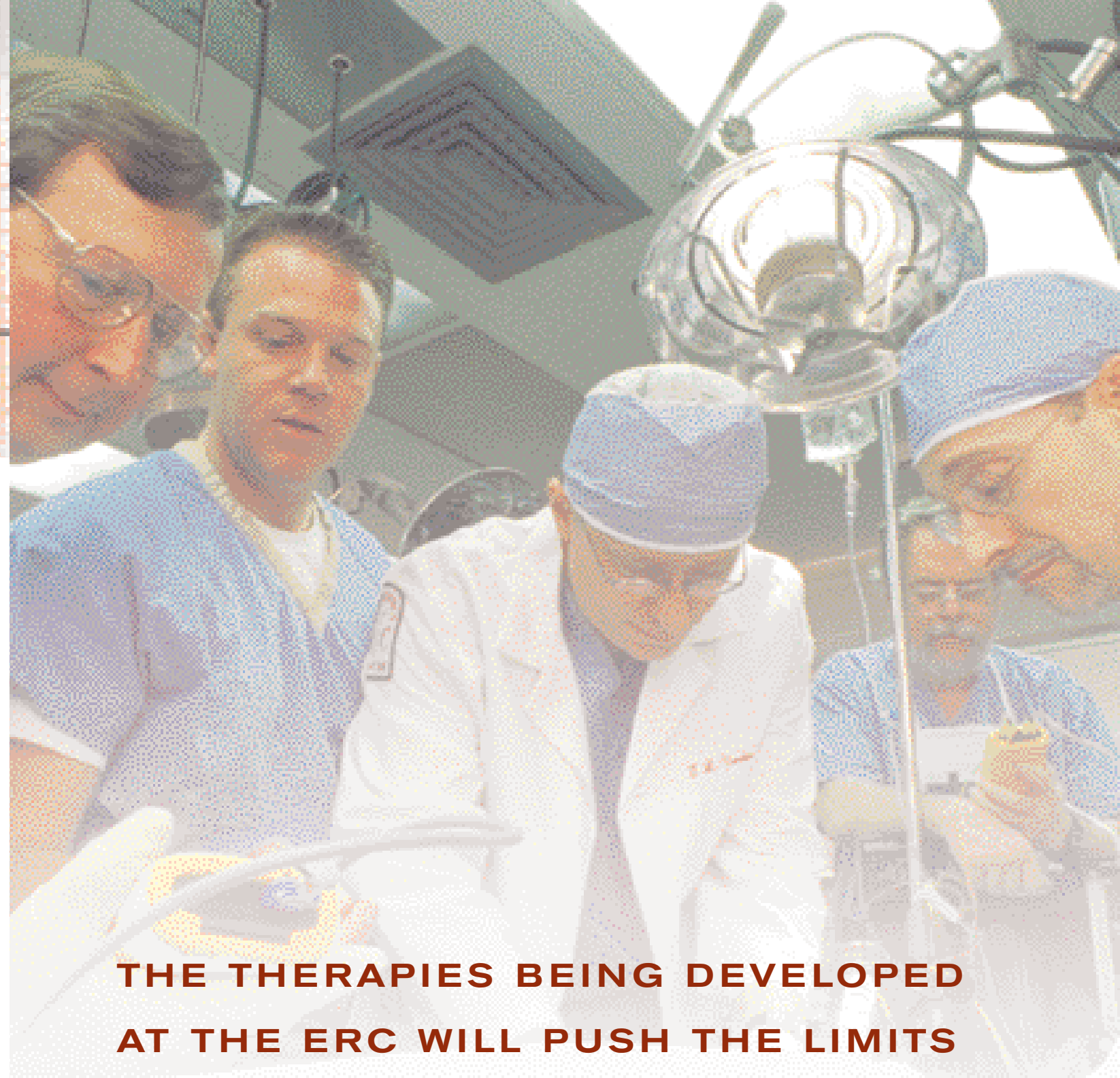


Photo courtesy of Zuohui Shao

Using heart cells from chickens (left), researchers simulated cardiac arrest and found that reintroducing oxygen damaged cells.



THE THERAPIES BEING DEVELOPED AT THE ERC WILL PUSH THE LIMITS FOR RESTORING LIFE FOR THOUSANDS OF VICTIMS, EVEN AFTER THEIR HEARTS HAVE STOPPED BEATING.

Together with the Argonne group, the ERC researchers envision a future in emergency medicine where people with little or no medical training will be able to improve the odds of survival for cardiac arrest victims by hooking them up to a slurry-producing appliance and simply switching it on. (See related story on page 31.)

A COUNTERINTUITIVE FIND

Alongside their work on cooling, Becker, Vanden Hoek and colleagues are working to unravel the cellular events that take place during cardiac arrest.

Zuohui Shao, a senior research professional with ERC, is part of this effort. Inside the tidy, well-lit lab that she runs, multiple rows of small dishes sit neatly on glass shelves inside a cabinet. In each dish lies a layer of beating heart cells.

Each fragment is a cluster of cardiac cells that throb rhythmically, like an independent heart. Seen under a microscope, the cells expand and contract at regular intervals, presenting a haunting, surreal image of life.

Two days a week Shao extracts these cells from fertilized eggs. The cells serve as models for understanding what goes on at the cellular level in the heart during a cardiac arrest, and later when blood flow is restored.

Vanden Hoek and his colleagues have spent the past several years inducing cardiac arrest in heart cells taken from mice and chickens and studying the events that follow. In 1996, the researchers made a startling discovery: They found that heart cells starved of oxygen — or induced with ischemia, the condition that occurs during cardiac arrest — seemed to suffer greater injury when oxygen was brought back to them than when it was taken away.

“It was totally counterintuitive,” Vanden Hoek says. “These cells are gasping for air, so you expect them to thrive when they get air. But instead, they die quickly.”

The finding meant that reperfusion, or restoration of blood flow — which had for decades been thought to be the most important step in resuscitating cardiac arrest victims — posed an equivalent if not greater risk to the patient than the oxygen-starved phase.

In later experiments, Vanden Hoek and his colleagues found that cell death was reduced by 60 percent if the temperature of the cardiac cells was lowered from 37 degrees Celsius to 25 degrees Celsius immediately after reperfusion. Cooling the cells just before reperfusion offered them even better protection, decreasing cell death by 73 percent.

“What these experiments are telling us is that the key to saving cardiac arrest victims might lie in the conditions under which blood flow is restored,” Vanden Hoek says. “How quickly you cool the patient’s organs, for instance, and when you decide to perform reperfusion could determine the patient’s chances of survival.”

In addition to cooling, the ERC group is investigating other strategies to prevent and reverse heart cell injury following cardiac arrest. One involves monitoring the action of free radicals, which are produced during both ischemia and reperfusion. Another involves collaborating with researchers at the university’s Tang Center for Herbal Medicine Research to investigate the potential of Chinese medicinal herbs, such as huang qin, that might prevent oxidant damage associated with low blood flow.

In an adjoining laboratory, ERC researcher Kimm Hamann is attempting to unravel the programming that lead cells to commit suicide, or apoptosis, during ischemia and reperfusion. In recent laboratory tests, researchers have found various drugs have the potential to prevent apoptosis.

“We know there is no single magic bullet to save victims,” Becker says. But taken together, he says, the therapies being developed at the University of Chicago and Argonne have fantastic promise and will push the limits for restoring life for thousands of victims, even after their hearts have stopped beating.

For more information about the Emergency Resuscitation Center, access <http://errc.bsd.uchicago.edu>.