



COLD RELIEF

TWO PHILADELPHIA DOCTORS ARE CHAMPIONING AN UNCONVENTIONAL NEW TREATMENT FOR KEEPING CARDIAC-ARREST VICTIMS ALIVE, WITH AS LITTLE BRAIN DAMAGE AS POSSIBLE: JUST GIVE THEM HYPOTHERMIA

BY MELINDA WENNER PHOTOGRAPHS BY JOHN B. CARNETT

AT 3 P.M. last June 22, Pam Barco's heart stopped. The 46-year-old ER clerk at the Children's Hospital of Philadelphia was near the end of her shift when she felt dizzy, put her head down on her desk, and suddenly stopped breathing. A nearby co-worker saw Barco slump over and shouted, "Staff emergency!" Minutes later, a dozen doctors and nurses surrounded Barco's body. They shocked her with a defibrillator. No response. They shocked her twice more. Nothing. Then: Beep. Beep. Beep.

On TV, this is when everyone breathes a sigh of relief. In real life, though, 9 out of 10 cardiac-arrest patients whose hearts are restarted end up dying in the hospital; of the survivors, one out of eight suffers permanent brain damage. Every minute that the heart isn't pumping starves the brain and other organs of oxygen, deprives their cells of energy.

Although Barco's heart was beating, her blood pressure was dangerously low, and she wasn't getting enough oxygen. Doctors inserted a breathing tube. When she was stable enough to be moved, they wheeled her next door to the University of Pennsylvania hospital and up to the cardiac-care unit on the eighth floor.

Nurse Jamie Weller had everything set

up. First she gave Barco a sedative to knock her out, and then another drug that paralyzed her so she wouldn't shiver. She hooked Barco's IV up to a bag of 35°–40°F saline and wrapped her legs and torso in what looked like bubble wrap with cold water flowing through it. By the morning, Barco's body temperature was 91°, cold enough that she officially had hypothermia, just as the doctors intended. She stayed like that for 24 hours.

Barco was lucky. She happened to collapse next door to the Penn Center for Resuscitation Science, where doctors Lance Becker and Benjamin Abella are convinced that a procedure that sounds like torture would in fact increase Barco's chances of surviving, while minimizing brain damage. The treatment is called therapeutic hypothermia, and it's based on the idea that what damages tissue in the heart and brain isn't the heart stopping, but rather its sudden restarting and the destructive natural reactions that occur when the oxygen comes back—unless the body is cold enough to slow the process. Two clinical trials in 2002 showed that cooling resuscitated patients within four hours of defibrilla-

tion increased their survival rate by 20 percent, even if they had been clinically dead for as long as an hour. A more recent study at the University of Pittsburgh School of Medicine, which has been using the technique for five years, showed that among certain groups, cooling doubled the number of survivors.

Yet many people have never heard of therapeutic hypothermia, and few doctors are using it. For all its promise, inducing controlled hypothermia is a complex procedure that requires doctors to develop and learn a protocol, buy special equipment, and train staff from multiple departments—all for something that sounds entirely counterintuitive. It's also a procedure that punishes imprecision: Cool a patient a few degrees too far, and you could stop her heart again.

But the U. Penn doctors who are the treatment's biggest proponents say that not only should the procedure be standard, but that doctors should go even further. They're running studies on mice and pigs that suggest that it's better to start cooling *before* restart-



ing the heart. Soon they will start testing this idea on humans with a machine that would let emergency-medical technicians run a “frozen slushie” IV into patients. In Becker and Abella’s ideal world, at least 15 percent of the 166,000 people who have a cardiac arrest outside the hospital every year will be frozen and paralyzed before they even reach the ER.

WHY COLD WORKS

Becker, the director of the Penn Center for Resuscitation Science, seems like a friendlier version of TV’s Gregory House—a detective in a white coat and scrubs. As a medical resident in Chicago in the early 1980s, he found himself attracted to the ER (to the “really, really sick patients,” he says) because he found the task of deducing what was wrong with them more interesting than the treatment.

After spending his early career at Michael Reese Hospital in Chicago, Becker started questioning the published statistics about cardiac arrest. (A heart attack is what happens when blood flow to the heart is restricted; cardiac arrest means the heart has suddenly just stopped. The latter is much rarer.) He had read that 18 percent of patients survive, but, he says, “I knew after working in the emergency department for a while that [that figure] wasn’t anything close to reality.” So in 1989 he analyzed data from hospital and paramedic reports for more than 3,000 local cases. He found that the rates were off by a factor of 10—only 1.8 percent of cardiac-arrest victims in Chicago lived. (The earlier studies were performed in small cities, where patients were typically reached more quickly and were more likely to receive CPR from a bystander.) Three years later, a study in New York City came up with a similar number: 1.4 percent.

But why were people dying even after their hearts had restarted? The question nagged at Becker as he began his assistant professorship at the University of Chicago Hospital in the early 1990s. Scientists believed that when the heart stopped pumping oxygen-rich blood, cells started to die. If that were true, then cells should fare better when the heart starts pumping again. “What we saw was almost the opposite,” he says. Becker

watched heart cells under a microscope as he deprived them of oxygen for an hour. Then he gave them oxygen, or “reperfused” them, for another three hours. Only 4 percent of the cells showed damage initially, but 73 percent showed signs of injury immediately *after* the oxygen came back. He realized that there was something destructive about the sudden recirculation of oxygen.

Two more years of experiments revealed one of the key mechanisms. Tiny organelles called mitochondria use oxygen to produce energy, and they do so very carefully—add or subtract an electron from an oxygen atom at the wrong time, and it becomes a free radical, an ion powerful enough to damage cell structures and mutate DNA. Cells have systems in place to prevent these dangerous chain reactions, and to maintain other delicate ion balances, but without oxygen those systems break down. When oxygen flow returns, the mitochondria start producing hordes of free radicals; other cellular ion levels also go awry. The injured cells start dying, and in response, the immune system releases chemicals that worsen the effect. The problem is most pronounced in the heart and the brain, which use more oxygen than other organs.

“THERAPEUTIC HYPOTHERMIA SEEMS LIKE A GOOD IDEA,” SAYS BARCO’S CARDIOLOGIST. “BUT THERE ARE JUST SO MANY VARIABLES.”

Around the same time, Becker made another surprising observation. As all scientists do, he kept his cells in incubators at 98.6°. But when he left them out for a few hours and they cooled a bit, “we found that there were differences in rates of cell death,” he says, because the mitochondria and the immune system aren’t as active at low temperatures.

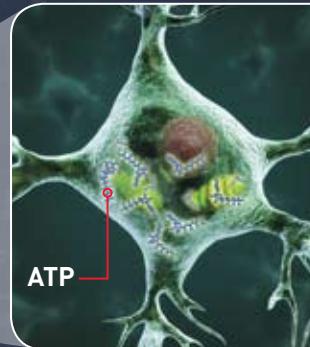
Although doctors had theorized as far back as the 1950s that cooling patients after cardiac arrest could help them survive, Becker’s reperfusion research was one of the first good explanations of why it worked at the cellular level. “But we had to ask ourselves this very difficult question,” he says. “Did what we were seeing in cells translate to people?” So after publishing his findings, he began experimenting on mice and, by 1999, pigs. All the results were consistent with what he’d seen in cells, and with what other researchers were finding. In 2002, doctors in Europe and Australia published the first human studies, showing that the treatment saved one out of every five patients who would have otherwise died. By 2003, Becker was using the treatment on his own patients in Chicago. In 2005 he and Abella even helped convince the American Heart Association to endorse hypothermia in its recommended guidelines. Today, ambulances in New York, Miami, Boston and Seattle will take cardiac-arrest victims only to hospitals that have cooling protocols. Freezing your patients has gained official acceptance.

THE TROUBLE WITH HYPOTHERMIA

But if the AHA endorsement represented a mainstreaming of the treatment, it didn’t result in widespread use, especially outside those urban areas. According to a 2006 survey by Abella, just 26 percent of U.S. emergency-room and cardiology doctors had ever cooled a patient after cardiac arrest. The guidelines advise doctors to use cooling, but they don’t go into detail about how best to do it. In addition,

HOW A COLD HEART CAN SAVE YOUR BRAIN

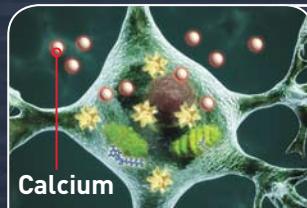
In **therapeutic hypothermia**, doctors intentionally cool cardiac-arrest patients to 91°. The idea is to slow the cellular reactions that can cause brain and other organ damage after the heart restarts. The physician Lance Becker found that giving oxygen to cells that had been starved while the heart was stopped causes the cell to produce too many free radicals, which sends it into suicide mode.



Usually, cells consume oxygen and glucose to produce the energy molecule ATP. Below, what happens to a cell when cardiac arrest cuts off the oxygen and the body is resuscitated, either normally or cooled.



WARM



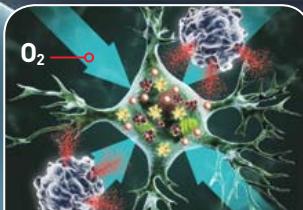
Calcium

When the cell's ion pumps shut down, the cell immediately begins hoarding excess calcium ions and dangerous free radicals.

COOLED



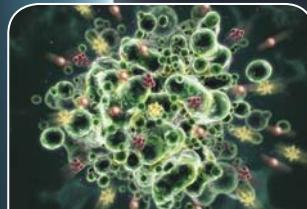
If doctors cool the patient after cardiac arrest, the cell's free-radical and calcium levels remain relatively low.



For reasons poorly understood, body-temperature cells with disrupted ion levels provoke the immune system to attack the cell.



With normal ion levels, the cell does not alert the immune system to any major problems when the oxygen returns.



Mechanisms inside the cell kick-start various processes that cause it to rip itself apart, essentially committing suicide.



The chilled cell is able to withstand the shock of restarting cellular metabolism, and it eventually recovers function.

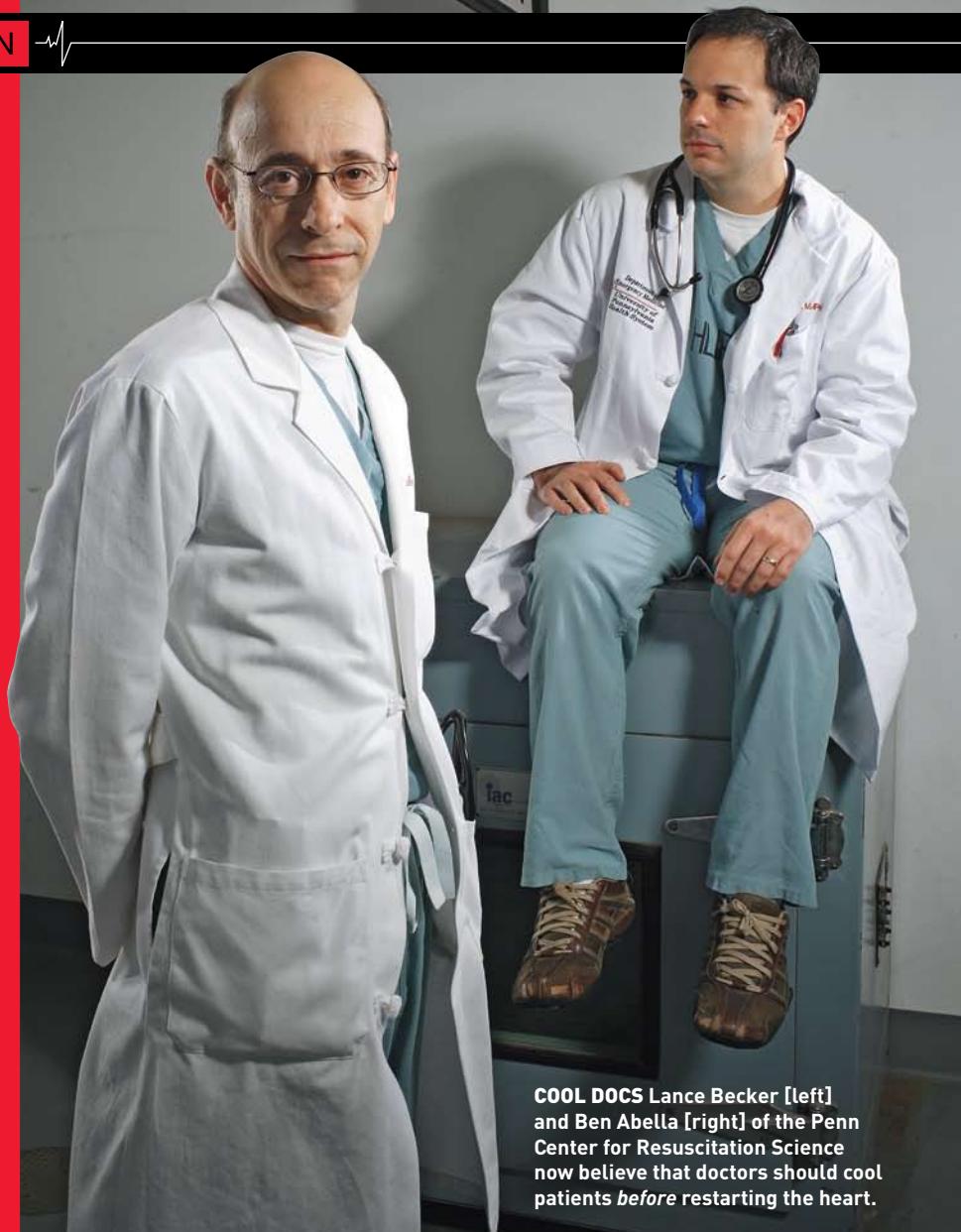
they recommend the treatment for only a subset of patients—those who experience ventricular fibrillation (one of four forms of cardiac arrest) and collapse outside of the hospital—because already hospitalized patients tend to be sicker, so cooling them is riskier. Perhaps as a result, few doctors seem to be using the technique.

“It seems like a good idea, but there are so many variables,” says Barco’s cardiologist, Jonathan Gomberg, who, despite working with Becker and Abella at Penn, still seems uncertain about hypothermia. If a patient’s heart has stopped for more than a certain length of time, is he still worth cooling? Penn’s limit is an hour; much longer than that, and severe brain damage is difficult to avoid. If a patient wakes up after resuscitation and seems OK, should he be sedated again for cooling, since more sedation can also pose risks? Penn says no. The list goes on. “When the science is clear, there’s one answer, and that’s what you do,” says Abella, now the hospital’s clinical-research director. But that’s not the case with hypothermia yet, so each hospital has to develop its own protocol. Even Penn cools only about 25 cardiac-arrest patients a year.

When Barco was brought to Penn from the Children’s Hospital, the ER doctors immediately called the cardiac-care unit so that nurses could ready the cooling equipment. The unit also had to find a nurse who wasn’t busy and could spend the entire night in Barco’s room in case something went wrong.

And a lot can. In the early stages of cooling, Barco’s heart wasn’t pumping strongly enough. The nurses kept her on blood-pressure medications and reduced her saline, because when the heart is not pumping properly, fluid can collect in the lungs. If her body temperature had slipped below 86°, her heart could have immediately failed.

Becker and Abella are now working to address at least some of the practical resistance to hypothermia by designing studies to determine the most effective ways to cool. If the parameters are more clear-cut, the protocol more established, they believe it will be easier for hospitals to adopt. Yet they may have just dug themselves a deeper hole. Their latest research, which indicates that patients may be bet-



COOL DOCS Lance Becker [left] and Ben Abella [right] of the Penn Center for Resuscitation Science now believe that doctors should cool patients *before* restarting the heart.

ter off if doctors begin cooling even *before* they restart the heart, will require more precision and an even greater trust in the treatment. How long will a doctor or EMT really let someone lie there with her heart stopped while he gets the ice ready?

AN IV SLUSHEE

On May 20, 1999, 29-year-old Anna Bagenholm was skiing with friends near Narvik, Norway, one of the most northerly towns in the world. A little after 6 p.m., on a path down a waterfall gully, she crashed and fell headfirst into a river. Her body wedged between some rocks and overlying ice; fortunately, she found an air pocket so she could breathe. Her

friends found her almost fully immersed underwater. But they couldn’t get her out.

Ten minutes passed as Bagenholm struggled in the icy water. Twenty. Thirty. After 40 minutes, her body went limp—either she had drowned or the cold had stopped her heart. When the rescue team arrived at 7:40, they cut a hole in the ice and took her body out. Her temperature was 57.9°. They inserted a breathing tube and began continuous CPR. Her heart wouldn’t restart, but pumping would at least get some oxygen to her organs.

An hour-long helicopter ride brought Bagenholm to the Tromsø University Hospital, where she was put on a heart-lung machine that breathed and pumped

HYPOTHERMIA IS CHANGING THE BOUNDARIES FOR WHEN WE CONSIDER SOMEONE LOST.

CHEATING DEATH

Back in the cardiac-care unit, Barco was finally rewarming after 24 cold hours. The cooling wraps and cold saline were gone. Nurse Dana Bower was carefully watching Barco's vital signs during the eight-hour process for signs of "rewarming shock," when blood pressure drops suddenly and mysteriously. Once Barco was back at 98.6°, Bower removed her breathing tube and stopped giving her paralytic drugs and sedatives. Doctors also checked her heart rhythm with an electrocardiogram, but it was irregular. Afraid her heart was failing, they told her family that she might need a transplant. No one knew yet how her brain was faring, either.

Barco remained unconscious for four days. She started having problems breathing, so the breathing tube went back in. She fluttered in and out of consciousness for a couple days. She started grabbing her breathing tube to try to pull it out. Doctors had to put her in restraints.

Eventually, Barco awoke for hours at a time. At first, she would talk to her kids but forget the next day what she had said. As she improved, though, doctors found no lasting brain damage. They removed the breathing tube and implanted a defibrillator in her chest. She left the hospital three weeks later.

Slowly, the weight of what had happened to her settled in. Barco realized that she had literally been within feet of certain death. If she had collapsed somewhere where people couldn't have found her, she might be gone. "I could've been in the bathroom, I could've been anywhere," she says.

Abella believes that the more doctors learn to use hypothermia, the less of a death sentence those circumstances will be. In the past, doctors refused to bring back patients who had been clinically dead for more than an hour because they assumed that the brain damage would be debilitating. Now "hypothermia is beginning to change the boundaries for when we would consider someone lost, or beyond the hope of resuscitation," Abella says. "Death was death. But it's increasingly evident that even after the heart is stopped, a lot of biological activities are going on in the brain, heart and other tissues—so the tissues aren't dead. It's exciting, it's really tremendous, but it's really humbling."

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LUCKY LADY After emergency-room clerk Pam Barco's cardiac arrest, doctors cooled her body to 91° for 24 hours. She recovered with no brain damage.



blood for her as she rewarmed. At 10 p.m. her heart started beating regularly on its own. By morning, her body was back up to normal temperature. Doctors sedated her for another three days and then slowly took her off the drugs. Eventually, she opened her eyes. She was alive and responsive, her brain virtually undamaged despite more than an hour without oxygen. After four months of rehabilitation, she went back to work.

Becker read Bagenholm's story in the medical journal the *Lancet* in January 2000, while he was deep into his own hypothermia research. He was stunned at how long she had survived without oxygen, but the variable was clear: Bagenholm was cold before her heart restarted. "It was one of the stories that exemplifies that there is great potential for [hypothermia] if we could figure out how to use it in an optimal way," Becker says. He and Abella now think "optimal" means "sooner."

In a study they published in 2007, the pair showed that mice

in cardiac arrest were more likely to survive if the experimenters waited to resuscitate them until after cooling had started. It was a provocative finding, because it suggested that the damage caused by a few extra minutes of oxygen deprivation is mitigated by getting a jump start on the cooling. The faster doctors can cool a patient, the fewer cells will die as they're reperfused.

With the help of postdoctoral engineer Josh Lampe, Becker and Abella have designed a machine that uses IVs to flush the body with an ice-water saline mixture—"like a slushee, a slurpee, a margarita," Lampe says. The machine makes its slurry on demand and should drop a person's temperature to 91° in two hours, versus the eight it takes now. If things go well with their first prototype, which they're currently testing on pigs, Becker and Lampe will apply for FDA approval to use the machine on cardiac-arrest patients in a clinical trial. It should be possible, Lampe says, to make it portable. "Dream comes true, it's in an ambulance and the EMT does it," he says.