Race against time. In cardiac arrest, stroke, and trauma, hypothermia may buy time and save lives.

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MEDICINE

The Big Chill

Lowering the body's temperature improves the chances of surviving a cardiac arrest and other types of trauma; but as cold therapy expands, researchers are struggling to understand why and for whom it works

PITTSBURGH, PENNSYLVANIA—In the first frantic minutes after a trauma victim rolls through the emergency room double doors at the University of Pittsburgh Medical Center, the medical team employs an arsenal to keep the patient's temperature up. The trauma rooms hold warm blankets and heated saline fluid in a small silver cabinet. Blood often runs through a warming device before a transfusion. Heat lamps glow next to a bulky x-ray machine.

Keeping warm helps protect the immune system and sustain blood clotting, but for the most grievously wounded, that's often not enough. More than 90% of patients with massive bleeding who lose a pulse will die—a figure that has remained stubbornly high. "What we do doesn't work" to save these people, says Samuel Tisherman, a soft-spoken, goateed surgeon at the medical center. And so, as a last-ditch effort, Tisherman, who has spent nearly all his life in this industrial city, wants to try something radical: Jettison warming, and put the critically injured who have lost circulation into a deep freeze of sorts, giving surgeons time to repair the wound. Infusing and draining up to 20 liters of cold saline fluid will plunge a patient's body temperature from 37°C to less than 10°C, "pickling" him, in the words of one researcher, in order to bring him back to life.

As drastic as it sounds, hypothermia—albeit not normally this profound—has had a lengthy, bumpy history in emergency medicine. At its core, the aim is to push the outer limits of survival. "When I was training, I learned [that] after 4, 5 minutes [without oxygen], the brain would die," says Lance Becker, director of the Center for Resuscitation Science at the University of Pennsylvania. With hypothermia, he says, "many of us are beginning to think it's possible to shift that" to 10 minutes and beyond. "We don't really have a fix on what death is" or when it's irreversible, says Becker. Although it's still not clear exactly how and why hypothermia works, physicians are using it against an assortment of maladies.

Mild hypothermia improves survival of people experiencing cardiac arrest and infants deprived of oxygen before birth. Clinical trials are testing it in head injury and stroke, and a vast European study is gearing up to refine hypothermia's effects in cardiac-arrest victims. Tisherman hopes that his much colder, profound-hypothermia trial will open within a year or so.

But there have also been high-profile failures and some safety concerns, a reminder of how much is left to learn. Once considered especially promising for those with brain trauma, hypothermia has proven unexpectedly fickle in this population. It has also proven exceptionally difficult to test in people, especially in the United States, where strict informed-consent guidelines mean that emergency-medicine trials are developed at what researchers contend is a glacial pace.

Beginnings

"I remember as a resident, we had patients in hypothermia for a week or longer," says Patrick Kochanek, a pediatric critical care specialist who directs the Safar Center for Resuscitation Research at the University of Pittsburgh. In those days in the early 1980s, Kochanek was at Children's Hospital San Diego in California, and youngsters with devastating head injuries were routinely cooled to 30°C, and sometimes less, for days, a trend that began in the 1950s. Pediatricians led the hypothermia charge, inspired by stories of children who had drowned in ice-cold water and been revived. "Everyone had their one miracle case of an amazing recovery," says Kochanek.

But cooling in brain injury was largely abandoned after life-threatening complications surfaced, including pneumonia, cardiac arrhythmias, and blood-clotting problems. Hypothermia continues to be used in many heart and brain surgeries to protect cells. But in the operating room, "we apply cooling before we deprive the system of oxygen," not after, which has different effects, says Hasan Alam, a trauma surgeon at Massachusetts General Hospital in Boston. The controlled conditions in surgery are also a world apart from the chaos in the emergency room.

The hypothermia field revived when a number of labs made a fortuitous discovery. For neurosurgeon Guy Clifton, now at the University of Texas Health Science Center in Houston, the insight came one winter in the mid-1980s while he was testing drugs in gerbils to prevent cell death during stroke. Animals in the control group, whose brains ought to have been seriously damaged, kept throwing off the experiments by staying healthy. The building in which Clifton was working was 100 years old and drafty. He found that the gerbils' body temperature had dipped 2°C—enough, it turned out, to protect them. "It was better than any drug we ever looked at," he says now.

A group in Miami made the same chance observation in rats, and another in Pittsburgh found similar responses in dogs. It dawned on the community that hypothermia need not be deep to be potent. "It wasn't just one laboratory showing that this works, it was almost everybody," says W. Dalton Dietrich, a neuroscientist at the University of Miami in Florida, one of the discoverers. Cooling a few degrees kept brain cells from dying.

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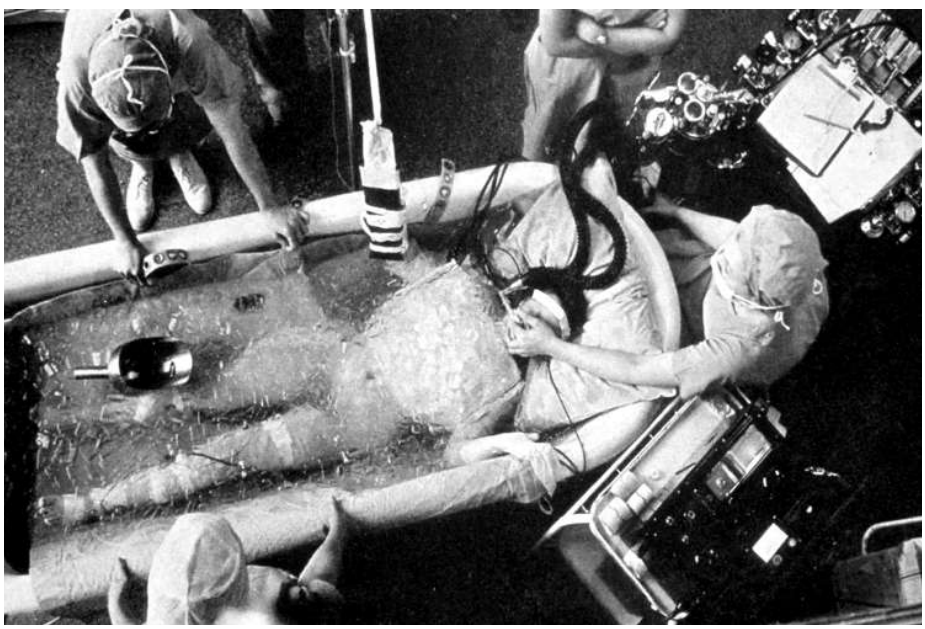
It's far from clear why. Hypothermia slows metabolism and lowers the body's demand for oxygen, which is especially useful in cases of ischemia, in which blood supply stops and there's little oxygen to be had. Hypothermia may also inhibit a destructive cascade of molecules that surge through brain cells after someone is resuscitated. Starting the heart up after a minutes-long pause can do serious harm to the brain, causing inflammation and damage from free radicals—a process called reperfusion injury. Reperfusion "adds a great insult to the injury" of ischemia in cardiac arrest and stroke, killing brain cells over many days, says Stephen Bernard, a critical-care specialist at Alfred Hospital in Melbourne, Australia. It is precisely this type of cellular death some scientists believe hypothermia can prevent.



Crude beginnings. A bathtub full of ice was one of the earliest ways doctors induced hypothermia in the 1950s.

But scientists are now finding that mild hypothermia, defined in humans as cooling from 37° to about 33°C, has more nuanced effects. "The assumption for many years was that hypothermia was primarily downregulating metabolism" and downregulating gene expression, says David Beiser, an emergency-medicine physician and biomedical engineer at the University of Chicago in Illinois. "But there's another aspect of this that is kind of puzzling." In a survey of 45,000 genes, Beiser and his colleagues found that when cooling clumps of cells or mice in shock from massive bleeding, just as many genes increased expression as decreased it. Beiser presented his findings at a June meeting and is preparing them for publication.

When the heart stops

As happens often in medicine, clinicians are concentrating more on how to use hypothermia than on understanding why it might work. "Our focus has always been on outcomes, not on what various molecules are doing," says Tisherman. This goal-driven mentality runs deep in the field, in part because of the man who shaped it: Peter Safar, widely considered the father of CPR and a believer in hypothermia long before it was in vogue.

The animal studies showing benefits from mild hypothermia immediately prompted clinical trials. One of the first was led by Fritz Sterz, a paramedic turned emergency-medicine doctor who had spent 3 years at Pittsburgh with Safar.

Cooling at Vienna General Hospital in Austria, where Sterz returned after his Pittsburgh sojourn, was a decidedly low-tech enterprise. Sterz invited over the local firefighters, who agreeably carted mammoth ventilators into his emergency room and blasted ice-cold air onto unconscious cardiac-arrest victims. That lowered body temperature 2° to 3°C. Sterz later graduated to a mattress blowing cold air, which dropped temperature by up to 5°C for 24 hours.

Simple as it was, the technique saved lives. In a clinical trial run by Sterz with 273 patients, 41% of those in the hypothermia group died within 6 months, compared with 55% in the control group. A second cardiac-arrest trial in Australia led by Bernard found that 49% of patients given hypothermia survived with minimal disability, compared with 26% in the control group. (Bernard wedged ice packs around his patients.) Both studies appeared in 2002 in *The New England Journal of Medicine*.

A 2005 study described equally compelling outcomes for babies deprived of oxygen before birth—a condition that affects the body much like a cardiac arrest. Among more than 200 newborns in the study, half were cooled to 33°C for 72 hours. Forty-four percent of those treated with hypothermia died or survived with significant disabilities. As grim as that sounds, the number was worse in the group that received standard treatment: 62%, or a difference of 19 babies.

"I was astonished that they were able to show a beneficial effect," says Kochanek. Some of the infants could have been deprived of oxygen for a day or two before birth. The cardiac-arrest studies, furthermore, suggested that doctors had been wrong in thinking brain damage was inevitable after more than 5 minutes without oxygen.

A knottier test

The next frontier, treating brain injury, has been far more difficult to cross. This is surprising, because it's brain cells that seem to benefit most when hypothermia is used against ischemia. Pediatric clinical-care specialist Jamie Hutchison of the Hospital for Sick Children in Toronto, Canada, concedes disappointment that his trial of 225 children with serious head injuries detected no benefit from hypothermia, a finding he first presented at a June meeting in Switzerland. This is consistent with an earlier head-injury trial of almost 400 adults, led by Clifton, which also flunked the hypothermia test.

The failures are of special concern because hypothermia is not harmless. The larger of the two cardiac-arrest trials, for example, saw more sepsis among treated patients (hypothermia depresses the immune system), more bleeding, and more cardiac arrhythmias. These were not considered significant, but they have long been associated with cooling. Perhaps the greatest risk comes not from cooling itself but from rewarming, which can sink blood pressure to life-threatening lows.

Why the dispiriting results in the head-injury trials? One possibility is that, whereas ischemia from a cardiac arrest briefly shuts down oxygen to the entire brain, "trauma's a dirty disease," says pediatric neurosurgeon P. David Adelson of Children's Hospital of Pittsburgh. Traumatic brain injury can mean multiple injuries to different parts of the brain, or be combined with trauma elsewhere in the body. That variability is not reflected in

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lab studies, in which hypothermia has performed so impressively. There, "you hit a group of animals in the same place with exactly the same force," says Hutchison.

Another theory is that different injuries provoke different forms of cell death, and hypothermia may be more suited to preventing one form than it is another. For example, the apoptotic death of cells observed after a cardiac arrest, in which cells "self-destruct," may be more amenable to hypothermia than the necrotic cell death seen in head injury, says Kochanek.

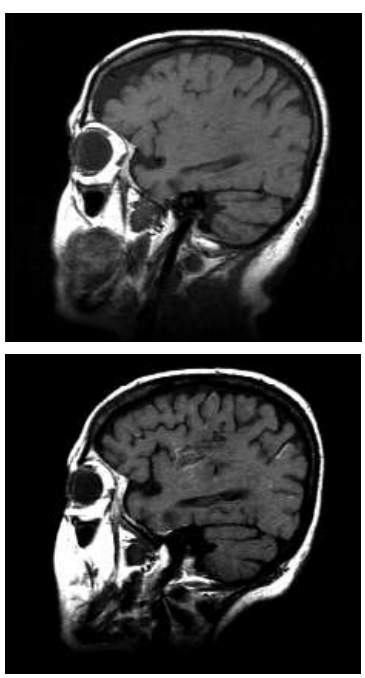
None of these ideas persuaded Clifton, who was baffled by hypothermia's lackluster showing in his head-injury trial. But parsing the data, he noticed that younger people whose bodies cooled spontaneously right after injury—a common effect of head trauma—and who then received hypothermia fared better. This suggested that early cooling could be key.

Narrowing his focus, Clifton has launched a second head-injury trial with $15 million in funding from the National Institutes of Health (NIH) in Bethesda, Maryland. He aims to enroll 240 people under age 45 and cool them within 2 hours of injury. Where possible, paramedics infuse chilly IV fluids in the helicopter en route to the hospital.

This time constraint presents a sticky problem: It's rarely possible to obtain informed consent so quickly from a patient's family. Relatives might be difficult to locate, or, in the worst case scenario, they might have died or been badly injured in the same accident. Many countries allow researchers to waive consent in emergency situations, though to do so in the United States, researchers must alert the community to their trial in advance. Clifton ran newspaper advertisements and met with community groups to describe the potential benefits and risks of cooling and how his study would be conducted. One man he met in Houston asserted that "only a Nazi would do this," says Clifton, adding, "but the majority of people ask a lot of questions and don't have a problem with it."

In Pittsburgh, Adelson also received an emergency waiver of informed consent from the university's Institutional Review Board (IRB) for a $15 million hypothermia study on head injuries in children, also funded by NIH. Although Hutchison's trial in Canada failed, Adelson says his trial, which he hopes to start this fall, will cool patients for longer: 48 hours instead of 24. And it will treat children within 6 hours rather than 8 hours of injury. Adelson is heartened by hints from a pilot trial he published 2 years ago that found that 44% of children treated with hypothermia were still showing improvements in cognition and behavior 6 months later, compared to 36% of those given standard care.

Tisherman is working toward approval and funding for his trial of trauma victims, the first that will cool injured patients dramatically, to 7° or 10°C. Alam of Mass General hopes to participate as well. Some consider this strategy especially risky because hypothermia is known to inhibit blood clotting, and these patients are already enduring massive internal bleeding. But "there really is no good alternative" treatment, says Jeannie Barone, assistant director of the Pittsburgh IRB.



A view of the brain. Half of this stroke victim's brain is healthy (*top*), but the other half is damaged by the loss and restoration of blood flow—harm that might be reduced by hypothermia.

SOURCE: CLINICALTRIALS.GOV; CREDIT: ELIANA BONFANTE

Spotty execution

Clinicians say that trials like these, as well as at least a half-dozen others in Europe, Asia, North America, and Australia, are crucial to learning how hypothermia might help. But the field is fragmented. Already the treatment is being used in situations not backed by clinical data and not used in situations that are. Frustration creeps into Adelson's voice as he describes how some centers refused to join his head-injury trial because they are reluctant to randomize their young charges. Instead, physicians are treating brain-injured patients as they come in, without the rigors of a clinical trial, says Adelson: "That's despite data showing it's not effective in probably 65% of patients."

Meanwhile, hypothermia's impressive ability to boost survival after a cardiac arrest prompted professional societies, beginning in late 2002, to recommend its use. Yet a 2006 survey of more than 2200 physicians in the United States, the United Kingdom, and Finland found that 74% in the United States and 64% in Europe had never used hypothermia to treat patients after a cardiac arrest. Often, hospitals don't adopt hypothermia unless it's foisted upon them. In Norway, Kjetil Sunde, an anesthesiologist at Ullevaal University Hospital in Oslo, spent 2 years pressing for the treatment. At first, many doctors, he says, "didn't believe in this." Now more than 90% of the country's hospitals use hypothermia in cardiac-arrest cases, he notes.

One reason hypothermia hasn't caught on is money, says James Grotta, director of the Stroke Program at the University of Texas Health Science Center. Drug companies don't develop it. The pharmaceutical industry provides "a substantial impetus for teaching, education, and practice patterns," says Grotta, who is studying hypothermia in stroke. When it comes to cooling, "nobody's pushing this. … There's nothing really patentable here."

Still, "it's almost, to me, scandalous" that the treatment remains so rare, says Clifton. "There are not that many cities where a patient can expect to get it."

–JENNIFER COUZIN

Trial by Ice: A Sampling of Hypothermia Studies

Condition	Patients	Home of Lead Center	Status
Head injury, adults	240	Houston, Texas	Ongoing
Head injury, children	225	Toronto, Canada	Complete, not published
Head injury, children	340	Pittsburgh, Pennsylvania	Opens in fall
Shock from bleeding	100	Pittsburgh, Pennsylvania	Seeking funds
Stroke	50	San Diego, California	Ongoing
Cardiac arrest	2000	Vienna, Austria; and Lund, Sweden	Seeking funds
Cardiac arrest, children	40	Toronto, Canada	Ongoing

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