



## COLD COMFORT:

Could lives be wrenched // from death's grip // by sending frigid fluid through veins, suspending animation?

# Dying to Live

■ BY CHARLES SCHMIDT // PHOTOGRAPHS BY JEFFREY STEPHENS

**I**n 1999 a 29-year-old physician fell headlong into a river while skiing in northern Norway. Friends watched helplessly as Anna Bagenholm was carried by currents and finally wedged beneath thick ice floes. More than an hour passed before she was pulled to shore. By then, she had no heartbeat and her core temperature had plunged to 57°F. Emergency crews started cardiopulmonary resuscitation and kept at it during the hour-long flight to Tromsø University Hospital. It took nine hours of treatment and slow warming before Bagenholm came to, and she spent 60 days in intensive care. Yet she was back at work within five months, and a year later she was skiing again.

Bagenholm hadn't really died in the biological sense. Her heart had stopped, but like her other vital organs, including her brain, it was likely preserved by her extraordinarily low body temperature. Metabolism is governed in part by temperature, and as the body cools, its cells need less oxygen. At 57°F, with her metabolism slowed to just 10% of its baseline rate, Bagenholm needed practically none. She was in a quasi-hibernating state of suspended animation, poised between life and death.

Bagenholm isn't the only person to have survived such an experience. In fact, these occasional medical "miracles" demonstrate the principles of what some physicians hope may become a powerful clinical tool. Medical researchers

have induced suspended animation in animals by cooling them to superlow temperatures or giving them low levels of gases that safely slow metabolism under controlled conditions. Human trials may begin soon. It's already possible to cool humans to extremely low temperatures and drain blood from the body to fix otherwise inoperable aneurysms. If progress continues, suspended animation could emerge as a way to save victims of heart attacks, central nervous system injuries and trauma. The aim, explains Patrick Kochanek, director of the Safar Center for Resuscitation Research at the University of Pittsburgh School of Medicine, is to pause metabolism while medical teams fix normally lethal injuries or make repairs that wouldn't be feasible at normal body temperatures. "We want to suspend the body's need for oxygen while we tend to the emergency," Kochanek says.

**T**he notion of protecting patients by cooling them isn't new. In the early 1950s, Canadian cardiologist Wilfred Bigelow, a co-developer of the cardiac pacemaker, wrapped patients in cooling blankets and ice packs to push core body temperature to as low as 82°F during heart surgery, allowing time to perform difficult procedures. Inducing even milder hypothermia, cooling patients to no lower than 91.4°F, has since become almost routine during surgery for heart, brain and spinal cord injuries, among other applications. The cooler temperature helps prevent cell death in the affected tissue while physicians try to repair the damage.

But suspended animation requires profound hypothermia, a state in which body temperature is forced down to 50°F or cooler, and inducing such a state has had its problems. Doctors couldn't achieve rapid body cooling consistently using blankets and ice packs, and even cooling the blood by circulating it through heat exchangers connected to heart-lung bypass machines ran the risk of leaving some body parts too warm. Also, shivering was hard to control. Because of these challenges and others—including evidence of irreversible brain damage to children who were cooled to low temperatures to allow controlled cardiac arrest—hypothermia fell out of favor during the 1970s.

But in 1986, Robert Spetzler, now director of the Barrow Neurological Institute at St. Joseph's Hospital and Medical Center in Phoenix, attempted a procedure in which he cooled a patient's body to a very low temperature, using a variation on a technique first tried in the 1960s. In those days, surgeons opened the heart to attach a catheter, then cooled the blood by running it through a bypass machine to prepare for surgery; about half the patients died.

In his variation, which now has been performed more than 100 times, Spetzler inserts the catheter into the femoral artery and uses barbiturates to reduce metabolic activity. Working with a team of neurosurgeons, cardiologists and anesthesiologists, he uses a bypass machine to cool the blood until the patient's body temperature reaches about 60°F. At that temperature, the heart stops beating—an induced condition called cardiac standstill—and the team can drain the body of blood. Spetzler then snakes a catheter into the brain to treat hard-to-reach aneurysms. Without blood flowing through it, an aneurysm deflates, allowing Spetzler to attach a clip that prevents the aneurysm from reinflating when blood is returned to the body and the heart is restarted.

Spetzler can keep patients in cardiac standstill for as long as 72 minutes. The risks are high, with a mortality rate of about 25%, and he does it only when not operating would mean almost certain death. "It's a very invasive procedure," he says, with some patients dying weeks or even months later, though it's difficult to determine whether their deaths are attributable

to the procedure or to residual problems with the aneurysms.

In another approach to suspended animation, Sam Tisherman, a University of Pittsburgh surgeon and Safar Center researcher who is a colleague of Kochanek's, is preparing to lead a clinical trial of trauma victims suffering from exsanguination cardiac arrest, a condition in which the heart stops as a result of blood loss. Patients who lose a pulse because of massive bleeding die more than 90% of the time. "You can't start the heart because the tank's on empty," Kochanek explains. "And if you give blood intravenously, it just leaks out."

Tisherman hopes to save these patients by cooling their bodies to 50°F prior to surgery. His approach originated in the mid-1980s, when Peter Safar, a Pittsburgh professor and critical care pioneer, persuaded Tisherman, then a fellow in Safar's lab, to launch a series of studies. Safar, now deceased, knew that there is a brief window during which the brain and other vital organs stay viable after the heart stops, and he wanted Tisherman to create an animal model to investigate





how suspended animation could be used to save victims of exsanguination cardiac arrest.

Today, Tisherman and a research team at the Safar Center are perfecting their approach. Dubbed emergency preservation and resuscitation, or EPR, it relies on massive infusions of ice-cold saline. First, an anesthetized dog is bled until its heart stops. Then a device called a roller pump, hooked to the aorta or femoral artery, flushes the dog with an infusion of ice-cold saline (as much as 20 liters may circulate through the dog's body to cool it to the desired temperature). As the cooling fluid moves through the animal's body, draining out through a catheter in the jugular vein, researchers monitor

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brain temperature until it reaches 50°F. (According to several studies, that's the optimal temperature for decreasing metabolism without causing brain damage.) At that point the dog is packed in ice, and surgeons inflict and repair a wound to the spleen, mimicking human trauma. Finally, a cardiopulmonary bypass machine slowly returns the animal's preserved, oxygenated blood. Most dogs that have undergone EPR, followed by 36 hours of mild hypothermia that researchers maintain with a cooling blanket and fan, recover without brain damage or other problems, according to research findings described in the April 25, 2006, issue of the journal *Circulation*.

Hasan Alam, a Safar Center collaborator, trauma surgeon and director of trauma research at the Massachusetts General Hospital, has achieved similar results in multiple studies. Alam uses ice-cold fluid to induce suspended animation in exsanguinated animals, but unlike the Safar Center scientists, he works in the laboratory with human-size Yorkshire pigs. His latest

findings, described in the April 2007 issue of the *Journal of the American College of Surgeons*, confirm that a temperature of 50°F preserves vital organs while surgeons repaired inflicted wounds to the colon, spleen and vascular system. Each surviving animal recovered without brain damage, future learning impairments or evidence of organ dysfunction.

**B**olstered by success in animal models, Tisherman is preparing to test EPR in humans, with one of the most daring clinical trials ever attempted in trauma care. The idea is to rush victims of gunshot wounds and other penetrating injuries to participating trauma centers. If a patient's heart stops after transfer to a trauma center, a medical team will employ the same method developed in animals, using a roller pump to circulate through the patient's body as much as 30 liters of ice-cold saline saturated with dissolved oxygen and glucose. Time is of the essence, Tisherman emphasizes. His

animal studies suggest cooling won't save brain function if it's delayed by more than eight minutes after cardiac arrest.

During the procedure, the fluid enters through a large catheter, usually inserted into the femoral artery that runs from groin to knee. But if the patient's chest has already been opened by an emergency thoracotomy (in the field or after arrival in the ER), the catheter can be threaded into the aorta, which serves as an arterial pipeline from the heart to other vessels. (Thoracotomy is a standard procedure for locating and stopping internal bleeding from chest wounds.) The goal is for the cold saline, pumped at a rate of two to three liters per minute, to saturate the brain, heart and other organs, reducing core temperature to roughly 50°F.

With the body fully cooled, its biochemical processes should pause, bringing metabolism to a virtual standstill and reducing the demand for oxygen by as much as 95%. In the operating room, wounds will be plugged and vessels repaired, and then cardiopulmonary bypass equipment will begin circulating blood through a heat exchanger, slowly raising the body temperature so that a heartbeat can be restored.

"I think this could be the beginning of something huge," says Thomas Scalea, physician-in-chief at the R. Adams Cowley Shock Trauma Center in Baltimore, considered one of the best in the world. "It's a fantastic leap in sophistication."

Tisherman concedes the approach carries substantial risk.

Hypothermia reduces clotting, which can be problematic when trying to save a patient who has already lost a great deal of blood. And cold raises the threat of infection because immune cells that protect the body from viruses and bacteria lose their effectiveness when body temperature drops. But the biggest worry is that the patient might suffer permanent brain damage.

The best way to avoid poor outcomes, Kochanek asserts, is to select the right patients—those who have been healthy and strong; haven't had extensive brain trauma; are already at an appropriate trauma center; and can be prepped for EPR within the critical eight-minute window. It's that last part that will be especially difficult. "The technical feasibility of doing this fast enough is our biggest stumbling block," Kochanek says.

Tisherman hopes to launch the trial in five top trauma centers, in which EPR will be compared with the standard treatment for trauma victims who have lost a pulse: blood infusions, emergency thoracotomy and CPR. Surgeons will be trained to perform the new procedure, which involves some skills—using cardiopulmonary bypass equipment, for example—that may not figure in their clinical repertoire.

**T**he trial faces additional challenges, including regulatory hurdles at the FDA and the Department of Defense, which is providing funding. Unlike ordinary clinical trials where patients can give informed consent, the trauma victims in this trial will be unconscious and near death, and there likely won't be time to ask relatives to agree to the procedure. So researchers will have to secure in advance what's known as an exception from informed consent, an authorizing statement from each community served by the trauma centers in the trial. Assuming most communities assent and federal agencies give the green light, a launch is expected later this year, Tisherman says.

As Tisherman prepares for his clinical trial, another researcher, biologist Mark Roth of the Fred Hutchinson Cancer Center in Seattle, has developed an altogether different way

## Roth's mice sleep peacefully for hours in levels of oxygen that would typically kill them within 15 minutes. "We use hydrogen sulfide as if it were a dimmer switch," he says.

to reduce metabolic demand for oxygen—using hydrogen sulfide. Because the gas binds readily with vital oxygen receptors in the cell, it slows down metabolism, sending cells into a sort of hibernating trance.

Hydrogen sulfide interferes with a metabolic pathway called oxidative phosphorylation, which converts oxygen and nutrients to energy. When oxygen drops to levels that can't sustain life, the pathway goes haywire and spits out free radicals that destroy cell membranes. But a priming dose of hydrogen sulfide blocks that process, protecting animals from declines in oxygen that would normally kill them.

When Roth first exposes mice to a low dose of hydrogen sulfide, causing their metabolic rates to decline as much as 90%, the animals sleep peacefully for hours in air that has 5% oxygen content instead of the normal 21%. (Typically this atmosphere would kill a mouse within 15 minutes.) When Roth turns on the oxygen again, the animals wake up with no discernible problems. "We use hydrogen sulfide as if it were a dimmer switch," Roth explains. "The more we give, the more we suppress oxygen demand."

Roth thinks that using hydrogen sulfide to suppress metabolism could go a long way toward saving victims of heart attacks and central nervous system trauma and even patients whose hearts have stopped from loss of blood. The therapeutic aim, he says, would parallel that of EPR: to preserve vital organs while medical teams tend to a primary injury.

Hydrogen sulfide might offer a faster, less invasive path to suspended animation, says Warren Zapol, chief of anesthesiology and critical care at the MGH. Gian Paolo Volpato, a postdoctoral fellow working with Zapol, has shown that even very low exposure to inhaled hydrogen sulfide can sharply reduce metabolism and heart rates in mice. What's more, metabolic rates decreased even when Volpato kept the mice warm. That's intriguing because the extreme cold of EPR lessens blood's clotting ability and increases risk of infection. (Volpato's results were published in April in the journal *Anesthesiology*.)

"Hypothermia is a good way to slow metabolism," Zapol

says. "But it has its problems, particularly when normal blood flow has been severely disrupted. It would be hard to rapidly cool the heart and brain if the aorta has been torn."

Still, research with hydrogen sulfide is at an earlier stage than Tisherman's work. The gas has yet to be thoroughly tested in larger mammals, which may be less sensitive to hydrogen sulfide and require larger inhaled doses, and that could pose challenges for delivery because the gas would harm the lungs at higher concentrations. Whereas Volpato used inhalable gas, an alternative approach uses a form of hydrogen sulfide that can be injected into veins. But human trials can't begin until after this approach has been used safely and successfully in at least two larger animal species.

In the meantime, infusions of ice-cold saline are headed for the clinic to launch what could be a lifesaving shift in trauma care. "I'm hoping it will give us a chance to save as many as 100 people a year in our hospital alone," says Scalea. "It's unbelievably frustrating to see an 18-year-old die because you can't restart her heart after repairing her injuries." ■

### → DOSSIER

1. "Hypothermia and Injury," by Samuel A. Tisherman, *Current Opinion in Critical Care*, December 2004. An introduction to the concept of inducing suspended animation with profound hypothermia during the treatment of exsanguination cardiac arrest.
2. "Induction of Profound Hypothermia for Emergency Preservation and Resuscitation Allows Intact Survival After Cardiac Arrest Resulting From Prolonged Lethal Hemorrhage and Trauma in Dogs," by X. Wu et al., *Circulation*, April 25, 2006. A detailed surgical description of the saline flush method.
3. "Inhaled Hydrogen Sulfide: A Rapidly Reversible Inhibitor of Cardiac and Metabolic Function in the Mouse," by G.P. Volpato et al., *Anesthesiology*, April 2008. An intriguing report that hydrogen sulfide can suspend animation in mice without lowering body temperature or blood pressure, thus avoiding hypothermia's attendant problems (increased infection risk, decreased blood clotting).