

a chill *to the* heart

A system to deliver local hypothermia could one day improve the lives of heart attack patients.

By Tom Merrill



On July 18, 2006, engineer Dean Cowles experienced a cardiac arrest. A product he works on at Medtronic Inc., a defibrillator, saved his life. With careful application his co-workers brought his pulse back, but he remained unconscious. He was still in trouble.

Restarting the heart is paradoxical: it sustains your life but it also can damage the quality of your life. After Dean Cowles's heart was restarted, biochemical processes initiated by lack of blood supply were endangering his brain's health.

Medical science has discovered that the damage from those processes can be reduced by small temperature reductions of only three or four

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► To protect vital organs, a catheter, like the Accutrol model at right, carries coolant that chills the entire body.

PHILIPS

degrees Celsius. Cooling the body slows cell metabolism and can reduce cell damage.

This knowledge has inspired a number of advances in a form of care called therapeutic hypothermia.

Therapeutic hypothermia, the idea of reducing body temperatures for benefit, takes many forms. An ice pack for an ankle sprain is the simplest form. Today, biomedical engineers and doctors are exploring new applications and devices that seek to save vital organs, particularly brains and hearts, from undergoing excessive damage after a heart has stopped and been restarted. Research is under way to make cooling more efficient by concentrating it on a specific organ of interest.

There are two broad categories of devices for inducing therapeutic hypothermia: external systems and internal systems. There are whole-body and regional cooling approaches. Each option involves trade-offs to consider involving ease of use, cost, safety, and effectiveness. Dean Cowles's doctors used an external system for whole-body cooling, and he recovered successfully.

Original methods of therapeutic hypothermia consisted of immersion in cold water or forcing cold air through blankets. Today's systems have come a long way.

For example, Medivance Inc. offers the Arctic Sun system, which has two major components, a cooling console and a series of cooling pads called ArcticGel pads. The console ensures that coolant circulates at the correct temperature for the correct amount of time. It's essentially a lab chiller with advanced controls for patient safety and care effectiveness.

An ArcticGel pad consists of three flexible layers so it can conform to the body. The outer layer, not in contact with the patient, insulates the pad so ambient thermal energy does not warm the coolant.

The middle layer provides a leak-tight internal coolant flow pathway. Its design involves subtle enhancements or flow obstructions to promote coolant mixing and thin boundary layers—those regions where temperature gradients are greatest inside the coolant flow. The system is designed to operate so that the internal coolant is always under vacuum pressure. While this ensures that the coolant will not leak if the pad is punctured, it also limits how much pumping pressure can be used to force the fluid through the middle layer. The enhancements are designed to boost heat transfer but not become overly demanding in terms of pressure drop or pumping power.

This same balancing act is what mechanical engineers face in the design of air conditioning systems. If a condenser coil has great enhance-

ments for heat transfer but the air-side pressure drop is too high, the design needs refinement.

The inner layer, in contact with the patient, is made of material that is thin, conductive, and gel-like. Heat-transfer conduction rates are directly proportional to conductivity, area, and temperature differences, and inversely proportional to material thickness. The gel-like quality ensures close contact between the pad and the skin, eliminating air pockets arising from large body features as well as small body features, like hair.

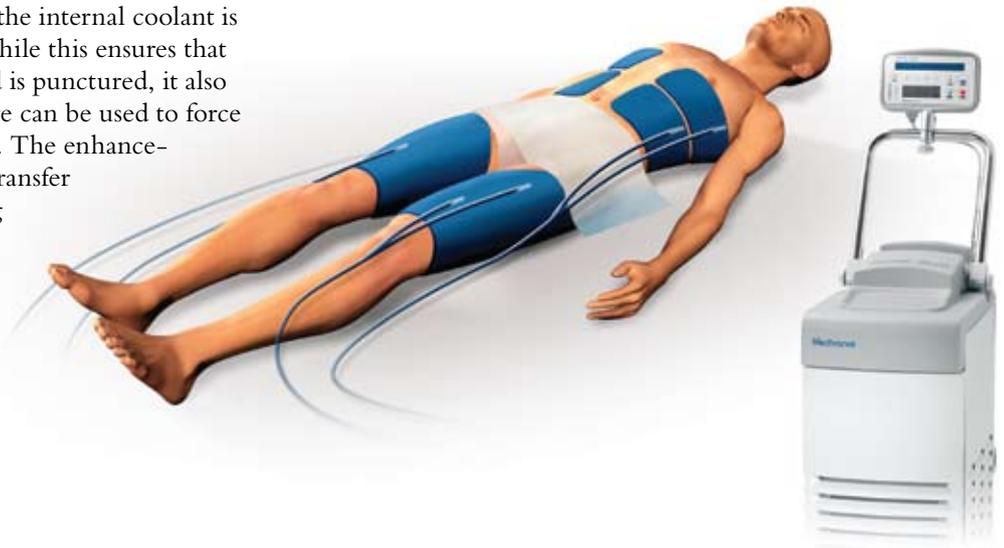
Medivance's Arctic Sun system is considered non-invasive, because all parts of the system are outside the skin. The advantages of non-invasive treatment are ease of use and safety.

Invasive, or endovascular, systems also exist. In these systems a cooling catheter is placed in the vena cava, a large vein leading to the heart. Invasive methods provide a more direct means of cooling.

Innercool Therapies Inc. developed the Accutrol cooling catheter, a metallic catheter that uses extended surfaces to disrupt and mix blood. It looks like a fluted baluster in a railing. Not only is it effective at transferring thermal energy from the blood to the coolant circulated inside, its baffles allow the device to flex as needed during insertion.

Radiant Medical Inc. and Alsius Inc. also created cooling catheters with names like Setpoint, Icy, and Cool Line. Today these designs are owned by Zoll Medical Corp. They are made of flexible polymers, so as coolant is circulated the catheters expand, increasing their heat exchange area inside the body. This balloon-like design enables the devices to be small during insertion and large during active cooling.

▼ Arctic Sun controls the temperature of water flowing through pads in contact with a patient's skin.



MEDIVANCE



◀ Olympic Medical's Cool Cap protects the brains of infants who suffer from a lack of oxygen.

KELLEY COOPER

Toward a Focused Approach

Arctic Sun, Accutrol, Setpoint, Icy, and Cool Line are whole-body cooling systems, and whole-body cooling has some drawbacks. Thermal capacitance or thermal mass of an adult human is considerable. If time to target temperature is critical to prevent death or organ damage—and it is—high cooling capacity devices are a must.

Our body's natural thermoregulatory system will fight any attempts of cooling. Our regulatory system is quite effective, normally keeping our body's temperature steady within a few tenths of a degree Celsius. Moreover, when the body is cooled, our shiver reflex must be suppressed with drugs.

There is a reason that the body prefers an accurate regulatory system. It's a healthy state. Even mild whole-body hypothermia (3 °C below normal temperatures) has been associated with wound healing problems and higher infection rates.

As a result, some companies have developed localized or regional cooling systems that only cool part of the body. Olympic Medical Inc., for instance, has developed a special cooling cap that provides brain protection for infants born suffering from hypoxia or lack of oxygen. Using classic heat-transfer principles the company has made a selective brain cooler. During the 72 hours of recommended treatment while the entire body is mildly hypothermic (34–35 °C), the infant brain is kept slightly cooler (32–33 °C). Heat lamps are used to offset shivering. Similar to Medivance's Arctic Sun, the device is made of three components: an external insulating layer, a middle support layer, and an internal layer made of serpentine-like pathways of soft flexible plastic, where the coolant flows.

Our medical device startup company, FocalCool LLC at Rowan University's South Jersey Technology Park, is working on an endovascular regional cooler for the heart. Funded by Small Business Innovative Research grants from the National Institutes of Health and by angel investment, our technology seeks to rapidly cool heart tissue during emergency angioplasty. These are

▶ A dilation catheter like this one and other instruments are delivered to the heart through catheters in the femoral artery.

angioplasty procedures when the coronary artery blockage is severe, causing ischemic damage with every minute that passes. They represent about 10 percent of the 1.1 million angioplasty procedures conducted each year.

FocalCool LLC began as a basement project in East Windsor, N.J. In 2004, Jay Yadav, a physician at the Cleveland Clinic Foundation, felt strongly that there must be an easier, more effective way to cool organs at risk. Combining Yadav's established entrepreneurship skills and medical knowledge with the author's heat transfer background, FocalCool LLC took off.

Recent American Heart Association statistics show that about 20 percent of first-time heart attack victims die within a year after their heart attack. Despite the array of tools we have today—angioplasty or balloon catheters, stents, and clot-busting drugs—many doctors believe our capability to improve outcomes has plateaued. We have hit a tissue-salvage wall.

To move beyond this point, we researched the injury process that occurs *after* a heart attack. During a heart attack a variety of chemical processes, called the ischemic cascade, take place to damage tissue, but the damage is not complete.

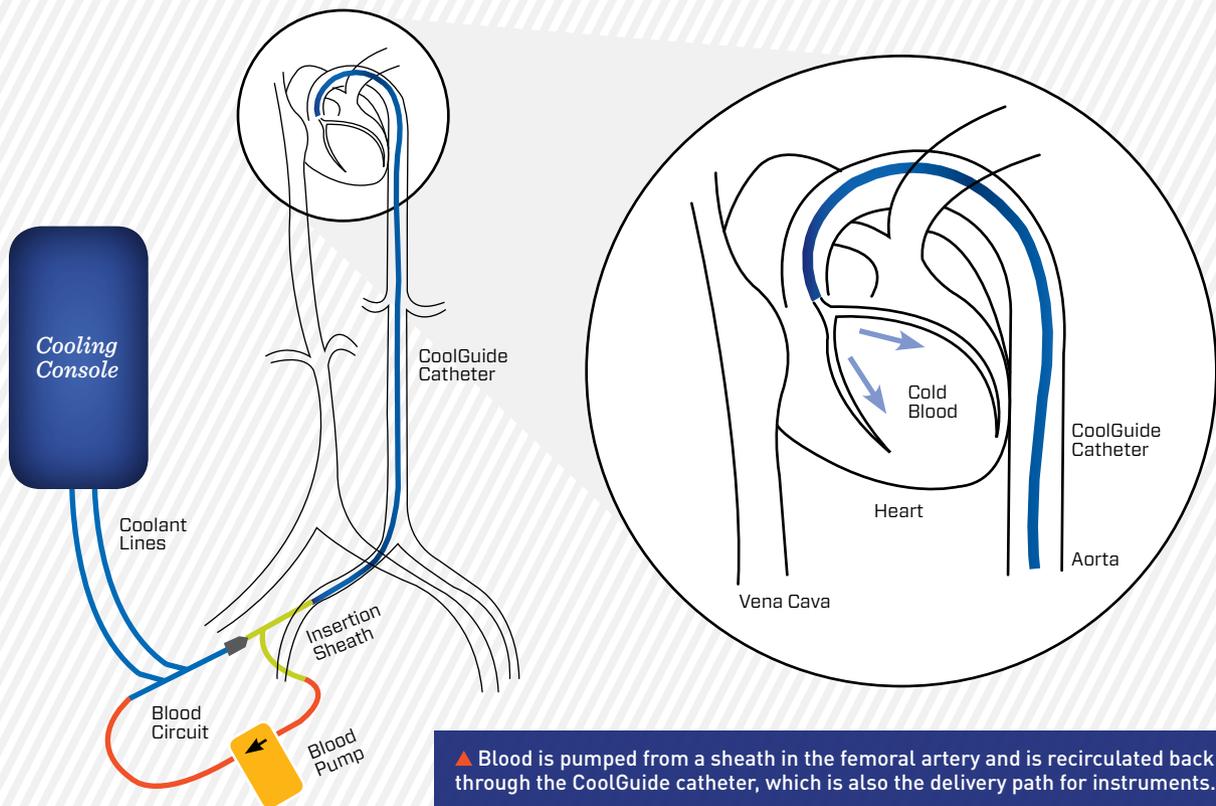
Like reestablishing heart function following cardiac arrest, reperfusion, the process of reestablishing blood flow to sections of the heart, is also paradoxical. While heart reperfusion is necessary to sustain viable heart tissue and perhaps life as a whole, reperfusion also creates further, more-extensive damage to heart tissue, perhaps as much as 50 percent of the total damage resulting from a heart attack. This is called reperfusion injury and currently there are no technologies or drugs that prevent it.

To come up with a solution we had to first understand reperfusion injury and the current care path for emergency angioplasty. At the cellular level we found that the production of oxygen free radicals, the calcium imbalances, and the overall metabolism increase during the reperfusion process. Mild hypothermia (a reduction of 2 to 4 °C) can limit the effects of all these developments and potentially reduce tissue damage.

The angioplasty care path involves a long list of steps. Here is a summary from a doctor's perspective: 1. insert



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▲ Blood is pumped from a sheath in the femoral artery and is recirculated back through the CoolGuide catheter, which is also the delivery path for instruments.

an introducer sheath into the femoral artery; 2. insert a guide catheter through the sheath so that its distal tip lies at the entrance to a coronary vessel; 3. insert a guidewire into the guide catheter and across a coronary blockage; 4. pass an angioplasty or balloon catheter over the guidewire and expand to allow reperfusion and perhaps install a stent to prevent reocclusion, and 5. remove the sheath, catheters, and guidewire, and close the entrance wound.

Guiding and Cooling

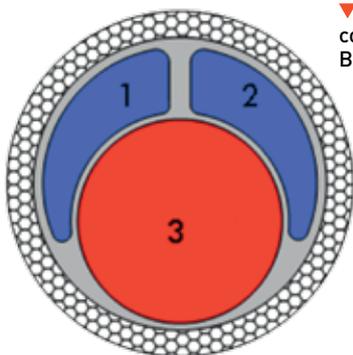
To integrate into this care path, FocalCool is developing a new guide catheter called CoolGuide. CoolGuide maintains the functionality of standard guide catheters, providing coronary artery access for devices like angioplasty catheters and stents, while also delivering targeted chilled blood to

heart tissue at risk. If enough tissue can be saved, patient outcomes may improve.

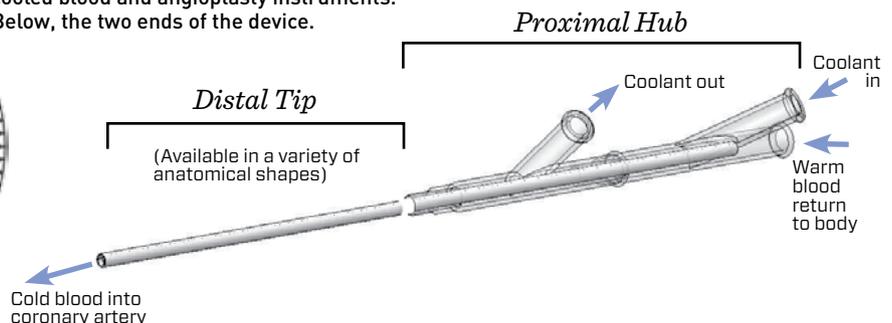
Today, working with Robert Gorman and Matt Gillespie of the University of Pennsylvania, FocalCool has demonstrated in preclinical testing that CoolGuide can reduce heart tissue temperatures by 3 to 4 °C in about five minutes. Early tissue salvage results are encouraging, showing that tissue damage can be reduced on average by about 50 percent.

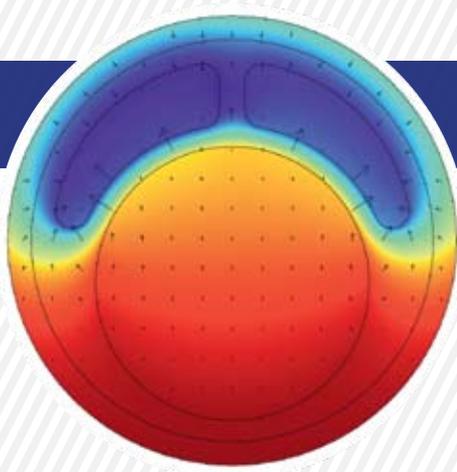
The key advantage of CoolGuide is that it works with current care practices with little or no systemic cooling. Based on American Heart Association figures there are approximately 100,000 emergency angioplasty procedures each year in the U.S. Despite the potential for improving patient outcomes, veteran cardiovascular interventionists like Zoltan Turi, director of the Vascular Center at the Cooper University Hospital, have told us that any new device that is introduced into the

CoolGuide Catheter



▼ Lumens 1 and 2 circulate coolant. No. 3 delivers cooled blood and angioplasty instruments. Below, the two ends of the device.





◀ An FEA model predicted cooling effectiveness of the CoolGuide catheter: Dark blue is 5 °C; dark red at bottom is 37 °C. ▼ The CoolGuide system, in prototype, cools blood 9-10 °C.



COOLGUIDE

market must be familiar and easy to use.

To create the cooling effect, blood is circulated and cooled as it flows through a central lumen. This same central lumen is used to deliver angioplasty catheters and stents. Two noncircular lumens carry chilled saline in a closed loop from the catheter hub to the distal tip located in a coronary vessel.

CoolGuide's distal tip is shaped to be easily placed in the coronary artery. The rear or proximal hub is designed to provide access to the multilumen core of the catheter, providing connections for interventional tools like angioplasty catheters and for coolant flow.

The outer shell is a composite structure made up of stainless steel braid and a polymer covering. The braid geometry as well the material properties of the steel and polymer dictate the flexibility and torsion carrying properties of CoolGuide.

The inner core is made of Teflon. While Teflon has an extremely low coefficient of friction, aiding the passage of interventional devices, Teflon's other material properties make extruding multilumen tubes particularly difficult. Zeus Tubing Inc. in Orangeburg, S.C., has expertise in this area. Starting with finite element analysis in Comsol Multiphysics we created a design that met our need to cool at reasonable pumping pressures. Zeus Tubing took our design and eventually, after several attempts, made an extrusion that was reasonably similar.

Medical Murray Inc. in Lake Zurich, Ill. helped finish the manufacturing process by taking the Zeus Tubing extrusion and carefully adding the outer shell. Focal-Cool engineers then added the rear hub and shaped the distal tip.

CoolGuide's manufacturing journey from concept to finished prototype gave us a new appreciation of the work that goes into a guide catheter. On the surface, guide catheters seem quite simple. What goes into that simple small plastic tube about one-eighth of an inch in diameter by about 40 inches long, however, is surprising.

Naturally, making prototypes is not enough. Before doing preclinical testing we measure the performance of the device in a laboratory setting using a water-

glycerol mixture to simulate blood. A peristaltic pump simulates the heart and a beautifully shaped piece of glass simulates the aorta and coronary vessels. Tests measure how well the device cools the blood analog at the expense of pressure drop.

Seeking the Care Path

Much work remains. While our initial pilot testing is promising, we are seeking better ways to integrate our technology into today's existing angioplasty care path. Unanswered questions include: When should the cooling be initiated, what should be the target temperature for heart tissue at risk, and how long should we cool the tissue? Future systems may be able to tailor patient temperature control for the optimal outcomes. Future systems may also be used to reduce brain tissue damage resulting from stroke, a leading cause of serious disability.

The need for therapeutic hypothermia is large: the American Heart Association states that heart disease and stroke are the number one and number three leading causes of death in the U.S., respectively. Therapeutic hypothermia can also improve lives by saving seemingly small amounts of tissue at risk, enabling vital organs to continue working well.

Therapeutic hypothermia is an exciting and evolving field of medical care. Mechanical engineers are making important contributions from thermal fluid and material science perspectives. Synergy and collaboration for complete solutions, actual products, however, is needed. Looking ahead, engineering expertise combined with medical doctors' physiology and clinical expertise may offer a way around or through our current "tissue-salvage wall." ■

Editor's note: Inventors and entrepreneurs can learn more about Small Business Innovative Research funding available from the National Institutes of Health at <http://grants.nih.gov/grants/funding/sbir.htm>.