

Therapeutic Hypothermia

in Treating Acute Stroke

This technique holds promise to be a strong option in the treatment of acute stroke.

BY KAMA GULUMA, MD

The use of therapeutic hypothermia is emerging as a potential option in the treatment of acute stroke. Investigations into the use of therapeutic hypothermia in acute cerebral ischemia represent an intuitive consideration of this modality as a form of neuroprotection in acute central nervous system ischemia. The endovascular induction of hypothermia may have capabilities and, therefore, specific advantages compared to traditional surface cooling methods.

TEMPERATURE AND STROKE

Body temperature has been shown to affect outcome in acute stroke. Azzimondi et al showed that a fever within the first few days of an acute stroke was an independent predictor of worse outcome.¹ Reith et al demonstrated improved outcome and lower mortality in acute stroke patients who presented with a body temperature of less than 36.5°C.²

Animal models have revealed that therapeutic hypothermia reduces infarct volume in acute stroke.³⁻⁵ The neuroprotective effects of hypothermia are not fully understood and appear to be plethoric. Work using animal models of ischemic and traumatic central nervous system injury has revealed that hypothermia decreases cerebral metabolism, stabilizes

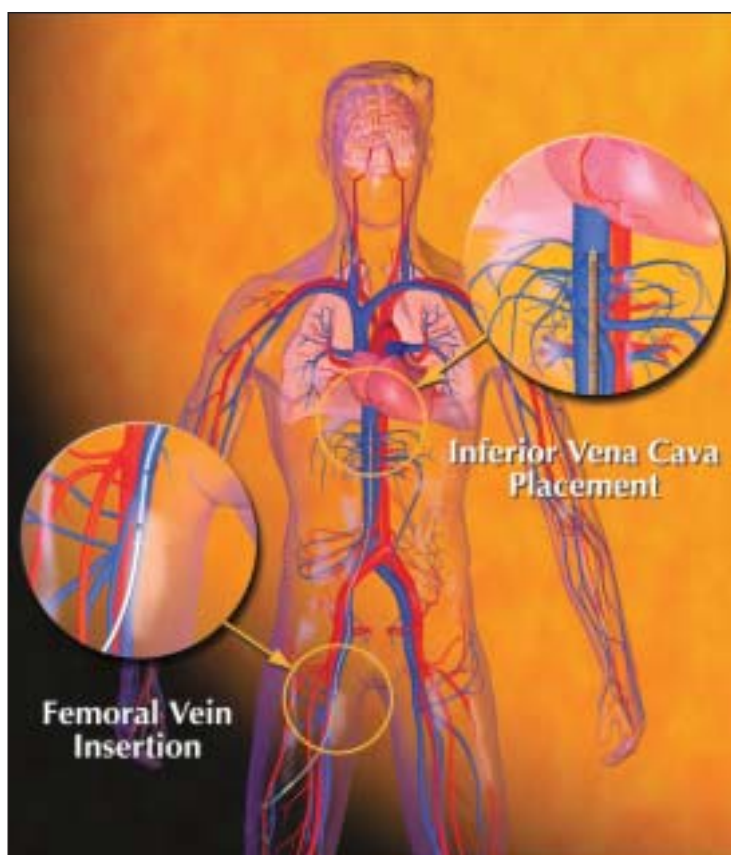


Figure 1. The Innercool (San Diego, CA) Celsius Control catheter in position within the inferior vena cava.

the blood–brain barrier and neuronal membranes, diminishes the toxic release of excitatory amino acids, and decreases cerebral edema.⁶⁻⁹

HUMAN TRIALS WITH THERAPEUTIC HYPOTHERMIA IN CEREBRAL ISCHEMIA

Trials in humans have demonstrated that therapeutic hypothermia is feasible and safe, and may be effective, in the setting of acute ischemic stroke. Schwab et al used a cooling blanket to cool 25 patients with severe middle cerebral artery (MCA) strokes to a target temperature of 33°C, for a total duration ranging from 48 to 72 hours, and then gradually rewarmed them during the ensuing 24 hours. Therapeutic hypothermia resulted in a reduction of intracranial pressure (ICP) from 21 to 13 mm Hg, although ICP tended to gradually rise again as patients were rewarmed.¹⁰ In the COOL AID study, a cooling blanket was used to cool patients who had received thrombolytic therapy for acute strokes, resulting in a trend (although not statistically significant) toward improved outcome.¹¹ In two recent trials, therapeutic hypothermia was shown to significantly improve survival and neurologic outcome in comatose survivors of cardiac arrest.^{12,13}

ENDOVASCULAR HYPOTHERMIA FOR ACUTE STROKE

Earlier trials of therapeutic hypothermia have utilized a variety of surface cooling techniques to achieve patient cooling. These have ranged from cooling blankets and ice packs to alcohol rubs.¹⁰⁻¹⁴ The effectiveness of these techniques has been reported to be negatively affected by a lag in time between initiation of therapy and attainment of a target temperature that may span several hours. In the study by Schwab et al, the time to reach a bladder temperature of 33°C ranged from 3.5 to 6.2 hours from the initiation of hypothermia induction.¹⁰ In the COOL AID study, the time to target temperature averaged 3.5 hours.¹¹ A contributing factor to this may be the tendency toward cutaneous vasoconstriction with skin cooling, which presumably limits the circulation of cooled peripheral blood to the core. In addition, surface cooling techniques have resulted in imprecise core temperature control, occasional overshooting of the target temperature,¹¹ and rebound hyperthermia on rewarming.¹⁴ These findings have brought endovascular induction of hypothermia, which enables direct, controlled core blood cooling and rewarming via a heat exchange device inserted into the central venous system, to the forefront in recent clinical trials of therapeutic hypothermia in acute stroke.

Trials with endovascular hypothermia have revealed it to be a technique that, when compared with traditional surface cooling methods, has the capability for more rapid tar-



Figure 2. The Radiant Medical (Redwood City, CA) Reprieve Endovascular Temperature Therapy System.

get temperature attainment and more precise control of temperature once it is achieved. In a primate model of acute MCA stroke, hypothermia to 32°C could be induced at $6.3 \pm 0.8^\circ\text{C}$ per hour with an endovascular device, and resulted in both a significant decrease in infarct volume, as measured by MRI, and a significant improvement in neurologic outcome compared to normothermic controls.¹⁵ In a pilot study of the endovascular technique in humans, Georgiadis et al utilized an endovascular heat exchange element inserted into the femoral vein to induce therapeutic hypothermia to a target temperature of 33°C in six intubated and paralyzed patients with MCA infarctions and noted a mean cooling rate of 1.4°C per hour, with a mean time to target temperature of 3 hours.¹⁶ Keller et al compared a surface cooling technique utilizing a cooling blanket and ice packs with endovascular cooling to a target temperature of 33°C to 34°C in intubated and paralyzed patients with subarachnoid hemorrhage, and found that the mean time to target temperature using the endovascular technique was significantly shorter than with surface cooling (186 minutes compared with 375 minutes) and resulted in significantly tighter temperature control.¹⁷ Outcome, as measured with the Glasgow Outcome Scale, appeared better in the endovascular cooling group, but limitations in the randomization scheme make this result difficult to interpret. In these studies, as well as in studies utilizing surface cooling techniques, induction of therapeutic hypothermia was attained in patients who were intubated and paralyzed with neuromus-

cular blocking agents. We have recently initiated a trial at our institution to investigate the induction of endovascular hypothermia to a target temperature of 33°C in awake, nonintubated patients who present with acute ischemic strokes.

ENDOVASCULAR HYPOTHERMIA DEVICES

There are several manufacturers of commercially available endovascular hypothermia devices. These include Innercool, which makes the Celsius Control system (Figure 1); Alsius Corporation (Irvine, CA), which makes several lines of catheters, including the Icy, Cool-line, and Fortius as part of the CoolGard 3000 Thermal Regulation System; and Radiant Medical, which makes the Reprive catheter as part of the Reprive Endovascular Temperature Therapy System (Figure 2). The systems work on a similar premise: an external device console containing a heat exchange bath cools a solution, such as saline, that is being circulated in a closed loop between the bath and a specialized catheter that has been designed to optimize heat exchange. The catheter is placed into the patient's central venous system (typically via the femoral vein into the inferior vena cava), where it in turn serves as a heat exchanger with circulating core blood.

The catheters come in various sizes, ranging from 8.5 F to 14 F, with varying lengths, and may be metallic in consistency (eg, the Celsius Control catheter made by Innercool, Inc., Figure 3), have expandable balloons (eg, some of those made by Alsius Corp), or have bellows through which cooled solution is circulated (eg, those made by Radiant Medical, Figure 4). The Celsius Control catheter has a built-in temperature probe that enables a direct measurement of core blood temperature during treatment. The catheters are typically inserted via percutaneous central venous access, through an introducer sheath. The time it takes to complete catheter insertion has been reported in clinical trials to be 10 to 25 minutes.^{16,17} The hypothermia device consoles are typically programmable, affording the capability to set a target temperature, cooling rate, and a controlled rewarming phase.

CARDIOVASCULAR, PHYSIOLOGICAL, AND HEMATOLOGICAL EFFECTS OF THERAPEUTIC HYPOTHERMIA

Moderate therapeutic hypothermia (ie, to approximately 33°C), whether obtained from surface or endovascular cooling means, tends to produce typical cardiovascular, physiologic, and hematologic effects. Sinus bradycardia, occasionally with PR and QT interval prolongation, is a common finding, but tends to be neither hemodynamically significant nor of a degree severe enough to require treatment.^{10,11,16} Therapeutic hypothermia tends to result in transient hypokalemia and thrombocytopenia, as well transient, reversible increases in serum amylase and/or lipase levels, although with no discernable clinical correlates of acute pancreatitis or other hepatobiliary injury, all of which gradually resolve in hours to days after return of normothermia.^{10,16} The coagulopathy (abnormalities in prothrombin time and partial prothrombin time) noted with deep hypothermia has not been noted with any discernable frequency in studies utilizing moderate hypothermia.

Pneumonia is frequently stated as a complication of therapeutic hypothermia, but the comorbidity of patients to whom therapeutic hypothermia is being administered, as well as the concurrent intubation and paralysis that has been used to facilitate this treatment, make it difficult to ascribe a direct correlation.^{10,14,16} In addition, recent studies

have shown no significant difference in infection rates between hypothermia versus control patients.^{11,13} Regarding other complications specific to endovascular hypothermia, Georgiadis et al noted no groin hematomas in their study, and Keller et al noted that the catheter infection rate in their subjects was comparable to that observed with central venous catheters in general.^{16,17}

CONCLUSIONS

The benefits of acute therapeutic hypothermia in conditions that result in both focal and global cerebral ischemia have become increasingly evident, as have its feasibility and safety.^{10,12,13} With this realization, the endovascular technique holds promise as a modality in which a target temperature can rapidly and accurately be



Figure 3. The Celsius Control catheter.



Figure 4. A close up of the Reprise catheter.

attained and then precisely maintained, rewarming can be controlled, and a more homogenous response to treatment can be obtained. ■

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