Therapeutic Hypothermia: Past, Present, and Future

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Therapeutic Hypothermia*
Past, Present, and Future
Joseph Varon, MD, FCCP; and Pilar Acosta, MD

Cardiac arrest causes devastating neurologic morbidity and mortality. The preservation of the brain function is the final goal of resuscitation. Therapeutic hypothermia (TH) has been considered as an effective method for reducing ischemic injury of the brain. The therapeutic use of hypothermia has been utilized for millennia, and over the last 50 years has been routinely employed in the operating room. TH gained recognition in the past 6 years as a neuroprotective agent in victims of cardiac arrest after two large, randomized, prospective clinical trials demonstrated its benefits in the postresuscitation setting. Extensive research has been done at the cellular and molecular levels and in animal models. There are a number of proposed applications of TH, including traumatic brain injury, acute encephalitis, stroke, neonatal hypoxemia, and near-drowning, among others. Several devices are being designed with the purpose of decreasing temperature at a fast and steady rate, and trying to avoid potential complications. This article reviews the historical development of TH, and its current indications, methods of induction, and potential future.

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Key words: cardiac arrest; cardiopulmonary resuscitation; cooling techniques; induced hypothermia; neuroprotection; temperature monitoring; stroke; therapeutic hypothermia

Abbreviations: ATP = adenosine triphosphate; ROSC = return of spontaneous circulation; TH = therapeutic hypothermia; VF = ventricular fibrillation

The concept and use of therapeutic hypothermia (TH) to improve neurologic outcome has gained popularity over the past few years. TH was introduced in the 1950s as a protective measure for the brain, and has been used routinely in the operating room in an attempt to provide anesthesia surgery. More recently, TH has been used in patients with traumatic brain injury and increased intracranial pressure who are refractory to medical management.

Several animal and human trials have shown the advantageous effects of lowering the core temperature of the body in a variety of circumstances. In particular, TH improves oxygen supply to ischemic areas of the brain and decreases intracranial pressure. Moreover, this technique has also shown beneficial effects during procedures in which cerebral blood flow needs to be interrupted, such as cardiac and intracranial surgery. Most recently, clinical studies have strongly suggested that the use of TH, after out-of-hospital cardiac arrest with return of spontaneous circulation (ROSC), improves global outcomes.

Historical Development of TH

The historical development of TH dates back millennia; however, its use in modern clinical medicine has been documented for the last 200 years. The Russian method of resuscitation, described in
1803, consisted of covering a patient with snow hoping for the ROSC.\textsuperscript{13} TH was used by Baron de Larrey during Napoleon’s Russian campaign in 1812 in an effort to preserve injured limbs as well as for its numbing effects during amputation.\textsuperscript{14} In 1937, Dr. Temple Fay “cooled” a patient to 32°C for 24 h, in an attempt to prevent cancer cells from further multiplying.\textsuperscript{15} Smith and Fay,\textsuperscript{16,17} in 1940, reported the physiologic effects that induced TH caused in a series of cancer patients. In 1953, using canine and monkey models, Bigelow and McBirnie,\textsuperscript{3} published a study reporting the beneficial effect of TH for the brain and the heart during cardiac surgery. Rosomoff and Gilbert\textsuperscript{18} demonstrated a direct effect between body temperature, and intracranial pressure and brain volume in 1955. These early investigators confirmed that TH reduced the cerebral oxygen consumption, blood flow, and metabolic rate of a normal dog brain.\textsuperscript{9} By 1959, induced TH was widely used by neurosurgeons for head and spinal cord injuries as well as during cardiac surgery.\textsuperscript{1}

Outside the operating room, TH had multiple indications, particularly in patients with neurologic injuries. Benson and colleagues\textsuperscript{19} described a case series of cardiac arrest victims who had a positive outcome after TH had been used. Despite its popularity, a great number of complications were also noted, including cardiac irritability and ventricular fibrillation (VF) with hypothermia (ie, <30°C)\textsuperscript{20} and the decreased clearance rate of staphylococcal bacteremia.\textsuperscript{21} Despite recognizing the protective effects of TH during brain ischemia and head injury, it became apparent that the complications of this therapy made its use risky, and soon thereafter the technique was essentially abandoned.\textsuperscript{14}

Between 1960 and the 1990s, the use of TH decreased because of its potential for complications. Though the approach had lost popularity, some clinicians continued to investigate its potential benefits.\textsuperscript{22} Animal models\textsuperscript{22} revealed that induced TH improved neurologic outcome and survival after cardiac arrest. The positive data supporting the benefits of TH have once again attracted research in this area.

In 2002, the American Heart Association, followed in 2003 by the European Resuscitation Council, recommended TH as a treatment modality for out-of-the hospital comatose victims of cardiac arrest.\textsuperscript{23-25} Based on the results of these trials, the American Heart Association and the European Resuscitation Council recommended TH as a treatment modality for out-of-hospital comatose victims of cardiac arrest.\textsuperscript{11,26} One of the trials\textsuperscript{11} was a blinded, randomized, multicenter, clinical trial conducted in Europe, which enrolled 275 cardiac arrest victims, including patients with an arrest secondary to VF. One hundred thirty-seven patients were treated with TH and 138 served as control subjects.\textsuperscript{11} To maintain temperature at approximately 32 to 34°C (ie, bladder temperature), the hypothermic group was treated with a cool circulating air device and ice packs for a period of 24 h.\textsuperscript{11} The results of this trial\textsuperscript{11} revealed significantly more favorable neurologic outcomes and reduced mortality rates in the hypothermia group compared with those in the standard-treatment group.

Pathophysiology of the Ischemic Insult

Since the early development of TH as a therapeutic approach, much has been learned about the pathophysiology of ischemic insult. During cardiac arrest, cerebral perfusion stops, and a cascade of events occur. Within 10 s, there will be a loss of consciousness, and after 20 s EEG activity will become isoelectric.\textsuperscript{7,27} which will be followed by anaerobic glycolysis leading to a decrease in energy stores. It has been theorized\textsuperscript{28} that the energy depletion occurs very fast.

In addition to energy depletion, there is depolarization and loss of the normal Ca\textsuperscript{2+} balance between the extracellular and intracellular compartments.\textsuperscript{7,27} The deficiency of intracellular adenosine triphosphate (ATP) affects transmembrane transport structures such as Na\textsuperscript{+}, K\textsuperscript{+}, ATPase, and Ca\textsuperscript{2+}, ATPase pumps.\textsuperscript{27} There is an increase in interstitial K\textsuperscript{+} and intracellular Ca\textsuperscript{2+}, as well as a large influx of Na\textsuperscript{+} and Cl\textsuperscript{−} into the cells. Studies using magnetic resonance spectroscopy have shown that phosphocreatine is depleted within 1 min and ATP within 2 to 3 min after the onset of the cardiac arrest.\textsuperscript{28} Additionally, intracellular acidosis, lipid peroxidation, and production of free oxygen radicals occurs.\textsuperscript{29} The cumulative effect of these processes results in cell death.\textsuperscript{29}

Even after normalization of the blood flow and energy storage replenishment, there is continued tissue injury. This type of damage during reperfusion is thought to be mainly secondary to the accelerated generation of free oxygen radicals.\textsuperscript{27} The initial neuronal damage after ischemia and reperfusion injury triggers an inflammatory response involving microglia-derived mediators, beginning a vicious cycle leading to a slow progressive neurodegeneration.\textsuperscript{7} These postischemic effects are exacerbated when the patient’s temperature increases by ≥ 0.5°C over 37°C.\textsuperscript{7}

Activation of the N-methyl-d-aspartate receptors occurs as body temperature increases, contributing to the elevation of intracellular calcium levels.\textsuperscript{30} The activation of N-methyl-d-aspartate receptors is also associated with the generation of nitric oxide.\textsuperscript{30,31} Pyrexia enhances the harmful effects of free radicals generated by the release of arachidonic acid.\textsuperscript{30,31} It is believed that the formation of free radicals, and their
Physiologic Effects of TH

Traditionally, the protective effect of hypothermia has been attributed to a reduction of metabolic rate. Specifically, the cerebral metabolism (ie, estimates of oxygen consumption, glucose utilization, and lactate concentration) is dependent on temperature, and hypothermia has been shown to reduce the cerebral metabolism by decreasing all of these parameters. It is estimated that for each 1°C decrease in temperature, the cerebral metabolic rate decreases by 6 to 7%.7,9

Mild-to-moderate TH (ie, temperatures of 32 to 34°C) has been shown to decrease cerebral blood flow due to cerebral vasoconstriction, particularly in patients with traumatic brain injury.3,32 This mechanism decreases the intracranial pressure and may act as an anticonvulsant.33 TH also affects the pH value, and for every 1°C decrease in body temperature there is an increase of 0.016 points in the pH value.32

The effects of mild TH on the cardiovascular system include decrease in heart rate and increase in the systemic vascular resistance.3 TH decreases cardiac output by 7% for each 1°C decrease in core body temperature.33 It also maintains the stroke volume and the mean arterial pressure. Moreover, TH decreases the minute ventilation to maintain Pco₂ in the normal range.1

Increase in renal blood flow accounts for the increased diuresis that is seen in patients with mild TH, especially during induction.33,34 During this phase, there is also an increased uptake of potassium inside the cells, leading to hypokalemia, and the correction of this derangement can lead to hyperkalemia during rewarming.3,35 Similarly, TH decreases phosphate concentrations.36 Careful interpretation of arterial and venous blood gas levels is required in patients undergoing TH, and corrections should be made according to temperature as the solubility of the blood gases increases as the body temperature decreases.3

For patients who undergo TH, it has been recommended that the start of enteral feedings be delayed, as gut motility is impaired during hypothermia.3 Hypothermia also decreases plasma insulin levels, and it has been hypothesized37 that this is secondary to catecholamine release. As a result, there is concomitant hyperglycemia, and exogenous insulin should be administered in patients undergoing TH.35,39

There is an association between prolonged hypothermia and abnormal bleeding. Hypothermia has unfavorable effects on platelet function, and prolongs prothrombin and partial thromboplastin times.40 Moreover, there is an increased incidence of neutropenia and susceptibility for infections, particularly in patients with pneumonia that has been associated with the use of TH.3,40 When considering the use of TH, prudence must be exercised to avoid these possible untoward effects, as the physician works to minimize the damage caused by the presenting condition.

Conventional and Innovative Cooling Techniques

There are several ways to induce TH.41,42 The ideal cooling device has yet to be developed, but ideally it would have a high rate of temperature reduction, preferential cooling on target organs, be capable of easy transport, and be able to be employed during cardiopulmonary resuscitation.43 Since there is no standard method or approach, the clinician should consider which technique is the best for each individual case.

Among the most commonly used techniques are surface cooling (Fig 1) and invasive cooling (Table 1). Surface cooling is relatively simple to use, but it takes longer to achieve the target body temperature (ie, average, 2 to 8 h). It can also be accomplished through the use of ice packs, circulating cold-water blankets, forced cold air forced blankets, alcohol baths, and cold-water immersion.42,44,45 One drawback of external cooling devices is that the shivering response to TH may be increased.46

Mayer and colleagues46 studied the efficacy of an external cooling device in neurocritical care patients in whom sustained pyrexia developed. The apparatus described included a series of self-adhesive, hydrogel-coated pads that circulated temperature-controlled water under negative pressure.46 When compared with conventional blanket cooling therapy, this surface-cooling method proved to significantly decrease the fever burden by 75% from 16.1 to 4.1°C-hours (p = 0.001).46 The improvement was thought to be related to the larger surface area that was covered when compared to that covered with cooling blankets. A recent observational study using the same technology (ie, hydrogel pads) showed a mean temperature reduction of 1.4°C per hour, and median time of 137 min to reach the target core body temperature.47

Other noninvasive methods for the induction of selective brain cooling have been reported.48 The most commonly used methods are cooling caps and helmets; however, some empirical analyses49 have theorized that these methods show poor efficacy in reducing deep brain temperature.

While external cooling is easy to apply, it is less efficient in reducing the temperature of some target organs such as the brain or the heart. Hence, other,
more invasive, approaches have been explored. These cooling treatments include cold carotid infusions, single carotid artery perfusion with extracorporeal cooled blood, ice-water nasal lavage, cardiopulmonary bypass, cold peritoneal lavage, nasogastric and rectal lavage, and the infusion of cold IV fluids.41,42,45,50

The infusion of cold IV fluids has been shown to be endurable and realistic, even in the prehospital setting.51 Virkkunen and coworkers51 demonstrated that ice-cold Ringer’s solution administered as soon as possible after the ROSC improved the neurologic outcome in cardiac arrest victims. Kliegel et al52 and Bernard et al53 rapidly infused large amounts (30 mL/kg) of Ringer’s lactate solution at 4°C, with a significant decrease in the core body temperature. In an emergency department (ED) study, Kliegel et al.52 infused 2 L of cold intravascular fluids for endovascular cooling without harmful side effects.

Another method to induce TH, developed by Zviman and colleagues,43 included a device that required the circulation of blood through an extracorporeal circuit, allowing for the rapid infusion of cold fluids, the oxygenation of blood during resuscitation, and the rapid delivery of IV drugs. These types of cooling strategies are the most rapid methods for reducing temperature but may only be accomplished in centers where there is staff readily available 24 h per day.54

Endovascular cooling is accomplished with an external heat exchange control device that is designed to circulate chilled saline solution through an intravascular catheter that is placed percutaneously in the patient.50,55 Several approaches can be accomplished using different catheters; even the use of a peripheral vein for the infusion of cold fluids is a successful method for inducing TH.56,57

Other techniques that have been utilized for selective brain cooling include femoral-carotid artery bypass, intraventricular cerebral hypothermia, and hypothermic retrograde jugular vein flush, which have been shown to be alternatives to achieve rapid brain cooling in animal models.58,59 Other techniques, such as blood cooling through the lungs and by the inhalation of gases, are still under investigation.54 In animal experiments, Yang and coworkers60 revealed that intrapulmo-

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<th>Table 1—Therapeutic Hypothermia Cooling Techniques</th>
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<tr>
<td><strong>Noninvasive Techniques</strong></td>
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<tr>
<td>Caps or helmets</td>
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<td>Air-filled</td>
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<td>Water-circulating</td>
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<td>Cooling blankets</td>
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<td>Water-circulating</td>
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<tr>
<td>Hydrogel-coated cooling pads</td>
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<td>Ice packs</td>
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<td>Immersion in cold water</td>
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Figure 1. The CritiCool TH device.
nary perfluorochemical fluids might be an effective technique to induce and/or augment hypothermia while supporting gas exchange, lung volume, and pulmonary architecture. The use of nasopharyngeal balloons is a promising technique.61

**Temperature Monitoring**

TH is considered to be mild at 32 to 34°C, moderate at 28 to 31.9°C, deep at 11 to 27.9°C, profound at 6 to 10.9°C, and ultraprofound at < 6°C.40 In most therapeutic applications, it is recommended to keep the temperature of patients at 32 to 34°C.23

Regardless of the means used to achieve TH, reliable temperature measurements are essential.62 The monitoring of core body temperature can be done with a variety of probes, including rectal, tympanic membrane, bladder, esophageal, and vaginal probes, or via pulmonary artery catheter.23 In one study,61 venous blood temperature was compared with the measurements obtained from other temperature probes. A temperature gradient of only 0.2°C was noted among the jugular vein, subdural, tympanic membrane, pulmonary artery, and bladder temperatures.62,63 Therefore, it appears that bladder temperature monitoring should be reliable and less invasive.

Tympanic membrane temperature is a noninvasive way to monitor temperature and correlates well with brain and epidural temperature;62 however, impaired readouts can occur, particularly when there is obstruction in the auditory canal (ie, cerumen).62,64 When using tympanic membrane temperature probes, cooling of the head should be avoided to reduce the chance of impaired readings.62,64,65 Rectal probes should also be avoided as they tend to be inexact due to fecal insulation and do not correlate with intracranial temperature.64 In instances when profound hypothermia is rapidly induced, temperature monitoring should not be performed at standard sites, as it may not reflect brain temperature accurately.66

**CURRENT CLINICAL APPLICATIONS AND POTENTIAL USES OF TH**

After rigorous evaluation of the published evidence, an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation was issued in October 2002,23–25,67 announcing recommendations with regard to the use of TH. TH with cooling to 32 to 34°C for 12 to 24 h was recommended for use in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest23 when the initial heart rhythm was VF. The panel also stated25 that TH may possibly be beneficial for treatment of other heart rhythms and for in-hospital cardiac arrest.

The use of TH in other clinical scenarios has also been investigated.3 As noted above, some of them include near-drowning, anoxic brain injury, traumatic head injury, traumatic cardiac arrest, stroke, newborn hypoxic-ischemic encephalopathy, hepatic encephalopathy, bacterial meningitis, cardiac failure, postoperative tachycardia, and ARDS.3,51,62,68–72

Near-drowning is a special situation in which TH has been shown to confer neuroprotection. Based on the premise that accidental hypothermia in near-drowning victims has had a beneficial neuroprotective effect, Modell and coworkers73 reported a case in which a 2-year-old boy was submerged for at least 20 min in a freshwater creek. Cardiopulmonary resuscitation was administered for approximately 1 h, and the patient’s Glasgow coma scale score was 3 with a rectal temperature of 26.7°C. At 72 h, in an ICU, the patient emerged from the coma and 6 months later he was neurologically intact.73 Similarly, Varon and Marik74 reported a case of warm-water near-drowning with cardiac arrest lasting > 30 min before the ROSC, with full neurologic recovery occurring after the late introduction of TH (12 h post-cardiac arrest).

Mild-to-moderate TH has also been used successfully with traumatic brain injury.4 A single-center clinical trial22 demonstrated an improvement in neurologic function in the patients where TH had been induced an average of 10 h after injury to 33°C over a period of 24 h compared to normothermic patients. Conversely, in other studies,75,76 TH has failed to demonstrate a neurologic survival benefit in patients with severe brain injury. This particular area of TH application requires additional study to develop the most efficacious treatment strategy and to identify candidates who would be the most likely to derive a benefit from the procedure.

Recently, TH has been shown to improve neurologic outcome in patients who have experienced acute cerebrovascular accidents. Schwab and coworkers,77 in a clinical trial with 25 patients with severe acute stroke of the medial cerebral artery, demonstrated that TH not only reduced intracerebral pressure but also reduced levels of extracellular excitatory amino acids compared to normothermic patients. These results correlated with an improvement in neurologic recovery in patients with acute ischemic stroke.

The use of systemic TH for the treatment of spinal cord injury has also shown beneficial results in animal models, acting as a protective agent against locomotor deficits78 and decreasing the number of dead neurons.79 It has also been reported74 that systemic TH improved neurologic outcome after cervical spine contusion.

Currently, there is considerable interest in the use of TH for the setting of transient cerebral hypoxia-ischemia in newborns.71 Patients with the most...
severe form of perinatal hypoxia-ischemia can end up having permanent neurodevelopmental injury, consisting of spastic quadripareisis, profound cognitive deficiency, and epilepsy. In a study performed in piglets, TH was induced for 24 h after asphyxic cardiac arrest, revealing decreased acute neuronal necrosis in the striatum and sustained neuroprotection at 11 days postrecovery with improved global functional recovery.

Another potential use of TH is in the treatment of liver failure, when fulminant altered mental status is present concomitant with an increase in intracranial pressure. In an experimental study in an animal model, Rose and colleagues showed that mild TH decreased levels of ammonia in cerebrospinal fluid, reduced cerebral extracellular concentrations of ammonia, and decreased levels of brain water, leading to a decline in intracranial pressure compared to normothermic control subjects. Likewise, Cordoba and associates, in a similar model, found that TH prevented ammonia-induced cerebral edema.

Villar and Slutsky, in a concurrent controlled, prospective study conducted at a single center in an adult multidisciplinary ICU within a teaching hospital, obtained a reduction of 34% in the mortality rate of patients with severe ARDS who had been treated with TH compared to normothermic control subjects (p = < 0.05). Based on the substantial interest in TH, it is clear that this therapy offers much potential for considerable therapeutic benefit across a variety of disease states.

Timing and Therapeutic Window

More recent data have suggested that TH should be initiated as early as possible after ROSC, since the extent of brain damage is related primarily to the length of ischemia. Data from animal studies have advocated for early cooling after reperfusion following cardiac arrest, as the earlier that TH was initiated the greater the likelihood of a positive outcome. Nonetheless, notable therapeutic benefit has also been seen in clinical studies where cooling was delayed for several hours. The current recommendations regarding the duration of TH from the International Liaison Committee on Resuscitation range from 12 to 24 h in the postresuscitation period.

Rewarming

After the recommended period of induced TH, rewarming should be initiated using heating air blankets that increases the temperature at a rate of 0.5 to 1°C per hour. In cases in which intracranial hypertension is controlled only with hypothermia, a slow rewarming period at a rate of 1 to 2°C per day should be established.

Table 2—Cooling Techniques and Possible Adverse Effects

<table>
<thead>
<tr>
<th>Cooling Techniques</th>
<th>Possible Adverse Effects</th>
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<tr>
<td>Caps or helmets</td>
<td>Low cooling rate</td>
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<tr>
<td>Cooling blankets</td>
<td>Low cooling rate, high incidence of shivering</td>
</tr>
<tr>
<td>Hydrogel-coated cooling</td>
<td>Low cooling rate, high incidence of shivering, high cost</td>
</tr>
<tr>
<td>Endovascular cooling</td>
<td>Rapid cooling rate, risk of infections, high cost</td>
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<tr>
<td>Nasopharyngeal catheter</td>
<td>Still experimental technique, potential use for selective brain hypothermia</td>
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</table>

Complications and Practical Considerations During TH

Shivering is considered one of the primary side effects of TH. Shivering increases temperature and overall oxygen consumption. During the treatment and rewarming periods, shivering should be avoided, and hypotension should be treated with IV fluids. This side effect can be avoided with proper sedation and the administration of neuromuscular blockers.

Other reported complications have mainly included dysrhythmias and coagulopathies. A decrease in the capacity to clear bacterial infections has been reported previously. A very conspicuous increase in the number of leukocytes has been observed, more frequently after the first 24 h of reduced body temperature (Table 2).

Conclusions

The induction of mild TH in patients after cardiac arrest is a useful method of neuroprotection against ischemic neuronal injury. The best technique to induce hypothermia is still not well defined and will likely vary depending on the patient’s presenting condition. Further studies need to be performed to identify other potential applications, to develop a better understanding of the benefits and detrimental effects of TH, and to identify the most efficacious TH strategy and the candidates who will be most likely to derive a benefit from undergoing the procedure.

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