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## LEARNING OBJECTIVES

- Review causes of sudden cardiac arrest and the use of hypothermia in this setting
- Describe how to monitor therapeutic hypothermia and the potential adverse effects of cooling
- Discuss pharmacologic agents used with therapeutic hypothermia
- Describe cooling and rewarming techniques

# Use of mild therapeutic hypothermia improves outcomes in cardiac arrest

Induced hypothermia is used to prevent brain ischemia during cardiac surgery. Two landmark studies demonstrated that it is also effective for treating out-of-hospital cardiac arrest.

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Cardiac arrest is common in the United States; it accounts for approximately 325,000 deaths every year.<sup>1</sup> Many patients with cardiac arrest in whom a return of spontaneous circulation is achieved ultimately have a poor functional outcome as a result of hypoxic-ischemic injuries sustained during and after the arrest. Despite many years of data analysis and improvements in CPR techniques and advanced cardiac life support protocols, the American Heart Association reports that median survival to discharge after sudden cardiac arrest is 6.4%.<sup>1</sup> Only 11% to 48% of patients who survive the acute event are discharged from the hospital with a good neurologic outcome.<sup>2</sup> Over the years, the prognosis after sudden cardiac arrest has remained unchanged in spite of massive educational efforts and improved technological advances. However, mild therapeutic hypothermia as a possible treatment modality has promising outcomes.

Actively cooling a patient to 32°C to 34°C, termed *induced therapeutic hypothermia*, is a technique that has been used for more than half a century to protect the brain from ischemia caused by a cessation of normal cardiac mechanical function. Introduced in the 1950s, induced therapeutic hypothermia was used to prevent potentially devastating ischemia to the brain during cardiac surgery. Soon after, clinicians used therapeutic hypothermia as treatment after an out-of-hospital cardiac arrest (OHCA). The practice was quickly abandoned, however, because of difficulties in attaining and maintaining the lower body temperature and an uncertainty about its benefits.

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Photo courtesy of Medivance

Induced therapeutic hypothermia via gel pads

Therapeutic hypothermia was reevaluated in the early 1980s because animal studies showed that hypothermia reduced postarrest neuronal damage.<sup>3,5</sup> The encouraging results found with animal models led to a resurgence of human clinical trials in the 1990s. The results of two milestone studies that demonstrated improved neurologic function and survival after sudden cardiac arrest in patients treated with the technique were published in 2002.<sup>6,7</sup> The International Liaison Committee on Resuscitation included therapeutic hypothermia in its published

“The resuscitation process must stop ischemic progression in a timely manner as well as avoid postresuscitation syndrome.”

recommendations in 2003, and in 2005, the American Heart Association included 12 to 24 hours of therapeutic hypothermia in its formal recommendations for treating survivors of OHCA. Hypothermia has emerged as an effective mode of neuroprotection after cardiac arrest and a preventive technique for other neurologic conditions that result from cardiac arrest, such as traumatic brain injury, stroke, and anoxic brain injury.

#### REVIEW OF KEY STUDIES

A thorough review of the data for mild hypothermia after cardiac arrest is beyond the scope of this article. However, a discussion and brief synopsis of the major studies that support the use mild therapeutic hypothermia is worthwhile. Cerebral ischemia may persist for hours after resuscitation, and the use of hypothermia may decrease the multifactorial effects. The stage was initially set by two landmark studies that evaluated the efficacy of therapeutic hypothermia after cardiac arrest (Table 1).

**Bernard and colleagues** conducted a randomized controlled study of 77 patients from four hospitals in Melbourne, Australia.<sup>6</sup> The study compared the use of therapeutic hypothermia with normothermia in patients with cardiac arrest who remained unconscious after resuscitation. The primary

end point was survival to hospital discharge with good neurologic function. Patients were randomized according to the day of the month; patients were assigned to hypothermia on odd-numbered days. The 43 patients assigned to the hypothermia group received early-initiated cooling by the ambulance service via cold packs with target core temperature of 33°C. Upon arrival at the hospital, a thorough neurologic examination was performed, and cooling was continued to the target temperature. All patients in both groups were started on midazolam (2-5 mg) and vecuronium (8-12 mg) for shivering. In addition, all patients were given lidocaine, a loading dose of 1 mg/kg followed by continuous infusion (2 mg/min) for 24 hours, to prevent recurrent ventricular arrhythmias. Core temperature of 33°C was maintained for 12 hours, and then patients were actively rewarmed over 6 hours via heated-air blanket.<sup>6</sup>

After adjustment for differences between the groups, this study found that 49% (21/43) of patients in the hypothermia group survived with good neurologic outcome compared with 26% (9/34;  $P=.046$ ) of patients in the normothermia group.<sup>6</sup> The adjusted odds ratio for good outcome between the two groups was 5.25 (95% confidence interval [CI] 1.47-18.76;  $P=.011$ ). A favorable outcome was defined as discharge to home or a rehabilitation facility. A poor outcome was defined as discharge to a long-term nursing facility or death. Mortality rates for the hypothermia and normothermia groups were 51% and 68%, respectively, with no statistically significant difference ( $P=.145$ ).<sup>6</sup>

**The Hypothermia after Cardiac Arrest (HACA) Study Group** conducted the second study.<sup>7</sup> This larger randomized controlled trial involved 275 patients from nine centers in five European countries. Again, the study compared the efficacy of therapeutic hypothermia with the efficacy of normothermia in patients with cardiac arrest as a result of ventricular fibrillation. Primary end points were a favorable neurologic outcome within 6 months after cardiac arrest, determined by the Pittsburgh cerebral performance scale (score of 1 [good recovery] or 2 [moderate disability]). Secondary end points were mortality within 6 months and the rate of complications within 7 days. Treatment assignments were computer-generated; 137 patients were randomly assigned to the hypothermia group, and 138 patients were assigned to the normothermia group.<sup>7</sup>

#### KEY POINTS

- Therapeutic hypothermia decreases energy use and oxygen consumption in the brain and heart and glucose consumption during the early stages of cardiac arrest.
- The patient is cooled as quickly as possible, within 3 to 4 hours, to a target temperature of 32°C to 34°C, and rewarming begins 24 hours after the initiation of hypothermia.
- Hypothermia is induced with cooling blankets and mattresses in conjunction with ice packs and, in some cases, cooled IV fluids. Other methods include ice lavage, surface cooling helmets, and endovascular heat-exchange catheters.
- Passive rewarming techniques are simply to remove the cooling device or to discontinue the cooling method and allow the patient to return to normal temperature. Active rewarming techniques use warming blankets or warmed IV fluids.

**TABLE 1. Summary of landmark clinical trials<sup>6,7</sup>**

Studies (location)	Methodology	Initial cardiac rhythm	Number of patients (hypothermia/control)	Target temperature	Neurologic outcome and survival (hypothermia/controls)	Complications (hypothermia/controls)	Study limitations
Bernard and colleagues (Australia)	Multicenter (4) RCT	VF or VT	43/34	33°C	<ul style="list-style-type: none"> <li>• Good neurologic outcome 49%/26% (<math>P=.046</math>)</li> <li>• Survival 49%/32% (<math>P=.011</math>)</li> </ul>	Mortality rate 51%/68% ( $P=.145$ )	<ul style="list-style-type: none"> <li>• Small sample size</li> <li>• Strict inclusion criteria</li> <li>• Excluded woman &lt;50 y</li> </ul>
HACA Study Group (Europe)	Multicenter (9) RCT	VF or VT	136/137	32°C-34°C	<ul style="list-style-type: none"> <li>• Good neurologic outcome 55%/39% (<math>P&lt;.01</math>)</li> <li>• Survival 59%/45% (<math>P&lt;.05</math>)</li> </ul>	Overall complications 98%/70% ( $P=.70$ )	Strict inclusion criteria

Key: HACA, Hypothermia after Cardiac Arrest; RCT, randomized controlled trial; VF, ventricular fibrillation; VT, ventricular tachycardia.

Patients in the hypothermia group were cooled via external cooling device to a target bladder temperature of 32°C to 34°C within 4 hours after the return of spontaneous circulation.<sup>7</sup> Hypothermia was maintained for 24 hours, followed by passive rewarming. Seventy-five (55%) patients in the hypothermia group and 54 (39%) patients in the normothermia group had favorable neurologic outcomes (adjusted risk ratio [RR] 1.47; 95% CI 1.09-1.82;  $P=.009$ ; number needed to treat [NNT]=6). Further analysis of data demonstrated a 6-month survival rate after cardiac arrest of 41% for the hypothermia group and 55% for the normothermia group (adjusted RR 0.62; 95% CI 0.36-0.95;  $P=.02$ ; NNT=7). The difference in complications (eg, bleeding, pneumonia, sepsis, and renal failure) among the groups was not statistically significant ( $P=.70$ ).<sup>7</sup>

#### RATIONALE FOR THERAPEUTIC HYPOTHERMIA

The brain is at risk of ischemia during cardiac arrest. Neuronal impairment and reperfusion are determined by arrest time, resuscitation time, reperfusion severity, and core body temperature.<sup>8</sup> Therefore, the resuscitation process must stop ischemic progression in a timely manner and avoid postresuscitation syndrome in order for the patient to have a favorable neurologic outcome. Postresuscitation syndrome has four possible mechanisms: (1) perfusion failure, eg, prolonged and/or multifocal hypoperfusion; (2) reoxygenation injuries, eg, oxygen-free radical inflammatory cell processes; (3) extracerebral causes, eg, postanoxic viscera; and (4) blood derangements, eg, stasis during cardiac arrest.

Cardiac arrest decreases cerebral blood flow immediately despite an ongoing consumption of oxygen, adenosine triphosphate, and glucose.<sup>3,9</sup> The brain loses its oxygen stores within 20 seconds, and a chain of cellular reactions is initiated by the lack of cerebral oxygen followed by cel-

lular death within minutes. Several hours after the cardiac arrest, excitatory amino acids and glutamate are released in the brain, thereby activating cytotoxic cascades including free radicals and nitric oxide.<sup>3</sup> The increase in glutamate level destroys neurons.<sup>10</sup> As ischemic progression continues, a late phase of cerebral injury, which can occur up to 24 hours after cardiac arrest, is likely to ensue. At this stage, the blood-brain barrier breaks down because inflammatory cells infiltrate the brain and release cytokines, which promote microvascular permeability. Cerebral edema develops, and is followed possibly by seizures and/or brain death.<sup>3</sup>

Therapeutic hypothermia is believed to slow down the cellular chain reaction progression after cardiac arrest. Initial studies demonstrated that hypothermia decreases energy use and oxygen consumption in the brain and heart<sup>4,5,9</sup> and glucose consumption<sup>11</sup> during the early stages of cardiac arrest (Table 2). Cooling the brain may lead to a 5% reduction in oxygen and glucose consumption per degree Celsius.<sup>9</sup> Furthermore, hypothermia decreases the release of excitatory amino acids<sup>12</sup> and other neurotoxic mediators,<sup>9,13,14</sup> which reduces nitric oxide production,<sup>15</sup> thereby delaying the increase of nitric oxide.<sup>16</sup> In addition, hypothermia may delay the deterioration of the blood-brain barrier and thus decrease cerebral edema seen in the late phase of cerebral injury.<sup>3,15</sup> Therefore, therapeutic hypothermia may provide cerebral protection, improve neurologic outcome, and mitigate brain damage after cardiac arrest.

#### COOLING/REWARMING TECHNIQUES

Therapeutic hypothermia has been used since the early 1950s. Its role has evolved in the past several decades, and the technique is becoming an essential part of postcardiac arrest management. Recent studies have made more information about hypothermia available and resulted in

the establishment of a treatment guideline. The patient is cooled as quickly as possible, within 3 to 4 hours, to a target temperature of 32°C to 34°C,<sup>17</sup> and rewarming begins 24 hours after the initiation of hypothermia.

Cooling must be initiated as early as possible and the lower temperature maintained for 24 hours to achieve maximum neurologic protection. In most of the studies reviewed for this article, hypothermia was induced with cooling blankets and mattresses in conjunction with ice packs and, in some cases, cooled IV fluids. Other methods that have been used to achieve the target temperature include ice lavage, surface cooling helmets, and endovascular heat-exchange catheters.

Various methods of thermometry are used to measure body temperature during cooling and rewarming, including esophageal, rectal, bladder, tympanic, and axillary routes. Infrared tympanic thermometry measurements and/or rectal or bladder thermometers were the most common methods used in the studies that expressed how body temperature was monitored. Some investigators used pulmonary artery catheters to monitor core body temperature.<sup>18</sup> Several of the studies indicated that some patients were or may have been insufficiently cooled with the surface or blanket/mattress/ice pack method.

Further studies are needed to determine the most efficacious way to cool patients and to keep their body temperature within the target temperature range; currently, no one method is proven to be superior to another. New information may come from a study by Marcus Ong, MD, and colleagues at Singapore General Hospital.<sup>19</sup> This prospective clinical study seeks to compare controlled therapeutic hypothermia using external and internal cooling with standard ICU therapy for postcardiac arrest treatment. Primary and secondary outcome measures are survival to hospital discharge (time frame: 30 days after arrest) and neurologic status of postresuscitation patients 1 year after discharge, respectively.<sup>19</sup>

**TABLE 2. Effects of hypothermia<sup>3</sup>**

Accelerates neuronal recovery
Attenuates free radical reactions
Improves glucose utilization
Lowers intracranial pressure
Mitigates intraneuronal calcium mobilization
Preserves adenosine triphosphate
Protects fluidity of plasma lipoprotein membranes
Reduces cytotoxic and vasogenic edema
Reduces excitatory neurotransmitter release
Reduces neutrophil migration into ischemic areas
Reduces production of nitric oxide, lactate, and tissue acidosis
Reduces production of superoxide anions

Rewarming techniques were rarely discussed in the studies reviewed for this article. Passive techniques are simply to remove the cooling device or to discontinue the cooling method and allow the patient to return to normal temperature. Active techniques use warming blankets or warmed IV fluids.<sup>18,20-22</sup> No studies have been reported on whether the method and/or timeline for rewarming significantly impact the success of hypothermia. However, some authors propose rewarming at a rate of 0.3°C to 0.5°C per hour to a target temperature of 36°C.<sup>17</sup>

### COMPLICATIONS

Hypothermia may cause adverse effects on multiple organ systems, including the circulatory, neurologic, hematologic, and endocrine systems. In the HACA study, complication rates for the normothermic (93 of 132 patients; 70%) and hypothermic (98 of 135 patients; 73%) groups were similar, with no difference in the overall rate of complications between groups ( $P=.07$ ).<sup>7</sup> Complications noted in the normothermic versus hypothermic groups were lethal or long-lasting arrhythmia (32% vs 36%), pneumonia (29% vs 37%), bleeding (19% vs 26%), renal failure (10% vs 10%), and sepsis (7% vs 13%), respectively. Other complications occurred equally in both groups, including pancreatitis, pulmonary edema, and seizures.<sup>7</sup> Although no specific complications were reported to be statistically significant, the risk of these potential complications occurring should be considered.

Initially, the effect on the **cardiovascular system** is an increased heart rate and hypertension caused by adrenergic stimulation, increased systemic vascular resistance, and vasoconstriction.<sup>23</sup> Further cooling will continue to slow down circulation by causing bradycardia, which is likely to be the direct effect of decreased spontaneous depolarization on the pacemaker rate, and reducing cardiac output by up to 25%.<sup>23</sup> In addition, hypothermia has the potential to cause cardiac arrhythmias if the body temperature falls below 30°C, with atrial fibrillation being the most common arrhythmia. Ventricular arrhythmias can occur if the body temperature drops below 28°C. These arrhythmias are most likely caused by decreases in metabolism and the direct effect of hypothermia on the heart.<sup>23</sup>

Secondary side effects to the **neurologic system** include decreased consciousness, lethargy, and coma caused by CNS depression. Electrical activity in the brain begins to significantly slow when body temperature goes below 33.5°C.<sup>8</sup>

Hypothermia has negative effects on the **hematologic system**. The number and function of platelets are reduced, which causes increased bleeding times and clotting times.<sup>24</sup> However, few bleeding complications were noted in the reviewed studies. Inhibition of the inflammatory responses reduces the number and function of white blood cells. The impaired immune function may contribute to more infections, pneumonia, and sepsis; however, inducing hypo-

thermia for a brief period of time (24 hours) reduces the risk of infectious complications.<sup>6,7</sup>

An important side effect of acute exposure to cold temperatures involves the **endocrine system**. Initial hyperglycemia is caused by catecholamine-induced glycogenolysis<sup>8</sup> and gluconeogenesis.<sup>25</sup> Insulin resistance and secretion are decreased by hypothermia, also contributing to hyperglycemia. The amounts of insulin that will be needed to keep glucose levels in the normal range are likely to be higher during hypothermia.

## MEDICATIONS

Currently, sedatives, analgesics, and neuromuscular blocking agents (NMBAs) are used for sedation and pain management and to prevent unwanted movements, reduce muscle oxygen consumption, and inhibit shivering in order to prevent myocardial ischemia<sup>26</sup> (**Table: Medications used in therapeutic hypothermia** in the online version of this article). However, the number of available human studies is limited; therefore, choosing which agents to use for the patient is difficult. The protocols from the studies reviewed here suggest initiating therapeutic hypothermia with an infusion of a sedative/anesthetic (either midazolam or propofol), with or without a narcotic infusion (eg, morphine, fentanyl); and administration of a NMBA (eg, vecuronium, cisatracurium, pancuronium) during induction, maintenance, and rewarming.<sup>27</sup>

The hypothermia process begins with administration of either midazolam or propofol to decrease the level of consciousness and further inhibit the thermoregulatory process.<sup>25</sup> Morphine, fentanyl and meperidine are commonly used as adjunct therapy during therapeutic hypothermia, but their roles have not been clearly defined. Although opioids may be used for pain management, these drugs appear to have antishivering properties that further minimize oxygen consumption. NMBAs have been used to control shivering after cardiac or neurologic surgery for many years; in therapeutic hypothermia, they are used to reduce muscle oxygen consumption and prevent unwanted movement during initiation, maintenance, and rewarming.<sup>28</sup>

Pharmacologic agents remain the most commonly used methods of preventing increased oxygen consumption and treating shivering during therapeutic hypothermia, which are essential for successful outcomes. At present, the limited number of therapeutic hypothermia studies and knowledge of its effects on both the pharmacokinetics and pharmacodynamics of many drugs make choosing the most effective agent(s) difficult, but clinicians should be aware of other

## “Prompt recognition of a patient’s eligibility for induced hypothermia and early initiation of treatment ensures a better outcome.”

available agents and alternatives. Further studies are needed to determine the most appropriate agent from each group of medications.

## CONCLUSION

Studies have proven that therapeutic hypothermia provides cerebral protection. Therapeutic hypothermia after sudden cardiac arrest in patients who remain comatose has been shown to improve short-term neurologic recovery outcomes and survival; however, the process is not without risk. The physiologic effects of hypothermia and the alterations in pharmacokinetics of medications warrant careful consideration before implementation.

Although therapeutic hypothermia is protective after cardiac arrest, an important note is that the landmark studies discussed in this article focused on specific subgroups of patients. The studies recruited patients whose arrests were witnessed, whose initial rhythms were ventricular fibrillation or pulseless ventricular tachycardia, and who had a return of spontaneous circulation within 60 minutes. Therefore, research that examines hypothermia in larger patient populations is needed. In addition, evidence of which cooling methods provided the best, fastest, and most reliable reduction in temperature; how long a patient should be cooled; and if induced hypothermia for other types of cardiac arrest would be beneficial is lacking.

With appropriate evaluation and treatment, clinicians can make a difference in a patient’s neurologic outcome after cardiac arrest. Prompt recognition of a patient’s eligibility and initiation of treatment ensures a better outcome. Clinicians who care for critically ill patients are encouraged to become knowledgeable about the indications for therapeutic hypothermia and the protocols used to induce cooling in patients after cardiac arrest. **JAAPA**

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## DRUGS MENTIONED

Cisatracurium (Nimbex)  
Fentanyl (Sublimaze)  
Lidocaine (Xylocaine, generics)  
Meperidine (Demerol, generics)  
Midazolam (Versed)

Morphine (Astramorph/PF, Duramorph,  
Infumorph, generics)  
Pancuronium (generics)  
Propofol (Diprivan)  
Vecuronium (generics)

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• **Table: Medications used in therapeutic hypothermia**

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**TABLE: Medications used in therapeutic hypothermia<sup>1</sup>**

Drug	Mechanism of action	Metabolism	Excretion	Elimination $\frac{1}{2}$ Life	Significant adverse effects	Other properties
<b>HYPNOTIC /SEDATIVES</b>						
Propofol (Diprivan)	Not well-defined	Hepatic	Renal	3-12 h	<ul style="list-style-type: none"> <li>• Acute renal failure</li> <li>• Bradycardia (4.8%)</li> <li>• Heart failure (up to 10%)</li> <li>• Hypotension</li> <li>• Involuntary muscle movement (17%)</li> <li>• Respiratory acidosis</li> </ul>	<ul style="list-style-type: none"> <li>• Decreases cerebral and myocardial blood flow</li> <li>• Decreases cerebral metabolic oxygen consumption</li> <li>• Decreases SVR</li> </ul>
Midazolam (Versed)	Short-acting BZD—via GABA receptors	Hepatic and GI—active metabolites	Renal	1.8-6.4 h	<ul style="list-style-type: none"> <li>• Cardiac arrest (rare)</li> <li>• Desaturation of blood (Pediatric patients 4.6%)</li> <li>• Hypotension</li> <li>• Involuntary movement (2%)</li> <li>• Respiratory depression (11%-23%)</li> </ul>	Possibly reduces shivering threshold <sup>2</sup>
<b>OPIOID</b>						
Fentanyl (Sublimaze)	Mu receptor agonist	Hepatic	<ul style="list-style-type: none"> <li>• Fecal: &lt;7%</li> <li>• Hepatic/renal: &lt;1%</li> </ul>	3.6-7 h	<ul style="list-style-type: none"> <li>• Cardiac arrhythmia (1%-3%)</li> <li>• Hypotension/HTN</li> <li>• Respiratory depression</li> </ul>	May reduce shivering TTZ <sup>3</sup>
Morphine (Astramorph/PF, Duramorph, Infumorph, generics)	Pure mu receptor agonist	Hepatic and GI—active metabolites	<ul style="list-style-type: none"> <li>• Renal: ~90%</li> <li>• Fecal: 7%-10%</li> </ul>	1.5-4.5 h	<ul style="list-style-type: none"> <li>• Cardiac arrest (&lt;5%)</li> <li>• Paresthesia (5%-10%)</li> <li>• Peripheral edema (5%-10%)</li> <li>• Pruritus (up to 80%)</li> </ul>	May reduce shivering TTZ <sup>3</sup>
<b>NEUROMUSCULAR BLOCKING AGENTS</b>						
Cisatracurium (Nimbex)	Skeletal muscle relaxant	Hepatic	<ul style="list-style-type: none"> <li>• Renal: ~95%</li> <li>• Fecal: ~4%</li> </ul>	0.5 h	<ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• Bronchospasms</li> <li>• Hypotension</li> </ul>	None related to therapeutic hypothermia
Pancuronium (generics)	Skeletal muscle relaxant	Hepatic and renal	<ul style="list-style-type: none"> <li>• Renal: ~40% unchanged</li> <li>• Biliary: ~11%</li> </ul>	1.5-2 h	<ul style="list-style-type: none"> <li>• Bronchospasms</li> <li>• HTN</li> <li>• Tachycardia</li> </ul>	None related to therapeutic hypothermia
Vecuronium (generics)	Skeletal muscle relaxant	Hepatic	<ul style="list-style-type: none"> <li>• Renal: 3%-35%</li> <li>• Biliary: 25%-50%</li> </ul>	1-1.25 h	<ul style="list-style-type: none"> <li>• Bronchospasms</li> <li>• Hypotension</li> <li>• Tachycardia</li> </ul>	None related to therapeutic hypothermia

Key: BZD, benzodiazepine; GABA, gamma-aminobutyric acid; HTN, hypertension; SVR, systemic vascular resistance; TTZ, thermoeffector threshold zone.

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