

Therapeutic Hypothermia After Cardiac Arrest

Despite its demonstrated benefit, many patients fail to receive this brain-saving treatment.

OVERVIEW: Irreversible brain damage and death are common outcomes after cardiac arrest, even when resuscitation is initially successful. Chances for both survival and a good neurologic outcome are improved when mild hypothermia is induced shortly after reperfusion. Unfortunately, this treatment is often omitted from advanced cardiac life support protocols. The authors discuss the efficacy of therapeutic hypothermia, indications and contraindications for its use, various induction methods, associated complications and adverse effects, and nursing care specific to patients undergoing this procedure.

Keywords: anoxic brain injury, cardiac arrest, induced hypothermia, therapeutic hypothermia

Cardiac arrest is a leading cause of death in North America, resulting in more than 330,000 deaths per year.¹ If resuscitation efforts fail to restore cerebral blood flow within minutes of cardiac arrest, brain damage may be irreversible. Even after blood flow is restored, however, secondary brain injury can occur if cerebral edema results from direct tissue injury or blood-brain barrier disruption. Death from brain injury is common after cardiac arrest, but the patient is more likely to survive and to have a better neurologic outcome when mild hypothermia—in which the patient is cooled to a core temperature between 89.6°F (32°C) and 93.2°F (34°C)—is induced as part of the care plan.²⁻⁶

In order for hypothermia to be effective, candidates must be identified rapidly and hypothermia induced soon after cardiac arrest and maintained for 12 to 24 hours once the desired core temperature has been attained.^{2,3} Candidates must be monitored closely for metabolic shifts and complications throughout induction, maintenance, and rewarming. Unfortunately, despite the demonstrated benefit of

therapeutic hypothermia, many patients who are eligible for this treatment after cardiac arrest do not receive it. This may be because of clinicians' lack of familiarity with data supporting the technique, their failure to incorporate therapeutic hypothermia into advanced cardiac life support protocols, and the limited availability of newer cooling devices that are less cumbersome than cooling blankets and ice packs.^{7,8}

In this article, we review the pathophysiology of anoxic brain injury and discuss the efficacy of therapeutic hypothermia in preventing its occurrence after cardiac arrest. We then describe indications and contraindications for the use of therapeutic hypothermia, the various induction methods, associated complications of treatment and adverse effects of cardiac arrest, and nursing care specific to patients undergoing this procedure.

ANOXIC BRAIN INJURY

Within seconds of cardiac arrest, blood flow to the brain ceases, causing loss of consciousness and a cascade of metabolic events that may lead to brain tissue anoxia and necrosis (see Figure 1). Tissue hypoxia



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inhibits adenosine triphosphate (ATP) production, precipitating cellular anaerobic metabolism, glucose depletion, and lactic acidosis within minutes as glutamate production, which rises during ischemia, directly damages neuronal tissue. ATP depletion also disrupts ion channel pump function and causes an efflux of glutamate, resulting in excitotoxicity, further damaging neurons.^{9, 10} In severe cases, cerebral edema may ensue, obstructing cerebrospinal fluid outflow and potentially leading to intracranial hypertension. Early cerebral edema is associated with higher mortality.¹¹⁻¹³

When circulation is restored, secondary injury from reperfusion may exacerbate brain damage over the minutes, hours, and days following the primary injury. The time frame for secondary injury varies, depending on which injurious mechanism(s) reperfusion activates. For example, in releasing oxygen free radicals, such as nitric oxide, reperfusion can directly damage tissue and DNA. Reperfused capillaries may develop microthrombi, inhibiting blood flow to brain tissue.⁹ In addition, clinical studies suggest that cerebral autoregulation is impaired during

the postarrest phase, which further complicates brain reperfusion.^{14, 15}

INDUCING HYPOTHERMIA TO PROTECT THE BRAIN

One way to reduce brain injury following cardiac arrest is to lower the brain's metabolic rate in the period following reperfusion by inducing mild hypothermia, which alters energy metabolism in the brain, reducing its oxygen requirements. In addition, animal studies have shown that hypothermia lessens or prevents histopathologic damage through multiple means unrelated to metabolism.¹⁶ It's been suggested that additional protective effects of hypothermia may include enhancing the stability of cellular membranes such as the blood-brain barrier and blood vessel walls; suppressing the release of cytotoxic free radicals, thereby reducing inflammation and cell death; and stabilizing neurons within the brain by promoting ion homeostasis.¹⁶

How the treatment evolved. During the 1950s, when open-heart surgery was performed without cardiopulmonary bypass, hypothermia was used to preserve cellular function by slowing the metabolism.

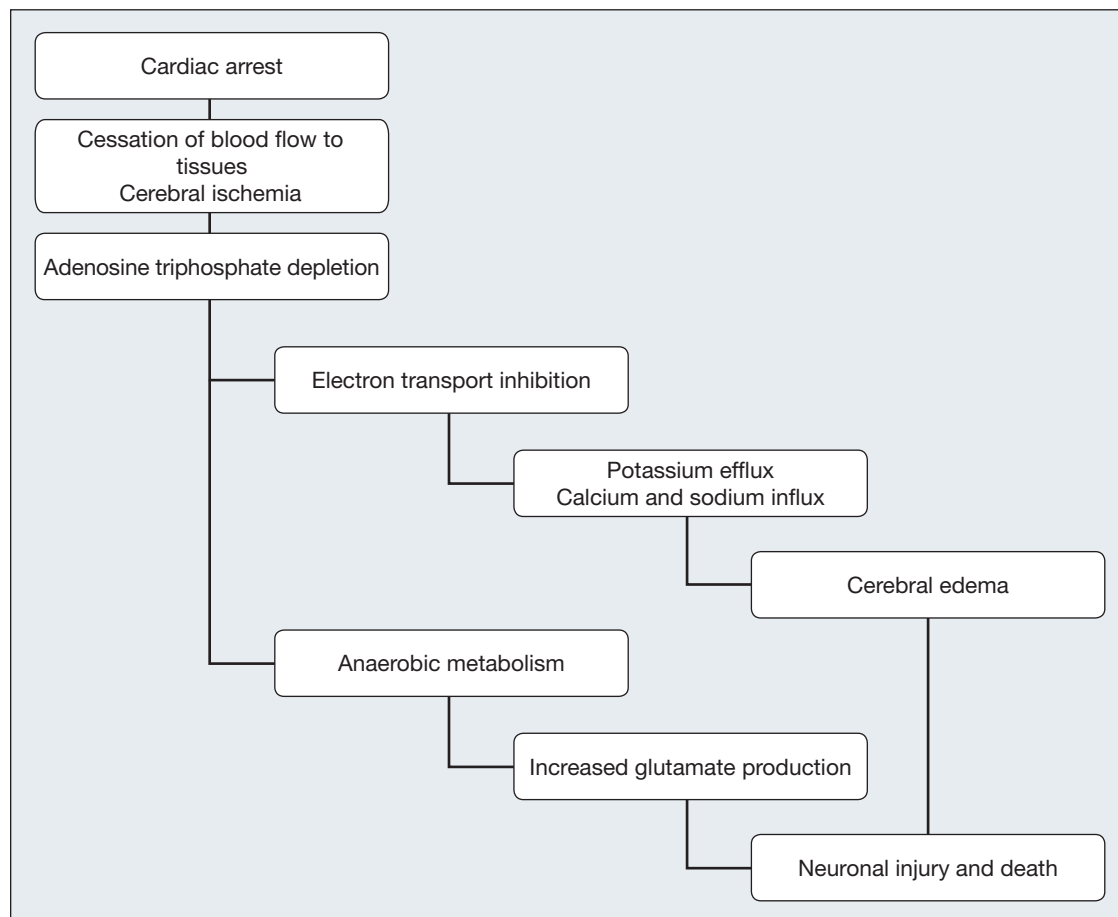
Its application, however, was not well developed, nor was cooling well controlled. Moreover, the extremely low target temperature of less than 86°F (30°C) was associated with a high rate of complications such as cardiac arrhythmias, seizures, airway obstruction, hypoventilation, downward drift of temperature (below 30°C), and shivering with hypoxia.¹⁷ Subsequently, the use of induced hypothermia as a therapeutic modality fell out of favor for some time.

In the 1990s, animal studies using mild hypothermia—93.2°F (34°C)—for brain protection after cardiac arrest began to show promise.^{18,19} In the late 1990s, reports of hypothermia's use in humans for the purpose of brain protection began to emerge.²⁰ In one randomized controlled clinical trial performed between September 1996 and June 1999, 77 patients who remained unconscious after resuscitation from cardiac arrest were randomly assigned to receive either standard treatment ($n = 34$), which meant remaining normothermic, or standard treatment with induced mild hypothermia ($n = 43$), which meant maintaining a core temperature of 91.4°F (33°C) for

12 hours.² The patients whose treatment incorporated mild hypothermia were significantly more likely to experience a good outcome ($P = 0.046$), defined as discharge to home or to an acute rehabilitation facility, than patients whose treatment did not (49% versus 26%). Similarly, in a multicenter study conducted between March 1996 and January 2001, 275 patients who had been resuscitated after cardiac arrest were randomly assigned to receive treatment either while hypothermic—with core temperatures maintained between 89.6°F (32°C) and 93.2°F (34°C) over 24 hours—or while normothermic.³ Researchers found that the induced hypothermia cohort was significantly more likely to experience a good outcome ($P = 0.009$), defined as a cerebral performance category score of 1 to 2 on a five-point scale ranging from good recovery to death, than the normothermic cohort (55% versus 39%).

Refining the procedure. More recently, research has focused on optimizing the timing, temperature, and duration of therapeutic hypothermia. One study compared the time required to achieve the target temperature of 91.4°F (33°C) and (because

Figure 1. Cascade of Adverse Events That May Follow Cardiac Arrest



target temperatures cannot always be achieved) the coldest temperature among 49 consecutive patients who had been resuscitated successfully after cardiac arrest.²¹ Of these patients, 28 were discharged with a good neurologic outcome, defined as absent-to-mild cerebral disability. In multivariate analyses, time to coldest temperature was the only variable significantly associated with neurologic outcome. When time to coldest temperature was excluded from the multivariate model, time to target temperature independently predicted neurologic outcome. For each hour delay in achieving the target temperature, the odds of a good outcome were reduced (odds ratio for a good outcome per hour: 0.69; 95% CI, 0.51-0.98; $P = 0.037$).

IDENTIFYING CANDIDATES

According to the American Heart Association (AHA), the induction of therapeutic hypothermia, with temperatures of 89.6°F (32°C) to 93.2°F (34°C) maintained for 12 to 24 hours, is a Class I recommendation (indicating “general agreement that the procedure or treatment is useful and effective”) for comatose adult patients whose circulation has returned spontaneously following out-of-hospital cardiac arrest associated with ventricular fibrillation.²² The AHA notes that therapeutic hypothermia may also be induced in comatose adult patients whose circulation has returned spontaneously following in-hospital cardiac arrest associated with any rhythm, or following out-of-hospital cardiac arrest associated with pulseless electric activity or asystole. In such cases the treatment is a Class IIb recommendation (indicating that “usefulness is less well established by evidence or opinion”).²² In clinical trials of therapeutic hypothermia following out-of-hospital cardiac arrest, inclusion criteria do not vary greatly from AHA recommendations.^{5,6}

Because animal studies have shown that temperatures below 93.2°F (34°C) impair coagulation,²³ induced hypothermia is contraindicated in patients with traumatic injury, active noncompressible bleeding, or a diagnosis of intracranial hemorrhage. Generally the treatment is also contraindicated in patients with a code status of “comfort measures only.”²⁵ Sample protocols for the induction of hypothermia after cardiac arrest are available by clicking on “PCAS” on the Center for Research on Emergency Medical Services Web site (www.emsresearch.org).

THE THREE STAGES OF THERAPEUTIC HYPOTHERMIA

Therapeutic hypothermia following cardiac arrest proceeds in three stages: induction, maintenance, and rewarming.

Induction refers to the rapid cooling of the patient by means of either invasive or noninvasive techniques. Invasive methods include rapidly infusing up to 30 mL/kg of normal saline or lactated Ringer's solution that has been cooled to 39.2°F (4°C) through

a peripheral line or an intravascular cooling catheter, which is placed in the femoral, subclavian, or internal jugular vein and connected to an external cooling device set to the desired temperature. The chilled fluid pumped into the central catheter remains in the catheter and does not come in direct contact with the blood. Advantages to central intravascular cooling include speed (cooling occurs at an average rate of 3.6°F to 4.5°F per hour [2°C to 2.5°C per hour]) and ease of use. Disadvantages include the potential risks associated with central catheter insertion—specifically, pneumothorax, infection, and venous embolism—as well as cost. A cooling device costs approximately \$28,500, and heat exchange catheters range from \$300 to \$1,170 per catheter.²⁴ A cold saline lavage of the stomach through a nasogastric or orogastric tube can supplement either invasive method. Noninvasive methods include lowering the room temperature or applying surface coolants, such as cooling blankets, pads, or ice packs.^{25,26}

To reduce rapid shifts in electrolyte levels, patients should be rewarmed at a slow, controlled pace.

The method of cooling does not appear to alter neurologic outcome. A review of 167 subjects cooled with either surface or intravascular cooling methods found no significant difference in survival with good neurologic function (defined as a cerebral performance category score of 1 to 2) either to hospital discharge or at six-to-12-month follow-up.²⁶ Time to goal temperature also did not differ significantly between the two methods.

Maintenance refers to the period during which the patient is kept at the target temperature of 89.6°F (32°C) to 93.2°F (34°C), which can range from 12 to 24 hours.^{2,3} The prevailing belief among clinicians is that shorter periods of hypothermia are unlikely to improve outcomes significantly.⁹ Within the recommended 12-to-24-hour range, there is no consensus on the optimal duration of hypothermia or the indications for rewarming. At the University of Pittsburgh Medical Center (UPMC), we use a fixed period of 24 hours of maintenance unless the patient develops life-threatening complications such as coagulopathy.

Rewarming may be passive (accomplished solely through the withdrawal of cooling devices) or actively managed (through external or invasive warming methods). Target rewarming rates are often set at 0.32°F to 0.33°F per hour (0.2°C to 0.3°C per hour),²⁷ based on data from studies demonstrating that rapid rewarming reverses the benefit of

Table 1. Adverse Events in Patients (N = 754) Treated with Therapeutic Hypothermia After Cardiac Arrest³²

Adverse event ^a	n (%)
Pneumonia	361 (48)
Hyperglycemia (blood glucose > 8 mmol/L)	277 (37)
Seizures	182 (24)
Hypophosphatemia (serum phosphate < 0.7 mmol/L)	141 (19)
Hypokalemia (serum potassium < 3 mmol/L)	134 (18)
Hypomagnesemia (serum magnesium < 0.7 mmol/L)	128 (17)
Bradycardia (pulse < 40 beats/min)	108 (14)
Ventricular tachycardia	76 (10)
Atrial fibrillation	70 (9)
Ventricular fibrillation	58 (8)
Tachycardia (pulse > 130 beats/min)	50 (7)
Bleeding requiring transfusion	43 (6)
Hypoglycemia (blood glucose < 3 mmol/L)	40 (5)
Sepsis	31 (4)

^aAlthough shivering was not addressed in this study, it occurs in nearly all cases in which hypothermia is induced.

therapeutic hypothermia in rats with traumatically induced axonal injury.^{28, 29}

MONITORING PATIENT RESPONSE

Nurses caring for patients undergoing therapeutic hypothermia administer the cooling protocol and assess all body systems, with the goal of preventing complications resulting either from hypothermia or from common sequelae of critical illness, such as immobility, sedation, and mechanical ventilation. A multiple-lumen, pulmonary artery catheter (Swan-Ganz) is generally used to monitor core temperature, volume status, cardiac function, central venous pressure, and cardiac output.²⁵ When a Swan-Ganz catheter is not inserted, the preferred means of monitoring the patient's temperature is by esophageal thermometer.³⁰ Bladder or rectal thermometers may be used if an esophageal temperature cannot be obtained; because of their variability, axillary and tympanic thermometers should not be used.³⁰

The cellular metabolic shifts from aerobic to anaerobic metabolism that occur during cardiac arrest elevate serum lactate, so nurses need to monitor levels during all three phases of treatment. Initial serum lactate levels suggest the duration of ischemia (the longer the patient is without circulation, the higher the lactate level), and persistently elevated levels may

represent ongoing ischemia.³¹ Both the initial lactate level and the rate of lactate clearance are associated with patient outcomes.³¹ Keep in mind that norepinephrine, which can cause vasoconstriction and impair perfusion, may raise lactate levels to some degree.

PREVENTING ADVERSE EFFECTS AND COMPLICATIONS

During all three phases of therapeutic hypothermia, patients should be assessed for treatment complications, as well as for signs of adverse events associated with cardiac arrest (see Table 1³²). Shivering, pneumonia, bleeding, hypoglycemia, sepsis, pulmonary edema, and bacterial translocation are some of the more common complications of therapeutic hypothermia, whereas seizures and cardiac arrhythmias may occur in any patient following cardiac arrest, regardless of whether hypothermia is induced.

Shivering, which occurs in almost all cases, can increase the patient's metabolic rate, oxygen consumption, and carbon dioxide production. Neuromuscular blocking agents, benzodiazepines, or opiates may be used to reduce shivering and other physiologic stress responses during all phases of therapeutic hypothermia and to facilitate mechanical ventilation. Because these drugs interfere with neurologic assessment, at UPMC we reduce sedation for up to an hour daily (depending on patient tolerance) to assess motor and brain stem function.

Aspiration pneumonia is a frequent complication of therapeutic hypothermia because airway reflexes are lost during cardiac arrest, and the majority of patients are not intubated prior to arrest. Watch for rising oxygen requirements as well as signs and symptoms of infection, such as elevated white blood cell count and rapid heart rate. Bear in mind that fever may be suppressed if the patient is in the cooling phase. Notify the primary care provider of any suspected infection so that antibiotic treatment can begin as soon as possible.

Seizures occur in about 24% of patients and are strongly associated with death.³² Continuous electroencephalographic (EEG) data collected between 2009 and 2010 on more than 100 patients consecutively admitted to a U.S. hospital after cardiac arrest suggest that associated seizures tend to occur within 12 hours after resuscitation.²⁷ Because the majority of seizures are nonconvulsive, EEG monitoring is warranted. In some centers, nurses are trained to recognize malignant EEG patterns and contact the neurologist when such patterns occur. All nurses, however, should remain vigilant for sudden changes in neurologic or hemodynamic status, which may be secondary to seizures.

Cardiac arrhythmias may develop during induction (particularly tachycardia), maintenance (particularly bradycardia), and rewarming as a result of electrolyte imbalances.³³ Hypothermia induction causes a transient increase in the glomerular filtration

rate, resulting in diuresis, which reduces serum phosphate and magnesium levels while shifting potassium into the cellular space, thereby lowering plasma volumes and producing hypokalemia. Rewarming shifts potassium from the cellular to the extracellular space, potentially producing hyperkalemia. For these reasons, potassium levels should be monitored every four to six hours, and magnesium and phosphate levels as clinically indicated. To reduce rapid shifts in electrolyte levels, patients should be rewarmed at a slow, controlled pace.³³

Bleeding time may increase when the patient's core temperature drops below 95°F (35°C) because hypothermia inhibits both coagulation protease activity and platelet function.^{23, 34} At core temperatures below 89.6°F (32°C), risk of death rises substantially. Stool guaiac and bleeding times must be closely monitored. If bleeding occurs during therapeutic hypothermia, it is standard clinical practice to rewarm the patient to 35°C as quickly as possible; in the hemorrhagic patient, stopping the bleeding takes precedence over preventing potential ischemic brain injury.

Glycemic abnormalities. Glucose levels should be closely monitored during rewarming. Hypothermia can result in a relative insulin resistance.^{33, 35} If the patient is receiving an insulin infusion during

Pulmonary edema and fluid overload may occur if hypothermia is induced through cool intravenous infusion. This complication is most likely to develop in patients with a history of congestive heart failure or renal insufficiency. Nurses should be vigilant for such signs as rales on lung auscultation and pink, frothy sputum in the endotracheal tube. Management varies according to hospital and physician preference.

Pressure ulcers. Skin integrity should be assessed frequently, because vasoconstriction in response to cooling can result in skin breakdown and infection, especially in patients who receive surface cooling. To reduce the risk of pressure ulcers, elevate the patient's extremities and apply a cold barrier cream to the back and heels. Hydrocolloid dressings can further protect bony prominences.

Bacterial translocation. Hypothermia reduces gastrointestinal motility, and cardiac arrest puts patients at risk for mucosal ischemia and breakdown. Together these conditions may permit bacteria to translocate from the gut into the bloodstream, an event most likely to occur 12 to 24 hours after admission.³⁶ Nutritional absorption through the gut helps preserve mucosal integrity; so if the patient is unable to eat, consider enteral feeding as a means of preventing bacterial translocation.

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hypothermia, the rate of the drip may need to be increased to control glucose levels. During rewarming, however, sensitivity to insulin normalizes and the patient may become hypoglycemic.

Sepsis. A 2002 multicenter trial that included 275 patients who were resuscitated in an ED after out-of-hospital cardiac arrest found that patients whose care plan included therapeutic hypothermia had a higher rate of sepsis and other infections than those who remained normothermic during treatment, even though the differences were not statistically significant and hypothermia's benefit was deemed greater than its potential for adverse effects.³ The elevated risk of infection associated with therapeutic hypothermia may result from slowed inflammatory processes and impaired wound healing. Patients should be monitored for fever and physiologic changes consistent with sepsis, such as tachycardia, hypotension, and elevated lactate or white blood cell levels. Sepsis should be suspected in patients in whom hypothermia is especially difficult to induce or maintain.

KEEPING THE FAMILY INFORMED

It's important to keep the patient's family and friends apprised of the care the patient is receiving. Be sure to explain the reason therapeutic hypothermia is being used, all required medications and their purpose, the patient's anticipated cognitive status over the coming days, and potential complications.

Explain that on the first day of hypothermia induction, the patient is kept cooled for 24 hours. During this time, vital signs, laboratory values, and neurologic status are monitored in order to assess progress and minimize potential complications. Brain wave data are continuously monitored to determine if there is any seizure activity so it can be treated if necessary.

On day 2, the patient is slowly rewarmed over 14 to 16 hours; complications can arise if the patient is rewarmed too quickly. Vital signs, laboratory values, and neurologic functions (cough, gag reflex, pupillary response, and corneal movement) are monitored as well, since these reflexes are limited during the cooling phase.

On day 3, neurologic status is reevaluated, because when the patient is rewarmed completely it's possible to make a prognosis. Let the family know that both survival and neurologic function are greatly improved when these measures are taken. ▼

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