Therapeutic Hypothermia After Cardiac Arrest in Adults: Mechanism of Neuroprotection, Phases of Hypothermia, and Methods of Cooling

Yinlun Weng, MDb, Shijie Sun, MDa,b,*

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Sudden cardiac arrest is the main manifestation of ischemic heart diseases, which is the leading cause of death worldwide. Each year an estimated 300,000 people suffer from cardiac arrest in the United States, with a variable incidence ranging from 36/100,000 to 128/100,000.1–4 Approximately 7.9% of cardiac arrest victims survive to hospital discharge in the United States,5 whereas fewer than half of patients admitted to hospital achieve a favorable outcome. Permanent severe brain damage accounts for the high mortality after successful resuscitation in the hospital.

Mild hypothermia, defined here as a reduction of core temperature to 32°C to 34°C, is the only proven therapy to improve survival and neurologic outcome after sudden cardiac arrest in clinical trials, and recommended by the American Heart Association (AHA) as the routine intervention for selected comatose adult victims of witnessed out-of-hospital cardiac arrest.6–10 This article addresses the mechanism of neuroprotection, phases of hypothermia, and cooling methods.

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* Corresponding author. The Weil Institute of Critical Care Medicine, 35100 Bob Hope Drive, Rancho Mirage, CA 92270.
E-mail address: shijiesun@aol.com

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MECHANISMS OF NEUROPROTECTION

In recent years, there has been significant progress in our understanding of cerebral injury after cardiac arrest. There are three phases in cerebral injury after hypoxic insult: early, intermediate, and late. In the early stage, absence of cerebral blood flow occurs immediately after cardiac arrest despite ongoing consumption of oxygen, adenosine triphosphate, and glucose.11–14 In the intermediate phase, release of excitatory amino acids and glutamate in the brain activates destructive cytotoxic cascades such as free radicals and nitric oxide hours after the arrest.12 In the late phase, a series of injuries may occur up to 24 hours after cardiac arrest, including breakdown of the blood–brain barrier, exacerbation of cerebral edema, and neuronal death.11,12 Therapeutic hypothermia might exert neuroprotection by multiple mechanisms in the single or synergistic aforementioned phases, including reduction of brain metabolism, attenuation of reactive oxygen species formation, inhibition of excitatory amino acid release, attenuation of the immune response during reperfusion, and blockage of apoptosis.

Reduction of Brain Metabolism

Hypothermia produced a decrease of cerebral metabolism by 6% to 10% per 1°C reduction in core body temperature, reflected by decreases in energy utilization and consumption of oxygen and glucose.15–30 This mechanism was not the only explanation for the dramatic difference seen despite the certain role of metabolic decrease in neuroprotection.31

Attenuation of Neuroexcitotoxic Cascade

Depletion of ATP after hypoxia results in intracellular and extracellular acidosis, failure of ATP-dependent Na⁺,K⁺-ATPase, imbalance of the cellular Na⁺ gradient, and Ca²⁺ influx into neurons. This would further lead to cellular depolarization that causes a release of excitatory amino acids such as glutamate. In turn, it further promotes Ca²⁺ influx. Because of the characteristic of ATP or oxygen dependence, the Ca²⁺ sequestration ultimately collapses, leading to loss of the calcium-buffering capacity. Hypothermia has been proved to potentially attenuate the aforementioned steps of neuroexcitotoxic cascade that causes cell death.32–34

Abolition of Reactive Oxygen Species

Another important destructive process is the release of reactive oxygen species that followed reperfusion of oxygenated blood after cardiac arrest. Reactive oxygen species could directly damage numerous cellular components such as neuronal lipid membranes, proteins, and DNA through peroxidation.35 Even if neurons possess various enzymatic and nonenzymatic antioxidant mechanisms that prevent peroxidative injury, these intrinsic effects are overwhelmed by the production of free radical production after ischemia–reperfusion. Antioxidant depletion and byproducts of peroxidation have shown to peak up to 16 hours after restoration of circulation, suggesting that neuronal injury continues long after the initial resuscitation.36,37 Hypothermia significantly decreased the quantity of free radicals, which would reserve more space or time for endogenous protective mechanisms in counteracting the oxidative damage.38–41

Inhibition of Apoptosis

Cells suffering from ischemia and reperfusion face three fates: necrosis, apoptosis, or full or partial recovery. The initiating and determinant factor for induction of apoptosis
is the interaction of proapoptotic and antiapoptotic factors; it is influenced by the disturbed energy metabolism, dysfunctional mitochondria, and the release of caspase enzymes. Hypothermia appears to affect these processes in different ways. In the presence of hypothermia, the antiapoptosis protein Bcl-2 is enhanced whereas proapoptosis BAX is suppressed. Hypothermia would interfere with depletion of energy metabolism, which would lead to overload of calcium and release of glutamate and contribute to the induction of apoptosis. Hypothermia to some extent attenuated the mitochondrial dysfunction by inhibition of translocation of cytochrome c into cytosol. Inactivation of caspase enzyme would further contribute to the prevention of apoptosis by hypothermia. In addition, apoptosis occurs relatively late in the postperfusion phase and lasts for 48 to 72 hours or even longer, providing a wide window of opportunity for intervention.

**Suppression of the Inflammatory Response**

The inflammatory response in most types of ischemia cerebral injury is mediated by proinflammatory mediators such as tumor necrosis factor-α (TNF-α); interleukin (IL)-1, -2, -10; macrophage inflammatory protein-1α; and growth-related oncogene/KC. The chemotaxis of activated leukocytes across the blood–brain barrier is then stimulated, leading to accumulation of inflammatory cells in the injured brain and expression of adhesion molecules on leukocytes and endothelial cells, while the passage of neutrophils and monocytes–macrophages is activated by the complement systems. The inflammatory response begins and peaks within 1 hour and lasts for up to 5 days. Because the inflammatory response may be physiologic, the extent of cytokine production and leukocyte infiltration would then determine if the physiologic response would not be overwhelmed by the destructive aspects of inflammation. Hypothermia has been proved to effectively suppress the ischemia-evoked inflammatory response by inhibiting neutrophil infiltration, reducing lipid peroxidation and leukotriene production, and decreasing the overexpression of nitric oxide.

**Protection of Blood–Brain Barrier Integrity**

Blood–brain barrier integrity was destroyed after ischemia and reperfusion after cardiac arrest through decreased fluidity and integrity of cell membranes and increased vascular permeability of microvascular endothelial cells in the brain. The entire process was mediated by vascular endothelial growth factors via release of nitric oxide. The disruption of the blood–brain barrier would further contribute to exacerbation of brain edema. Hypothermia significantly prevents the progressive development of vascular permeability and the resultant formation of edema after ischemia reperfusion.

**TEMPERATURE PHASES IN HYPOTHERMIA**

Temperature modulation during therapeutic hypothermia occurs in three phases: induction, maintenance, and rewarming.

**Induction Phase**

Optimal variables, such as onset of cooling, target temperature, and the rate of cooling to the target temperature remain unclear. In the setting of cardiac arrest, there are numerous data supporting the importance of early initiation of hypothermia as soon as possible after restoration of spontaneous circulation (ROSC); in animal models, efficiency is enhanced when hypothermia is initiated before arrest or coincident with the arrest. More data prove that with the delay of implementation
of hypothermia, the beneficial effects of hypothermia were negated in overall performance, neurologic deficit, and brain histopathologic damage.\textsuperscript{65–68} It is unrealistic for sudden cardiac death to induce therapeutic hypothermia before cardiac arrest except accidental hypothermia. There is no human study indicating the time from initiation of therapy to achieve therapeutic temperature is a significant predictor of outcome, and the optimal rate of cooling is unknown. Notably, immediate side effects such as hypovolemia, electrolyte disorders, and hyperglycemia occur in the induction period, representing the greatest patient management problems.\textsuperscript{69–71} In this sense, to reduce the risk, it would be more appropriate to provide a rapid induction of hypothermia, including shortening the duration of the induction phase and reaching the more stable maintenance phase as quickly as possible. With respect to the target temperature, it is recommended to cool down to 32°C to 34°C based on the American Heart Association (AHA) guideline\textsuperscript{6}; however, Gal and colleagues proved that therapeutic hypothermia with the target temperature of 34°C to 35°C was more easily attainable, feasible, safe, and efficient in patients after cardiac arrest and with fewer side effects.\textsuperscript{72} A significantly decreased rate of refibrillation and need for late defibrillation was found when the milder hypothermia of 35°C was applied.\textsuperscript{73}

**Maintenance Phase**

In this phase, there are two marked issues: the duration of hypothermia and stability in controlling the core temperature. Although the 2010 AHA guideline recommended providing duration of 12 to 24 hours of hypothermia, there are different viewpoints. Dietrich and colleagues\textsuperscript{74} demonstrated that hypothermia of 30°C for 3 hours after global brain ischemia produced short-term protection (3 and 7 days postischemia) but not long-lasting protection (6 months), which was reported to be present in extended hypothermia of 32°C from 12 to 24 hours in gerbils and 32°C to 34°C for 48 hours in rats in the studies by Colbourne and Corbett.\textsuperscript{75,76} Hickey and colleagues\textsuperscript{77} demonstrated that even spontaneously hypothermia, which initiated within several hours and recovered to nomothermia within 24 to 36 hours, still had a neuroprotective effect. Recently the study in a rat model of 2 hours of occlusion of the middle cerebral artery (MCAO) by Shintani and colleagues\textsuperscript{78} identified that mild hypothermia at 35°C should be introduced within 4 hours after MCAO and maintained for longer than 4 hours to achieve neuroprotective effects. Conversely, Agnew and colleagues reported a prolonged effect without negative side effects using a prolonged (>24 hours) cooling period in asphyxic cardiac arrest piglet models.\textsuperscript{79} It also has been proved that a longer duration of cooling should decrease the volume of infarction of after cerebral artery occlusion.\textsuperscript{80} The discordance between these studies suggests that the window and duration of hypothermia depend on the animal model, the severity of the injury, and even the paradigm of hypothermia. As to the stability, it would be better to control core temperature tightly with minor or no fluctuation (maximum 0.2°C–0.5°C).\textsuperscript{81} With a lower incidence of shivering response, hypovolemia, and electrolyte loss in the maintenance phase, attention should be shifted toward the long-term side effects such as nosocomial infections and bedsores.

**Rewarming Phase**

There is still controversy regarding the rewarming rate. In general, the successful protection provided via hypothermia intervention is associated with a relatively slow course of posthypothermia rewarming. Bernard and coworkers found 1.0°C per 1.4 hours of rewarming has no adverse hemodynamic effects.\textsuperscript{7} The HACA study group indicated that passive rewarming with a rate of 1.0°C every 2 hours did not counteract the effect of hypothermia.\textsuperscript{6} Busch demonstrated that a rewarming rate of 1.0°C every
2.5 hours benefits the outcome, accompanied with an occasional rebound hypothermia. In contrast, when most animal studies were replicated with more rapid rewarming, not only were the beneficial effects of hypothermia eliminated, but in most cases, the ensuing pathology also was markedly exacerbated. In terms of the mechanistic perspective, the damaging consequences of rapid rewarming are not yet fully understood; numerous evidence suggests injury resulting from rapid rewarming was related to exacerbation of mitochondrial permeability transition and enhanced generation of oxygen free radicals. First, rapid rewarming could cause electrolyte disorders caused by shifts from the intracellular to the extracellular compartment. Second, insulin sensitivity could increase during rewarming. Third, rapid rewarming could lead to loss of some or even all of the protective effects of hypothermia.

**COOLING METHODS**

An ideal cooling method is expected to be characterized by the following features: rapid cooling, homogeneous cooling, cost effectiveness, easy implementation, portability, safety, and effective control. A growing number of cooling methods are emerging, which could be simply classified as noninvasive surface cooling and invasive cooling. Surface cooling devices are noninvasive and range from simple ice packs to sophisticated machines with automatic feedback controls. Invasive cooling methods include the administration of ice-cold fluids intravenously, intravascular cooling catheters, body cavity lavage, extracorporeal circuits, and selective brain cooling.

**Surface Cooling**

Ice packs are considered one of the simplest approaches for inducing hypothermia. It is as simple to apply as just attaching into head, neck, torso, and extremities. Ice packs are reported to provide a relatively slow cooling rate of 0.9°C per hour. Even combined with towels soaked in ice water, it still takes a median of 7.5 hours to achieve mild hypothermia. In addition, the use of alcohol and fans is limited because of safety and hygiene concerns. However, one of the primary limitations of these methods is inferior temperature control. Therefore, it would require more dependence on nursing care to avoid overshoot of cooling and unintentional rewarming.

Some surface devices such as cooling blankets (Arctic Sun, Medivance, Louisville, CO, USA) make it possible to operate with feedback control by circulating water through specially designed pads and conductively exchange heat with skin to achieve a cooling rate of 1.2°C per hour. In addition to its servo control, this device is radiolucent to facilitate the imaging study without causing a fluctuation of temperature by removal the device. However, there are some disadvantages of this technique, such as inability to monitor the condition of skin under the blanket and risk of skin sloughing.

Immersion of the body in ice water would be a highly efficient strategy but difficult to control. This approach is adopted by Thermosuit System (Life Recovery Systems, Kinnelon, NJ, USA), which surrounds patients directly with cool water and also possesses a feedback control unit with a safe and effective underwater defibrillation. Animal studies suggest that it provides a cooling rate of 9.7°C per hour in 30-kg pigs, in contrast with 3.0°C per hour in human data.

EMCOOLSPads (Emcools, Vienna, Austria) is another feasible, safe method. It uses plates of mixed ice and graphite to enhance thermal conductivity, avoiding the low efficiency when water melting on ice cubes inhibits effective cooling with ice alone. In addition, this device is independent of power supply, thus making it especially
appropriate for out-of-hospital use. It has been used by emergency medical services (EMS) in 15 patients in a prehospital study with a cooling rate of 3.3°C per hour.\textsuperscript{91,96}

Nasopharyngeal evaporative cooling with the Rhino-Chill-device (BeneChill, San Diego, CA, USA) is a novel method that sprays a convective coolant via a catheter in the nasal cavity, thus cooling the basal brain region. It is demonstrated to exert a cooling rate of 2.4 and 1.4°C per hour for tympanic and core temperature, respectively, and seemingly related to improved defibrillation success.\textsuperscript{91,97} In addition, this device operates independent of energy source, which makes it appealing for use out of hospital.

**Invasive Cooling**

The infusion of cold fluids has the advantage of being inexpensive, effective, and easily available. Infusion speed and muscle paralysis are two factors affecting the effectiveness, so that clinically large-gauge cannulas and pressure bags are adopted to increase the speed and muscle paralysis is included to avoid shivering.\textsuperscript{91} Berard and colleagues used infusion of cold Ringer’s lactate at a rate of 30 mL/kg for 30 minutes in cardiac arrest survivors, and found it could provide a rate of 3.4°C per hour.\textsuperscript{98} Notably, no pulmonary edema occurred as a result of the fluid load; instead, a rise in mean artery blood pressure was observed.\textsuperscript{98} Another study by Kim and coworkers adopted a protocol of infusion of 2000 mL of ice-cold saline over 30 minutes, demonstrating no effect on electrolyte balance, cardiac function, central venous pressure, pulmonary pressures, and left atrial filling pressure, and even a slight improvement in ejection fraction 1 hour after infusion.\textsuperscript{95} Data are available to support that the effectiveness of cold fluids is dependent on choice of fluid, such as saline, lactated Ringer’s solution, or others.\textsuperscript{98–102} As Kin and coworkers demonstrated, an approximately 1.24°C reduction of temperature was achieved in a 63-patient randomized trial with no adverse effects, supporting that administration of cold saline also proved to be suitable for out-of-hospital use.\textsuperscript{103} The use of cold fluids for advanced cardiac life support (ACLS) has been demonstrated in animal and human studies, suggesting that this method also produced a beneficial outcome including achievement of mild hypothermia and improved defibrillation without an adverse effect in the hemodynamic variable of cerebral blood flow.\textsuperscript{73,104–107} One disadvantage of infusion of cold fluids is its fluctuation of maintaining the target temperature after induction; only a small percentage of patients did not rewarm spontaneously during observation after induction without other intervention.\textsuperscript{91} Based on the compatibility of cold fluids, a combination of other interventions to avoid spontaneous rewarming is recommended, such as a cooling catheter and cooling blanket.

Intravascular devices are designed to exchange heat through a catheter containing circulating saline at a controlled temperature with a feedback of patient temperature. The CoolGard System (Alsius, Irvine, CA, USA) is one of the products adopting this mechanism. This system has been used in patients after resuscitation, yielding a cooling rate of approximately 1.0°C per hour in human studies.\textsuperscript{108,109} This method is advantageous in close temperature control for maintenance and rewarming from hypothermia, but disadvantageous in risks of bleeding, vessel thrombosis, and catheter-related infection.

**Other Approaches**

Recently pharmacologic hypothermia has been considered for its easy implementation. An analogue of neurotensin was reported to induce hypothermia rapidly in rats after intravenous administration in a model of asphyxic cardiac arrest and reduce
neurologic injury as compared with external cooling.\textsuperscript{110} Sun and colleagues have demonstrated that the nonselective cannabinoid receptors agonist WIN55, 212-2 induced a reduction of 3.2°C in blood temperature within 4 hours and benefited postresuscitation myocardial and neurologic function without compromised hemodynamics.\textsuperscript{111} Cholesystokinin octapeptide (CCK8) was also proven to induce a decrease of 2.2°C in blood temperature within 4 hours in a rat model of cardiac arrest and resuscitation and produced a significant beneficial effects in postresuscitation myocardial and neurologic function.\textsuperscript{112}

Venovenous cooling is a dialysis method using a double-lumen catheter to connect with the femoral vein and an extracorporeal heat exchanger for rapid blood cooling. The method in the pig study allowed for a cooling rate of 8.2°C per hour.\textsuperscript{113} However, this method can also be invasive and, with the risks of bleeding and infection, likely no more useful than other less invasive devices.

Total liquid ventilation with perflourcarbon produces effective hypothermia while allowing oxygenation and ventilation; it has been proved in a swine model of cardiopulmonary resuscitation (CPR) to improve the ROSC rate.\textsuperscript{114,115} Ice slurries, smoothed 100-mm ice particles at a subzero temperature, provide another relatively more effective cooling method than conventional cold fluid, with a reduction of 4°C in brain temperature in a pig experiment.\textsuperscript{91}

Although many devices are available to achieve therapeutic hypothermia, there are no current data recommending one method over another. All of the factors involving the individual institute and the condition of patients should be taken into consideration when making a decision regarding the optimal method to apply.

SUMMARY

Mild therapeutic hypothermia proved to be the first treatment to reverse postischemic cerebral injury in clinical studies. To maximize the efficiency of cooling, more attention should be focused on understanding the mechanisms underlying its protective effects, the phases involving its management problems, and the methods relevant to its realistic strategy. Inevitably, there are other aspects that are not appreciated or somewhat overestimated, raising the great need for further research and more comprehensive knowledge of therapeutic hypothermia.

From the perspective of neuroprotection, more issues need to be explored such as onset and duration of hypothermia, target temperature, rewarming strategy, and more detailed and feasible protocols in choosing the individual cooling device. Most importantly, avoid discouragement, as even the simplest method, such as ice packs, can be effective.

REFERENCES


