Hypothermia in Neurocritical Care

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KEYWORDS

• Therapeutic hypothermia • Traumatic brain injury • Cardiac arrest • Shivering • Spinal cord injury

KEY POINTS

- The ability of hypothermia to protect tissue from ischemic damage is primarily related to its effects on metabolism, with oxygen use decreasing linearly by 5% to 9% per degree centigrade.
- Therapeutic hypothermia applied within hours of injury designed as a neuroprotective strategy and delayed TH designed to mitigate the effect of increased intracranial pressure (ICP).
- At present, hypothermia has only been shown to be an effective therapy for cardiac arrest and reducing ICP.
- Shivering and immune suppression are the most significant concerns during the maintenance phase of cooling.
- Rewarming is the most dangerous phase of cooling because of the increased risk for rebound cerebral edema and increased ICP.

INTRODUCTION

Although use of hypothermia has only recently become commonplace, the neuroprotective properties of cooling have been studied for decades. Beneficial effects of hypothermia during cardiac arrest were first described in case reports during the 1940s, and the findings were reproduced in animal studies in the 1950s.[1–5] Findings from animal studies later suggested that induction of mild hypothermia (32–35°C) could achieve neuroprotective benefits while avoiding serious adverse effects caused by deep hypothermia.[6] Two randomized clinical trials in 2002 showed that hypothermia improved neurologic outcomes in patients following cardiac arrest.[7,8] Since these landmark trials the use of therapeutic hypothermia (TH) has gained momentum and its clinical use has increased substantially over the past decade.

Effective clinical use of TH requires a firm understanding of the mechanisms by which cooling induces neuroprotection, the physiologic consequences of hypothermia, and the potential for serious complications following temperature reduction. Given the complexity of the application of TH and the physiologic changes caused by mild hypothermia, standardized clinical management protocols are essential for optimal patient care, regardless of the indication.

MECHANISM OF ACTION

Preclinical trials have shown that hypothermia exerts multiple neuroprotective effects in models of both global and focal injury. The ability of hypothermia to protect tissue from ischemic damage is primarily related to its effects on metabolism, with oxygen use decreasing linearly by 5% to 9% per degree centigrade,[9] resulting in decreased oxygen requirements and tolerance of lower tissue perfusion.[10] When oxygen and glucose delivery is limited there is a reduced risk of energy failure, which causes failure of sodium pumps, calcium influx, and cell death.[11]

A broad range of beneficial effects of hypothermia have been well described, including effects

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on many cellular and molecular processes from microRNA responses to differential gene expression.[12,13] The response to hypothermia causes an overall reduction in excitotoxic neurotransmitter release, free radical formation, sustained electrical depolarizations, and inhibition of proinflammatory and apoptotic pathways.[14–19] These mechanisms stabilize the blood-brain barrier, decrease edema, and reduce intracranial pressure (ICP).[20]

The effect of TH on these mechanisms depends on the timing of the therapy (**Fig. 1**). Hypothermia applied within hours of the injury is designed to optimize the potential for neuroprotection, working primarily at a cellular level to arrest pathologic processes that play a significant role in secondary injury. As injury progresses, TH is administered to reduce the impact of cerebral edema and mass effect that the primary injury has on uninjured areas of the brain. The distinction between neuroprotective and ICP-reducing mechanisms is important when administering hypothermia in the neurocritical care unit (NCCU).

INDICATIONS

Cardiac Arrest

During no-flow states such as observed in cardiac arrest, there is membrane depolarization, calcium influx, glutamate release, acidosis, and activation of lipases, proteases, and nucleases. This process allows for reoxygenation injury involving iron, free radicals, nitric oxide, catecholamines, excitatory amino acid release, and renewed calcium shifts.[21] During postischemic reperfusion, even after prolonged ischemic periods, the high-energy ATP load recovers rapidly and approaches normal levels quickly after return of spontaneous circulation (ROSC); however, tissue injury continues after reperfusion. The observation of morphologic changes (cytosolic microvacuolation) seen in hippocampal hilar, CA1 pyramidal neurons, and cortical pyramidal neurons of layers 3 and 5 after reperfusion has led to the concepts of reperfusion injury and selective neuronal vulnerability.[21] As a result, much of the brain injury after even brief periods of anoxia is caused by the reperfusion injury after ROSC. Experimental studies have shown that these mechanisms can be minimized or prevented with the application of hypothermia.

Despite knowing the benefits of TH after experimental cardiac arrest for several decades,[22] it has only recently been studied extensively in humans. A decade has passed since the results of 2 randomized controlled trials provided evidence that TH (32°–34°C) for 12 to 24 hours is an effective treatment of patients who remain comatose after resuscitation from out-of-hospital cardiac arrest when the initial cardiac rhythm is ventricular fibrillation.[7,8] As with other therapeutic interventions after brain injury, time to treatment is important and this therapy should only be initiated within 6 hours of injury and without delay. In 2010, the American Heart Association recommended as part of routine post–cardiac arrest care that comatose adult patients surviving out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours. Further, less robust recommendations were made for TH for comatose adult patients after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac

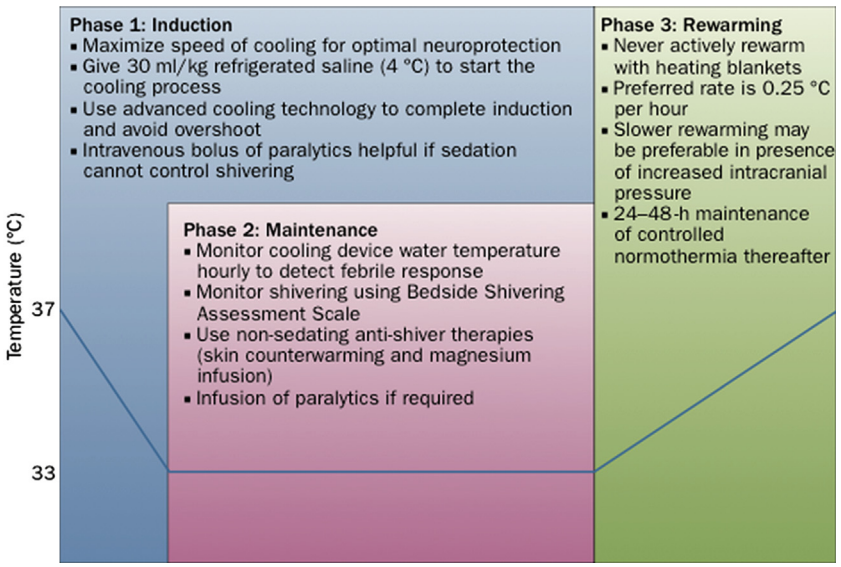

Fig. 1. Key management points during the 3 phases of TH.

arrest with an initial rhythm of pulseless electric activity or asystole.[23]

Traumatic Brain Injury

The application of hypothermia after traumatic brain injury (TBI) can have different effects based on patient selection as well as the timing, duration, and depth of cooling. Cooling within minutes to hours after the injury is designed to act as a neuroprotectant, mitigating many of the cellular mechanisms that eventually result in further damage. As hours and days after injury continue, the cumulative effect of these mechanisms is observed clinically, and TH can also be applied as an effective therapy for processes leading to increased ICP.

Thirteen controlled single-center studies conducted on adult patients with TBI showed significantly better outcomes associated with TH.[24] In contrast, 3 multicenter randomized controlled trials that tested early short-term (maximum 48 hours) TH[25–27] found no benefit with regard to survival and neurologic outcome.

The most recent study published is the National Acute Brain Injury Study: Hypothermia II (NABIS: H II), a multicenter trial including patients who were 16 to 45 years old after severe, nonpenetrating TBI, treated with TH.[27] The trial was stopped after inclusion of 108 patients, and no effect on outcome was seen. Subgroup analysis found that patients with surgically evacuated hematomas treated with TH had better outcomes, whereas those with diffuse brain injury treated with hypothermia had a trend to poorer outcome. The reasons for improvement in such a subpopulation may include the impact of temperature control on reperfusion injury–related spreading depolarizations, as recently reported by the Cooperative Study of Brain Injury Depolarizations (COSBID) study group.[28,29]

There are 17 controlled trials investigating the impact of hypothermia on outcome in patients with severe TBI and refractory intracranial hypertension and most of these studies show that hypothermia is an effective method for reducing ICP, although the data on outcome are inconsistent.[24] The magnitude of the effect of TH on ICP reduction is estimated to be approximately 10 mm Hg (range 5–23 mm Hg). Across the studies analyzed, the effect of TH on ICP reduction was superior to that achieved with moderate hyperventilation, barbiturates, and mannitol, but less effective than hemicraniectomy and hypertonic saline.[30]

The optimal target temperature of TH when used for ICP control is not well defined. There is experimental evidence that decreasing body temperature to between 35 and 35.5°C effectively treats intracranial hypertension, while maintaining sufficient cerebral perfusion pressure without cardiac dysfunction or oxygen debt.[31] Resting energy expenditure and cardiac output decreased progressively with hypothermia, reaching very low levels at temperatures less than 35°C.[31] At core temperatures less than 35°C there is a concomitant significant decrease brain tissue oxygenation.[32] Thus, 35 to 35.5°C may be the optimal temperature at which to treat patients with intracranial hypertension following severe TBI. However, instead of applying fixed temperature targets, TH may be better applied by titrating temperature to maintain ICP at less than 20 mm Hg. Although, from a meta-analysis, some have advocated that a duration of hypothermia of more than 48 hours may be beneficial,[33] the optimal duration of cooling is not known. Rather than focusing on optimal timing, a better target for cooling is ongoing efficacy for reduction of ICP weighed against the risk associated with deep sedation and impaired immune function that accompany prolonged cooling.

TH is effective in reducing increased ICP, and is therefore an appropriate option for reducing ICP after TBI. The Eurotherm3235 Trial, an international, multicenter, randomized controlled trial, will examine the effects of TH at 32 to 35°C as a treatment of increased ICP after TBI. The design of this study is adapted to overcome some of the failures of previous studies that have to do with patient selection, timing, and duration of treatment. Subjects are allowed to be enrolled up to 72 hours after TBI. The duration of cooling is titrated on the time to control ICP effectively (between 2 and 5 days), and rewarming is used at a rate of 0.25°C/h.[34]

Rewarming remains the most dangerous stage of hypothermia management. Large fluctuations in temperature can reverse the protective effects of cooling and aggravate secondary brain injury.[35,36] This is shown by impaired cerebrovascular vasoreactivity, hyperemia, and rebound intracranial hypertension.[37] Studies have documented rapid rewarming to be associate with increased episodes of rebound intracranial hypertension and worse outcomes.[27,38] A slow, controlled rewarming (0.1–0.2°C/h) should be used to reduce the risk of rebound cerebral edema and intracranial hypertension.

Subarachnoid Hemorrhage

The focus of TH in the acute phase of subarachnoid hemorrhage (SAH) is on mitigating the effect of the initial hemorrhage. Experimental studies have shown that mild to moderate hypothermia

reverses acute cerebral perfusion pressure–independent hypoperfusion, enhances recovery of posthemorrhagic cerebral blood flow, and reverses edema formation. The vascular effects may be attributed to hypothermia-induced vasodilatory effects or to the prevention of autoregulatory impairment, whereas prevention of lactate accumulation may help reverse post-SAH cerebral edema.

In the clinical setting, few retrospective, nonrandomized studies have been reported examining the effect of mild hypothermia soon after SAH. Gasser and colleagues[39] reported the results of a study to evaluate the feasibility and safety of long-term hypothermia (>72 hours) in the treatment of severe brain edema after poor-grade SAH. Among 156 patients with SAH, 21 patients were treated with mild hypothermia and barbiturate coma. Of these, 9 patients were treated for less than 72 hours and 12 for longer than 72 hours. Functional independence at 3 months, defined as a Glasgow Outcome Scale (GOS) score of 4 or 5, was achieved in 48% of patients, but this was no different between the 2 groups. The most common form of complication was infection. Regardless of favorable results from case reports, conclusions regarding impact of TH on outcome are lacking, because there are no data from controlled prospective studies.

Intraoperative deep hypothermia (26°C) has been successfully used in patients undergoing high-risk cardiac and neurosurgical procedures requiring cardiopulmonary bypass and temporary circulatory arrest.[40] The Intraoperative Hypothermia for Aneurysm Surgery Trial[41] failed to show any improvement in mortality or functional or cognitive outcome, most likely because most subjects were in good clinical condition, with no acute brain injury and no temperature-modifiable brain injury (ie, temporary vessel occlusion) during surgery.

The application of hypothermia after parenchymal hemorrhage is understudied. Similar to SAH, clinical studies in intracranial hemorrhage have not been adequately designed to understand the impact of TH on outcome, although there has been a consistent demonstration of cooling to effectively reduce hemorrhage-related cerebral edema.[42,43]

Ischemic stroke

The perceived need for a secure airway, mechanical ventilation, and shivering control has limited the use of hypothermia as a therapeutic approach in patients after stroke. However, some studies have shown that it is possible to cool nonintubated patients after stroke, albeit with variable success.[44–46] Schwab and Mayer[47] reported on 2 noncontrolled trials of induced hypothermia as salvage therapy for patients with established middle cerebral artery (MCA) infarction. Patients were admitted to an intensive care unit and hypothermia was achieved with surface cooling. ICP was monitored with intraparenchymal sensors placed ipsilateral to the infarct. In the first of these studies, published in 1998, hypothermia was induced in 25 malignant MCA infarct patients an average of 14 hours after stroke onset, and temperature was maintained at 33°C for 48 to 72 hours.[47] There was significant morbidity-associated cerebral edema caused by uncontrolled rewarming. Further data in patients with MCA infarct suggests that controlled rewarming rates of 0.1°C per hour or less allow for improved control of ICP compared with patients in whom rewarming is achieved in a passive, uncontrolled fashion.[47,48]

In a prospective randomized study, Els and colleagues[49] enrolled 25 consecutive patients with an ischemic infarction of more than two-thirds of 1 hemisphere to either hemicraniectomy alone, or in combination with hypothermia. Safety parameters were compared between both treatment groups and the clinical outcome was assessed at 6 months. Overall mortality was 12% (2 of 13 vs 1 of 12 in the 2 groups), but none of these three patients died because of treatment-related complications. There were no severe side effects of hypothermia. The clinical outcome showed a tendency for a better outcome in the hemicraniectomy plus moderate hypothermia group after 6 months. Delayed cooling for the treatment of cytotoxic brain edema does not provide definitive treatment of malignant cerebral edema, and should not be used as an alternative to the proven therapy for hemicraniectomy.[50,51] However, these results suggest that hypothermia may still be of benefit even in those patients who have undergone hemicraniectomy.

Many questions remain unanswered regarding the role of hypothermia as an adjunct to thrombolysis in the treatment of ischemic stroke. A trial sponsored by the National Institutes of Health is currently underway to evaluate the safety of a 6-hour window for intravenous thrombolytic therapy when coupled with hypothermia in the Intravascular Cooling in the Treatment of Stroke–Longer TPA Window trial. Other investigators are studying the effects of mild hypothermia combined with additional neuroprotective agents, such as caffeine and ethanol, in patients after ischemic stroke; however, until tested in a prospective controlled study, hypothermia therapy, either standalone or as an adjunct, remains experimental.[52,53]

Spinal Cord Injury

Approximately 11,000 to 12,000 individuals sustain a spinal cord injury (SCI) from motor vehicle accidents, sport-related injuries, and direct trauma.[54] Recent surgical advancements have reduced mortality and morbidity but long-term disability remains a significant problem.[55] There are currently no proven medical treatments that protect against the consequences of SCI. Experimental models have reliably shown a strong benefit of TH.[54] The only evidence thus far in the literature is a single-center study from the University of Miami that reported the results from 14 patients with an average age of 39.4 years (range, 16–62 years) with acute, complete (American Spinal Injury Association [ASIA] A) cervical SCIs using an intravascular cooling catheter to achieve modest (33°C) systemic hypothermia for 48 hours.[56] In this small series, the cooling approach was found to be feasible with no difference in rate of complications. Even though they noted that 6 of 14 patients converted from ASIA A status, large prospective studies are needed before TH can be considered as part of standard of care in this population.

Critical Care Management Issues of TH

Clinical management of hypothermia can be separated into 3 phases: induction, maintenance, and rewarming (**Fig. 2**). The widespread use of advanced temperature modulating devices has simplified bedside management of hypothermia. Each system works to induce and maintain core body temperature through conductive heat loss either by surface cooling or intravascular cooling. Surface cooling systems consist of pads that are applied to the skin of patients with circulating forced cold air or fluid,[57,58] whereas intravascular cooling systems consist of endovascular heat-exchange catheters that are placed via the femoral or subclavian vein to cool the blood.[59,60] Both methods can effectively induce and maintain hypothermia.[61] All of these devices work via a feedback loop that adjusts the temperature of the water circulating through the cooling system to maintain a constant target body temperature measured in the bladder or esophagus.[62]

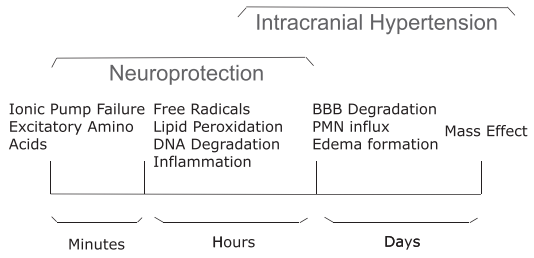

Fig. 2. Timeline for hypothermic protection. BBB, blood-brain barrier; PMN, polymorphonuclear leukocyte. (*From* Choi HA, Badjatia N, Mayer SA. Hypothermia for acute brain injury–mechanisms and practical aspects. Nat Rev Neurol 2012;8:214–22; with permission.)

When treating patients with hypothermia, induction should be as rapid as possible to reach the target temperature. Application of ice packs to a patient and the infusion of cold intravenous fluids (4°C normal saline or lactated ringers at 30–40 mL/kg over 1 hour) is the simplest and least expensive method of inducing hypothermia.[57,63–65] The use of large-volume (30 mL/kg) cold (4°C) fluid infusions has been well studied in postoperative and critical care settings and found to be an effective method to induce hypothermia. When used in conjunction with advanced temperature-modulating devices, a bolus of isotonic fluid can decrease core temperatures by 4°C/h. Even with large volumes administered, there seem to be no episodes of pulmonary edema or cardiac arrhythmia.[63] In addition to its rapid onset, the large volume of infusion can help offset the fluid imbalance that may be observed as a result of cold-induced diuresis during the induction of hypothermia.

During the maintenance period, advanced cooling technology can maintain core body temperature with only minor fluctuations (±0.5°C). Fever is the most frequent clinical sign of infection, but no longer occurs when hypothermia is induced. Monitoring the temperature of the circulating water in the cooling device can be used as a surrogate marker for increased heat production by the patient and may indicate a febrile response and possible infection.[66]

Rewarming is the most dangerous phase of hypothermia, particularly in patients with intracranial mass effect who are at risk of increased ICP. Rapid increases in body temperature can cause systemic vasodilation and hypotension, which in turn can trigger cerebral vasodilation and ICP plateau waves.[67–69] In general, rewarming should be performed as slowly as 0.1°C/h if increased ICP is a concern.[68,70] If ICP increase is observed, rewarming should be slowed or even halted. In most cases, a rewarming rate of 0.25°C/h is recommended, and in all cases rewarming should be performed in a controlled manner to avoid overshoot and hyperthermia.[71]

COMPLICATIONS AND ADVERSE EFFECTS

Shivering

Shivering is a thermoregulatory defense to maintain body temperature at the hypothalamic set point. In healthy humans, peripheral vasoconstriction is triggered at 36.5°C and shivering at

35.5°C.[72] Temperature thresholds for vasoconstriction and shivering are higher than normal in brain-injured patients; therefore, these thermoregulatory defenses may occur at higher temperatures.[73]

Control of shivering is essential for effective hypothermia, because shivering fights the cooling process and can trigger large increases in systemic and cerebral energy consumption and metabolic demand.[74,75] The first step in managing shivering is to have an effective tool for measurement. The Bedside Shivering Assessment Scale is a simple, validated, 4-point scale that enables repeated quantification of shivering at the bedside (**Table 1**).

Therapy for shivering should ideally stop or suppress the central thermoregulatory reflex rather than just uncoupling this response from skeletal muscle contraction, because this does not mitigate the ongoing cerebral and systemic stress response. Initial measures should focus on minimizing the use of high doses of analogosedatives, which can impair the ability to track neurologic examination changes and increase the risk for complications related to prolonged mechanical ventilation.[76]

The first step (**Table 2**) uses acetaminophen, buspirone, and magnesium infusion.[77–79] In addition, patients should be treated with forced warm-air skin counterwarming. An increase in mean skin temperature by 4°C, without affecting core body temperature, can increase the sensation of warmth and blunt the shivering reflex by 1°C.[74,80] Approximately half of the patients who shiver in response to TH require additional pharmacologic therapy to prevent this response. Dexmeditomidine is a central-acting alpha-2 receptor agonist that has been shown to decrease the shivering threshold.[81] Propofol and the opioid meperidine is also effective at reducing shivering, but can cause oversedation and prolong the need for mechanical ventilation when given at high doses.[81,82] If all other options to prevent shivering are exhausted, paralysis (induced with vecuronium or cisatracurium) may be needed.[76]

Table 1
The Bedside Shivering Assessment Scale (BSAS)

Score	Shivering Status	Description
0	None	No shivering noted on palpation of the masseter, neck, or chest wall
1	Mild	Shivering localized to the neck and/or thorax only
2	Moderate	Shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe	Shivering involves gross movements of the trunk and upper and lower extremities

The Bedside Shivering Assessment Scale is measured by palpating the temples and masseters, neck and shoulders, pectoralis muscles, biceps, and quadriceps.

Data from Lavinio A, et al. Cerebrovascular reactivity during hypothermia and rewarming. Br J Anaesth 2007;99(2):237–44.

Reduced Electrolyte Levels

In addition to decreased systemic and cerebral metabolism, other physiologic changes routinely occur in patients treated with hypothermia. Cooling drives electrolytes into the intracellular compartment and results in decreased levels of serum potassium, magnesium, and phosphate.[83] However, during rewarming these electrolytes are released from intracellular stores and move to the extracellular spaces. Care should therefore be taken to avoid excessive potassium replacement during the maintenance phase to avoid rebound hyperkalemia during rewarming.[84]

Acid-Base Status

As patients are cooled, carbon dioxide becomes more soluble, carbon dioxide partial pressure (P_{CO_2}) levels decrease, and the pH rises. There are 2 ways to manage acid-base status during induced hypothermia: alpha-stat management refers to the practice of interpreting blood gas values at 37°C regardless of the patient's body temperature, and pH-stat management is correcting blood gas values to account for the colder body temperature. To maintain normal P_{CO_2} and pH levels with pH-stat management, a state of hypoventilation and hypercarbia is maintained, which results in cerebral vasodilation and could, in theory, lead to an increase in cerebral blood flow and ICP. Substantial controversy exists over which method of acid-base management, if either, is preferable.[21,85,86] In general, a given center should adopt 1 method and develop a protocol for respiratory management accordingly.

Insulin Resistance and Kidney Dysfunction

Insulin resistance occurs during hypothermia, which leads to hyperglycemia. During rewarming, insulin sensitivity may increase rapidly, and may lead to hypoglycemia if the insulin dose is not adjusted appropriately.[84] Peripheral vasoconstriction during hypothermia can cause a diversion of

Table 2
Antishivering protocol

Step	Level of Sedation	Intervention for Shivering	Dosage or Goal
0	Baseline	Acetaminophen Busiprone Magnesium sulfate Skin counterwarming	650–1000 mg Q 4–6 h 30 mg Q 8 h 0.5–1 mg/h IV; goal, 3–4 mg/dL Maximum temperature, 43°C
1	Mild	Dexmedetomidine Opioids	0.2–1.5 μg/h Meperidine 50–100 mg IM/IV
2	Moderate	Dexmedetomidine Opioids	0.2–1.5 μg/h Meperidine 50–100 mg IM/IV
3	Deep	Propofol	50–75 μg/kg/min
4	Neuromuscular blockade	Vecuronium	0.1 mg/kg IV

Abbreviations: IM, intramuscular; IV, intravenous; Q, every.

blood to the kidneys, which can result in mild renal tubular dysfunction. The combination of cooling and kidney dysfunction causes a cold diuresis effect,[87–89] which can make fluid management during TH challenging.

Cardiac Function

Core body temperatures between 33 and 35°C are generally well tolerated by the heart. As long as shivering is well controlled, cooling results in bradycardia and reduced myocardial contractility, which causes reduced cardiac output and blood pressure. Temperatures less than 32°C can lead to serious cardiac arrhythmias such as atrial and ventricular tachycardia and fibrillation.[84,90] For this reason, 33°C is generally considered the safe lower limit of target temperature.

Impaired Immune Function

Cooling impairs leukocyte phagocytic function and immunosuppression, which explains the increased risk of pneumonia and other bacterial

Table 3
Evidence for the clinical usefulness of hypothermia in the NCCU

Clinical Scenario	Efficacy of TH	Type of Evidence	General Protocol	Level of Evidence
Cardiac arrest	Effective	2 phase III RCTs	32–34°C for 12–24 h	Level I
TBI	Ineffective	Multiple phase III RCTs, ongoing studies	32–34°C for 24 h	Level I
Cardiac arrest (PEA or asystolic)	Possible	Observational case series	32–34°C for 12–24 h	Level IIb
Increased ICP	Effective	Multiple RCTs and cohort studies	32–35°C titrated to ICP	Level II
Ischemic stroke	Feasible	Small feasibility trials, ongoing phase III trial	35.5°C for non–mechanically ventilated patients 32–35°C for mechanically ventilated patients	Level III
Intracerebral hemorrhage	Unknown	Observational case series	33–35°C	Level III
Subarachnoid hemorrhage	Unknown	Observational case series	33–35°C	Level III
Spinal cord injury	Feasible	Nonrandomized Prospective Study	33°C for 48 h	Level III

Abbreviations: PEA, pulseless electrical activity; RCTs, randomized controlled trials; TH, therapeutic hypothermia; VF, ventricular fibrillation; VT, ventricular tachycardia.

infections during hypothermia.[41,53,91] The risk for infectious complications seems to increase with prolonged hypothermia, although it is not clear at which time point the risk becomes universal. Tracking the development of infections can also be difficult in the absence of temperature increases and impaired white blood cell counts. Many of the temperature-modulating devices allow bedside clinicians to track the work of the device, which can be used as an indirect indicator of a mounting infection.

Hematologic Effects

Coagulopathy and thrombocytopenia seem to occur more frequently in spontaneous hypothermia after trauma than after medically induced hypothermia. Platelet dysfunction, increased fibrinolytic activity, and decreased activity of coagulation cascade enzymes all contribute to bleeding during hypothermia. Mild coagulopathy and platelet dysfunction also occur at temperatures of more than 35°C, but most trials have not shown an increased risk of serious bleeding, even in patients with preexisting intracranial hemorrhage.[92]

SUMMARY

Over the past decade, hypothermia has emerged as a mainstream intervention for many diseases seen in the NCCU. Studies in patients who have undergone cardiac arrest have unequivocally shown that the application of hypothermia to these individuals is safe and effective. However, the translation of neuroprotection with TH to other disease states has not been as successful (**Table 3**). Challenges in the safe and effective application of TH include adequately controlling shiver reflex and minimization of complications including infection, metabolic derangements, and cardiac arrhythmias. Many questions regarding the optimal timing, depth, and duration of cooling, and appropriate clinical management of the patient remain to be answered. Further prospective controlled studies focusing on the effects of TH on brain physiology and outcome in stroke, trauma, and other disease states in humans are needed before therapeutic hypothermia can be validated for use in these diseases in the NCCU.

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