Therapeutic Temperature Modulation in Neurocritical Care

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The ability to effectively achieve and maintain long-term temperature control is an important goal that has been previously unachievable in the neurocritical care setting. Previous attempts have been limited by the inability to overcome physiologic defense mechanisms, short duration of action, or significant adverse effects. Recent advances in technology have made therapeutic temperature modulation feasible. In this review, current concepts of therapeutic temperature modulation are presented. New advances in technology may provide an important breakthrough in the ability to reduce fever-associated morbidity in neurocritically ill patients. What remains to be seen is whether the advantages of these technologies will outweigh the risks associated with therapeutic temperature modulation.

Introduction

The concept of modulating body temperature as a method by which to protect the brain after injury is certainly not new. For years experimental studies have demonstrated that hyperthermia worsens outcomes after brain injury, and that mild hypothermia (32°–34°C) is neuroprotective. In modern clinical practice, Fay [1] was the first to report on the use of therapeutic hypothermia as a treatment for acute brain injuries. However, the treatment itself has been associated with significant adverse effects, and, therefore, is rarely recommended [2]. Although therapeutic hypothermia has not been shown to be protective in some forms of brain injury, hyperthermia has been associated with worsened outcomes in all forms of acute brain injury [3]. Clinically, however, therapeutic normothermia has been virtually impossible to maintain for long periods of time.

Both technologic and pharmacologic advances have now made achieving therapeutic temperature modulation a realistic goal in the neurocritical care setting. In this review, the methods utilized to induce therapeutic temperature modulation as well as current management concepts are presented.

Methods to Induce Therapeutic Temperature Modulation

Antipyretic drugs

Endogenous pyrogens released by leukocytes in response to infection, drugs, blood products, or other stimuli cause fever by stimulating cerebral prostaglandin-E synthesis and as a result raise the hypothalamic temperature set point [4]. Antipyretic agents including acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAID) are believed to block this process by inhibiting cyclooxygenase-mediated prostaglandin synthesis in the brain, resulting in a lowering of the hypothalamic set point. This activates the body's two principal mechanisms for heat dissipation: vasodilation and sweating [4]. The effectiveness of antipyretic agents is tightly linked to conditions where thermoregulation is intact. Therefore, they are more likely to be ineffective in brain-injured patients with impaired thermoregulatory mechanisms. Corticosteroids also have antipyretic properties but are not used clinically to treat fever because of their side effects.

Whether acetaminophen alone is more effective than placebo for treating fever in adult intensive care unit (ICU) patients is still unclear. Most studies have been conducted in the pediatric population, where weight-adjusted doses have been shown to be effective in reducing fever. In the adult neurocritical care population, acetaminophen has been most widely studied in an attempt to maintain normothermia in patients with acute stroke. Koennecke et al. [5] showed that treatment with acetaminophen in a daily dose of 4000 mg resulted in a substantial reduction of the proportion of patients with body temperatures over 37.5°C (the amount of temperature reduction was not reported). Kasner et al. [6] observed a difference of 0.2°C in body temperature in favor of treatment with acetaminophen (approximately 4 g/d) as compared with placebo in patients with hemorrhagic or ischemic stroke, although

this was not statistically significant. Two recent phase II studies have demonstrated that perhaps a higher dose of acetaminophen (6000 mg/d) is more effective in maintaining normothermia/preventing fever [7,8]. Based on the results from these studies, a large phase III study assessing the ability to maintain normothermia after acute ischemic stroke is planned [9•].

Ibuprofen has been widely studied in the pediatric population with equivalent or superior efficacy as compared with acetaminophen. However, only one randomized controlled study has been conducted in adult patients with brain injury. This study demonstrated that ibuprofen (2400 mg/d) was not better than acetaminophen or placebo in maintaining normothermia after ischemic stroke [8]. In a recent in vivo study it was shown that the concomitant administration of ibuprofen but not acetaminophen antagonizes the irreversible platelet-inhibiting effect of aspirin [8]. Ibuprofen may, therefore, limit the already small beneficial effect of aspirin to improve outcome after ischemic stroke. This is an additional reason why acetaminophen may be preferable to ibuprofen for reduction of temperature in brain-injured patients who are at ongoing risk for cerebral ischemia.

External cooling

External cooling reduces body temperature by promoting heat loss without affecting the hypothalamic set point. Four modes of heat transfer constitute the basis of interventions to promote heat loss: 1) evaporation (eg, water sprays or sponge baths); 2) conduction (eg, ice packs, water-circulating cooling blankets, immersion); 3) convection (eg, fans, air-circulating cooling blankets); and 4) radiation (ie, exposure of skin) [10]. In patients with temperature elevations caused by impaired thermoregulation, such as what occurs after brain injury, antipyretic agents may be ineffective, and temperature reduction may only be achieved by external cooling. However, external cooling can result in reflex shivering and vasoconstriction, as the body attempts to generate heat and counteract the cooling process.

Few controlled studies have evaluated the efficacy of external cooling interventions for lowering body temperature in humans. Previous experimental studies have shown that the combination of evaporative and convection cooling, with water sprays or sponging and forced airflow, is more effective than conduction cooling or either method alone for reducing temperature in non–brain-injured patients with hyperthermia [11]. Like antipyretic medications, evaporative cooling has been studied more in the pediatric population, with mixed results [12].

In a study of febrile neurocritical care patients treated with acetaminophen, air-blanket cooling had a small benefit that did not reach statistical significance [13]. Air blanket therapy was stopped or interrupted because the patient refused or was unable to tolerate treatment in 12%, because of a nursing error in 5%, and because the device was not available in 4%. The authors concluded that although it was possible that a significant treatment effect might have been found had these interruptions not occurred, the interruptions accurately reflect the variation of clinical practice in the ICU setting [13].

Water-circulating cooling blankets, a form of conductive cooling, are the most commonly used treatment for acetaminophen-refractory fever in critically ill adults. However, there are few data regarding their efficacy. Two small controlled studies have evaluated external cooling in adult ICU patients. One study compared the use of acetaminophen alone with tepid water sponging, or with a water-circulating cooling blanket in febrile neurologic patients, and found no difference between the three treatments [14]. Another study of febrile patients under sedation, analgesia, and mechanical ventilation found that ice-water sponging was superior to two intravenous NSAIDs (paracetamol and metamazol) in a nonrandomized crossover study [15]. A large observational study found no difference in the mean cooling rate in febrile ICU patients treated with or without water-circulating cooling blankets [16]. A feature commonly found with water circulating blankets is the wide fluctuations in temperature that occur, with temperature overshoot being very common.

Arctic Sun

The Medivance Arctic Sun Temperature Management System, model 2000 (Medivance, Louisville, CO) involves four water-circulating energy transfer pads that are lined with a hydrogel to facilitate surface contact. Four pads are placed directly on the skin of the back, abdomen, and both thighs (total surface area between 0.60 and 0.77 m^2). The control module for this device adjusts the temperature of the water circulating through the cooling pads (range of 4°–42°C) to maintain core body temperature at a target level, based on either bladder or esophageal temperature readings. A recent study found the application of the Arctic Sun significantly reduced fever burden as compared with water-circulating blankets in a population of neurocritical care patients [17].

Intravascular cooling

Intravenous cold saline

Infusion of 4°C normal saline is an appealing option because it is inexpensive and easy to administer in the critical care setting. First described in healthy volunteers who underwent general anesthesia and neuromuscular blockade, a 30-minute infusion of 4°C fluid reduced core temperature by 2.5°C within 1 hour after the infusion was begun [18]. In a pilot study of ice-cold lactated Ringer's solution, 22 resuscitated cardiac arrest patients were cooled by 1.7°C [19]. A recently reported case series also found the rapid infusion of a large volume of cold saline to be a safe and effective method to achieve normothermia in select brain-injured patients [20]. In addition to its rapid onset, the large volume of infusion can help offset the fluid

imbalance that may be observed during the induction of hypothermia. Therefore, the administration of a large volume of cold saline should always be considered during the induction phase of temperature modulation.

Innercool

The Celsius Control system (Innercool Therapies, San Diego, CA) is a 10.7-French (Fr) femoral intravascular cooling catheter system that works to modulate temperature by circulating sterile saline through a bedside console through the intravascular catheter in a closed-loop circuit. The distal portion of the catheter incorporates a thermometer that records core temperature and contains a flexible, distal metallic heat transfer element that is designed to allow for direct exchange of thermal energy with blood circulating around the catheter. This catheter-based system has been shown to effectively maintain target temperatures in both the operative and intensive care setting [21,22].

CoolGard/Cool Line catheter system

The CoolGard/Cool Line catheter system (Alsius, Irvine, CA) utilizes an 8.5-Fr intravascular heat exchange catheter that can simultaneously function as a single- or double-lumen central venous catheter (subclavian jugular or femoral vein). Normal saline is pumped from the bedside unit, via the tubing set, through two balloons coaxially mounted on the catheter in a closed loop that returns the saline to the CoolGard system. Heat is transferred from the blood to the saline inside the balloon. Two moderate-sized studies have shown the CoolGard system to be an effective method by which fever can be prevented in the neurocritical care setting [23,24].

Clinical Applications of Therapeutic Temperature Modulation

Maintenance of normothermia/prevention of fever

Fever, defined as temperature higher than 38.3°C, has been reported to occur in between 25% and 50% of neurocritically ill patients. Approximately half of febrile cases can be attributed to infectious causes, with nosocomial pulmonary infections representing the largest contributor. In one fifth to one third of cases, fever remains unexplained even after extensive diagnostic work-up [25]. Many of these fever-of-unknown-origin cases can also be classified as central fever (ie, spontaneous elevations in temperature related to the acute brain injury).

Clinically, fever has been associated with increased mortality and poor functional outcome after acute brain injury. In ischemic stroke, not only does fever on admission correlate with larger infarct size and higher mortality rate, but each degree Celsius of temperature elevation doubles the relative risk for poor functional outcome. Fever also has been associated with vasospasm after subarachnoid hemorrhage (SAH) [26], poor outcome after traumatic brain injury (TBI) [27], and increased mortality and functional disability after intracerebral hemorrhage (ICH) [28].

Attempts to regulate fever after acute brain injury have not been successful using conventional methods, such as ice packs or surface cooling devices. Use of oral and parenteral antipyretic agents has been reported in limited nonrandomized series with variable success. All these methods have also been hindered by a prolonged time to achieving, and difficulty maintaining, normothermia.

Recent technologic advances, however, have made the possibility of achieving and maintaining normothermia feasible with both surface and intravascular devices (Table 1), although the timing for initiating treatment with these devices remains controversial. Despite the overwhelming data to support the notion that fever after brain injury leads to worse outcomes, there are insufficient data to support the empiric maintenance of normothermia. As a result, these devices are best utilized in cases where conventional methods of preventing recurrent fever have failed. The strategy for reducing fever in the ICU setting, therefore, should be stepwise and involve three basic steps: 1) investigation and elimination of the fever source; 2) appropriate antipyretic therapy; and 3) therapeutic temperature modulation (normothermia). A proposed algorithm for treating fever is presented in Figure 1.

TBI and intracranial pressure control

Although neurologic damage occurring at the moment of injury is probably irreversible, the subsequent (secondary) injury is not, and thus therapy for TBI has focused on prevention or mitigation of this secondary injury. In TBI, accumulation of vasogenic fluid can cause cerebral edema within hours, which can lead to a rise in intracranial pressure (ICP) and additional damage to injured and uninjured areas of the brain. The presence of local hyperthermic areas in the brain, where temperatures are substantially higher (up to 2°C) than the measured core temperature, also contributes to the formation of cerebral edema.

Therapeutic hypothermia was first considered for TBI in the 1940s, and since the early 1990s the results of 13 clinical studies, involving a total number of 1321 patients, have been published, with endpoints measuring ICP, neurological outcome, and survival [29]. It is important to note that all except one of these studies were performed in patients with high ICP. All authors reported that hypothermia (32°–34°C) was able to reduce ICP in patients with intracranial hypertension; however, unfortunately the results regarding effects on survival and neurologic outcome had been conflicting.

In the past 2 years the results of two new large clinical trials have been published, both of which reported significant improvements in neurologic outcome and survival in TBI patients treated with hypothermia. One of these studies observed statistically significant benefits of hypothermia

Table 1. Studies using new surface and intravascular techniques to achieve normothermia and/or reduce fever burden

Study	Patient population	Patients, *n*	Design	Intervention	Primary outcome measure	Results
Schmutzhard et al. [23]	NICU	51	Observational, no controls	Insertion of Cool Line catheter (Alsius, Irvine, CA)	Fever burden	Effective maintenance of normothermia; pneumothorax in 2 patients
Diringer et al. [24]	NICU	294	Randomized controlled trial	Acetaminophen, cooling blankets and gastric lavage plus Cool Line catheter	Fever burden over 72 h	Fever burden (> 38°C) reduced by 64% in Cool Line catheter group; shivering in only 4%
Badjatia et al. [41]	SAH	9	Observational, no controls	Celsius control catheter and acetaminophen	Achieving normothermia in 24 h	Normothermia achieved in 78%; DVT in 2 patients
Mayer et al. [13]	NICU	53	Randomized controlled trial	Arctic Sun system (MediVance, Louisville, CO) vs conventional water-circulating cooling blanket	Fever burden over 24 h	Significant reduction of fever burden with the Arctic Sun system

NICU—neurointensive care unit; SAH—subarachnoid hemorrhage.

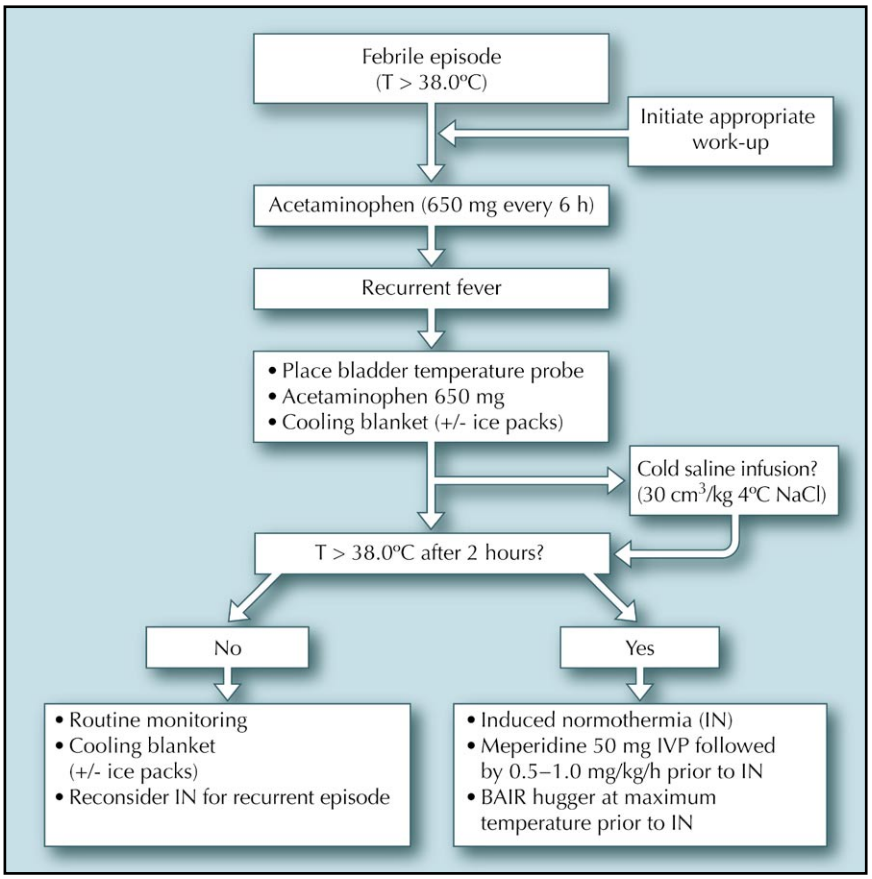

Figure 1. Proposed algorithm for therapeutic temperature modulation of fever in neurocritical care patients. (BAIR is a registered trademark of Arizant Health Care, Eden Prairie, MN.) IVP—intravenous push; T—temperature.

in neurologic outcome and survival [30], despite the fact that hypothermia was used only when other forms of therapy had failed to control ICP. The largest effects were seen in patients with Glasgow Coma Scale (GCS) scores of 5 or 6 at admission, where good neurologic outcome was 29% vs 8% in controls; and mortality was 52% versus 76%. In this protocol, ICP was used to guide timing and speed of rewarming, with cooling continued as long as ICP rose when rewarming was initiated. The other recently published study reported good neurologic outcome (38.8% vs 19.7%), moderate disability (22.7% vs 18.2%), and death (25.7% vs 36.4%) for hypothermia patients versus controls, respectively. In these studies hypothermia was maintained for longer periods of time (on average, 115.2 hours and 62.4 hours, respectively), and speed of rewarming was much slower compared with previous studies [31].

Differences in timing, duration, and discontinuation of therapeutic hypothermia, as well as a lack of heterogeneity in care in these two studies, may be the crucial differences that aided in improved outcomes as compared with previous studies. Although it is clear that therapeutic hypothermia is an effective treatment for intracranial hypertension, optimization of timing and duration of therapy need to be studied in order to improve clinical outcomes after TBI.

Ischemic stroke

As pointed out in a previous section, there have been many controlled studies investigating therapeutic normothermia in ischemic stroke with mixed results. Recent experience with therapeutic hypothermia after ischemic stroke is limited to case series of patients presenting with malignant middle cerebral artery infarction. These studies have been hindered by the slow rate of cooling, temperature overshoot, and high rates of infectious complications. However, in a recent pilot study, moderate hypothermia (33°C) was achieved within 3 ± 1 hours and maintained for prolonged periods with an intravascular cooling device that had built in feedback mechanisms, allowing for avoidance of temperature overshoot and for controlled rewarming. In this study, 18 patients were randomized to hypothermia treatment, with 22 in a control group. Two thirds of those in the hypothermia group were successfully cooled; however, there was no difference in outcome among the two groups at 30 days. On MRI examination, infarct growth was slightly lower in the hypothermia group than in the control group (90.0% vs 108.4%; $P = 0.71$) [32]. Several studies are underway assessing the impact of therapeutic hypothermia on cerebral edema as assessed by MRI.

Cardiac arrest

In sudden cardiac arrest, brain oxygen stores and consciousness are lost within 20 seconds, and glucose and adenosine triphospate stores are lost within 5 minutes. During no-flow states, there is membrane depolarization, calcium influx, glutamate release, acidosis, and activation

of lipases, proteases, and nucleases. This allows for reoxygenation injury involving iron, free radicals, nitric oxide, catecholamines, excitatory amino acid release, and renewed calcium shifts [33].

Despite knowing the benefits of therapeutic hypothermia after experimental cardiac arrest for several decades [34], it has only recently been studied extensively in humans. The results of two randomized controlled trials provide evidence that therapeutic hypothermia (32°–34°C) for 12 to 24 hours is an effective treatment for patients who remain comatose after resuscitation from out-of-hospital cardiac arrest when the initial cardiac rhythm is ventricular fibrillation [35,36]. 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. Further studies investigating the selection of nonventricular fibrillation patients, the time to treatment, depth, and duration of hypothermia are needed.

Subarachnoid hemorrhage

Similar to ischemic stroke, therapeutic temperature modulation in SAH can imply normothermia and hypothermia, although the timing for consideration of each is different. The focus of therapeutic temperature modulation in the acute phase of SAH is on ameliorating the effect of the initial hemorrhage. Experimental studies have demonstrated that mild to moderate hypothermia reverses acute cerebral perfusion pressure (CPP)-independent hypoperfusion, enhances recovery of posthemorrhagic cerebral blood flow (CBF), and reverses edema formation [37,38]. 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 recently been reported examining the effect of mild hypothermia soon after SAH. In one study, early induction of hypothermia resulted in a greater reduction of O_2 metabolic rate than CBF (so called luxury perfusion) in the majority of cases [39]. Another study found normalization of cerebral oxygen metabolism in selected cases of early hypothermia in poor-grade SAH [40]. Regardless of favorable results from case reports, conclusions regarding impact on outcome are lacking as there are no prospective data on the effects of hypothermia during the acute phase of SAH.

Fever is a frequent concern in critically ill patients with SAH and has been reported to be associated with an increased risk of developing vasospasm and poor outcome [41]. The peak temperatures occur approximately 1 week after hemorrhage, coinciding with the occurrence of vasospasm. Further understanding of the role of fever in SAH and vasospasm has, however, been limited by the inability to achieve and maintain an afebrile state in a controlled manner. In a small, uncontrolled study, normothermia was achieved and maintained with the use of an intravascular cooling catheter [42]. Overall, the catheter-based system was very successful in achieving target temperature, but as witnessed by the two treatment failures in this study, controlling shivering is essential in maintaining temperature control.

Adverse Effects of Therapeutic Temperature Modulation

The physiologic and pathophysiologic effects of therapeutic temperature modulation largely depend on the depth of temperature control. These changes also depend on the patients' age, underlying disease, comorbidity, and other factors. Some of these changes can be suppressed or prevented by medication, appropriate sedation, or other factors.

Cardiovascular and hemodynamic effects

Hypothermia is initially associated with sinus tachycardia, after which bradycardia develops. This is partly due to decreases in metabolism and partly to the direct effects of hypothermia on the heart. The risk of arrhythmias increases significantly as the temperature drops below 30°C. The initial arrhythmia is usually atrial fibrillation, which can be followed by the risk of ventricular flutter or fibrillation. An additional problem is that arrhythmias in deeply hypothermic patients are difficult to treat, as the myocardium becomes less responsive to defibrillation and antiarrhythmic drugs. Therefore, great care should be taken to keep temperatures above 30°C. The induction of mild hypothermia increases myocardial oxygen demand relative to supply, likely due to an increase in plasma levels of adrenaline and noradrenaline, leading to an increase in cardiac output and oxygen demand. With further reductions in temperature, decreases in heart rate and the slowing of metabolism will reduce cardiac after-load and oxygen demand. Mild hypothermia decreases cardiac output by about 25% and leads to increased vascular resistance and a rise in central venous pressure.

Coagulation

Hypothermia induces a mild bleeding diathesis, with increased bleeding time due to its effect on platelet count, platelet function, the kinetics of clotting enzymes and plasminogen activator inhibitors, and other steps in the coagulation cascade [43,44]. It should be pointed out that the laboratory results of standard coagulation tests such as prothrombin time and partial thromboplastin times will be prolonged only if they are performed at the patient's actual core temperature [45]. Despite the known effects on the coagulation system, the risk of significant bleeding is very low, even in patients with TBI [46]. Risks of bleeding should, therefore, not preclude the use of hypothermia if deemed appropriate. Platelets and/or fresh frozen plasma can be administered to improve coagulation if necessary.

Infection

Inhibition of inflammatory responses is likely one of the mechanisms through which hypothermia exerts neuroprotective effects; however, the nonspecific effect on the immune system can lead to an increased infection risk. Most of the clinical studies utilizing therapeutic temperature modulation in patients with stroke and TBI have reported higher risks of pneumonia when therapeutic hypothermia is used over long periods of time (> 48–72 hours), whereas short-term cooling (< 24 hours) does not appear to increase the risk of infection [47,48]. A higher risk of wound infections, including bed sores and catheter insertion sites, and impaired healing has also been reported with hypothermia. This may be related to both diminished leukocyte function and hypothermia-induced vasoconstriction.

One of the primary concerns when maintaining therapeutic temperature control is the appropriate method by which to survey for infectious disease. Because effective temperature modulation will eliminate febrile episodes, the rules governing clinical suspicion of new infections are altered. There is no one approach that has been shown to be more effective in surveillance. An approach utilized by some has been to perform routine cultures every 72 hours, whereas others have performed cultures only when there is a 20% increase from baseline in the total leukocyte cell count. Apart from overlooking an infectious source, it remains to be seen whether the use of therapeutic temperature modulation will lead to overuse of antibiotics.

Shivering

Despite the ease by which therapeutic temperature modulation can now be achieved with these devices, shivering remains a significant problem. Shivering results in an integrated series of responses that eventually lead to the activation of the alpha motor neurons in an involuntary, oscillatory muscular activity that augments metabolic heat production to raise the body temperature to the basal temperature. The shiver response has been shown to acutely increase metabolic heat production by up to 600% above baseline [49,50] and sustain heat production at twice basal rates for prolonged periods. These increased metabolic rates can result in increased oxygen consumption and carbon dioxide production [51–53], potentially leading to hypoxia and raised ICP, respectively, in addition to an impaired metabolic status. In a pilot study, estimated energy expenditures were found to be significantly greater in patients who shivered while undergoing therapeutic temperature modulation. A lack of control over shivering can eliminate the metabolic benefit of therapeutic temperature modulation and even in extreme cases be more costly metabolically than fever.

In current clinical practice, surface warming and oral buspirone, as well as continuous magnesium, meperidine, dexmedetomidine, and/or continuous propofol infusions, are utilized, depending upon the intubation status. Warming blankets counteract the peripheral vasoconstriction that occurs when the core body temperature is reduced. Each of the pharmacologic agents has previously been demonstrated to blunt the shiver response, with certain combinations, such as meperidine and dexmedetomidine or buspirone and meperidine, likely having synergistic antishivering effects. Despite aggressive nonpharmacologic and pharmacologic management, effective shiver control remains difficult to achieve, and as a result can eliminate the beneficial effects of therapeutic temperature modulation. Studies are currently assessing the best approach to this common problem

Fluid balance

The induction of hypothermia can lead to the loss of significant amounts of fluids due to hypothermia-induced diuresis. This may be especially problematic in patients with TBI, in whom administration of medication such as mannitol may exacerbate fluid losses. The impact of this may be significant in patients with TBI or SAH, where even very brief episodes of hypovolemia or hypotension can adversely affect outcome. Fluid losses should be treated proactively and vigorously, especially during induction phase of therapeutic hypothermia.

Electrolyte abnormalities

Severe electrolyte disorders (ie, low levels of magnesium, potassium, phosphorus, and calcium) have been reported during cooling of patients [54], which can lead to cardiac arrhythmias and/or episodes of hypotension that can result in significant decreases in cerebral blood flow. Closely monitoring magnesium is especially important, due to its specific role in mitigating not only neurologic injuries but also shivering [55]. Experimental studies have shown that magnesium depletion can result in an increase in reperfusion injury as well as cerebral and coronary arterial vasoconstriction. Clinical studies in ICU patients have shown that hypomagnesemia is associated with adverse outcome. Magnesium as well as other electrolytes, such as phosphorus and potassium, should be monitored closely and maintained in the high-normal range.

Drug metabolism and pharmacokinetics

The enzymes that metabolize most drugs are highly temperature sensitive, and thus drug metabolism is significantly affected by hypothermia. In one study, plasma levels of both propofol and fentanyl increased when individuals were at a temperature of approximately 34°C [56]. Overall, it is likely that clearance of many of the drugs utilized in the critical care setting is decreased; however, details regarding the effects of hypothermia on the metabolism of specific drugs are as yet unknown.

Other metabolic effects

Hypothermia decreases insulin sensitivity and insulin secretion, which can lead to hyperglycemia. As a result,

the amounts of insulin required to maintain glucose levels within the normal range are likely to increase during the induction of hypothermia [56]. A mild acidosis through various mechanisms, including increased synthesis of glycerol, free fatty acids, ketonic acids, and lactate, is also known to occur. These changes are normal metabolic consequences of hypothermia and should not be attributed to complications such as ischemia.

Controversies

Ventilation strategies

Two ventilation strategies during hypothermia have been reported in the literature: ph-stat and alpha-stat. During ph-stat management, the goal of ventilation is to achieve an arterial CO_2 tension of 40 mm Hg under hypothermic conditions. Alpha-stat management aims to achieve a pCO_2 of 40 mm Hg when the arterial blood gas is measured at 37°C. This management style results in higher pCO_2 levels for any given degree of minute ventilation and relative hyperventilation, and hence a lower cerebral blood flow than ph-stat management. Although alpha-stat strategy has been found to be beneficial in patients undergoing cardiac surgery (during cardiopulmonary bypass), there is experimental evidence that the alpha-stat strategy can lead to increased infarct size in models of focal cerebral ischemia [57]. By contrast, ph-stat management has been implicated in aggravating ICH after TBI. There are not enough clinical data to support either strategy in patients undergoing therapeutic hypothermia after brain injury. Clearly more study is needed before recommendations can be made on how to optimize ventilator management during therapeutic hypothermia. Final recommendations will likely depend on the depth of hypothermia as well as the state of CBF and cerebral edema at the time of treatment. At present, clinical standards are to maintain a consistent approach to ventilation management, whether that is ph-stat or alpha-stat.

Rewarming

Rewarming primarily presents as a problem for therapeutic hypothermia, although hyperthermic overshoot seen after the discontinuation of therapeutic normothermia may also be problematic in patients with underlying cerebral edema. The most common problem during rewarming is that the concomitant vasodilatation results in a reduction of MAP. In patients with intracranial pathology and disturbed cerebral autoregulation, this drop in MAP can result in increased ICP and fatal cerebral edema. In addition to the cerebral sequelae, rewarming has been reported to cause electrolyte abnormalities (hyperkalemia); a hypermetabolic, systemic inflammatory-like state; and pulmonary edema. These adverse effects are more likely to occur during both rapid passive and active rewarming. Only controlled rewarming should be applied to patients undergoing therapeutic hypothermia, at rates of less than 0.1°C per hour; however, rebound cerebral edema may still occur. The optimal method by which to discontinue therapeutic temperature modulation still needs to be elucidated.

Conclusions

As a result of increased pharmacologic understanding and technologic advancements, therapeutic temperature modulation is now an attainable goal for neurocritical care patients. However, the physiologic impact of manipulating an endogenous temperature set point remains unknown. Current and future studies focusing on these consequences will help determine the timing, depth, and duration of therapeutic temperature modulation that can best impact positively on patient outcomes.

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