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GUIDELINES FOR CLINICAL PRACTICE

Use of hypothermia in the intensive care unit

Jesse J Corry

Jesse J Corry, Department of Neurology, Marshfield Clinic, Marshfield, WI 54449-5777, United States
Author contributions: Corry JJ wrote and reviewed the article.
Correspondence to: Jesse J Corry, MD, Department of Neurology, Marshfield Clinic 4F3, 1000 North Oak Avenue, Marshfield, WI 54449-5777, United States. corry.jesse@marshfieldclinic.org
Telephone: +1-715-3875350 Fax: +1-715-3879184
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Abstract

Used for over 3600 years, hypothermia, or targeted temperature management (TTM), remains an ill defined medical therapy. Currently, the strongest evidence for TTM in adults are for out-of-hospital ventricular tachycardia/ventricular fibrillation cardiac arrest, intracerebral pressure control, and normothermia in the neurocritical care population. Even in these disease processes, a number of questions exist. Data on disease specific therapeutic markers, therapeutic depth and duration, and prognostication are limited. Despite ample experimental data, clinical evidence for stroke, refractory status epilepticus, hepatic encephalopathy, and intensive care unit is only at the safety and proof-of-concept stage. This review explores the deleterious nature of fever, the theoretical role of TTM in the critically ill, and summarizes the clinical evidence for TTM in adults.

Key words: Targeted temperature management; Therapeutic hypothermia; Cardiac arrest; Normothermia; Intracerebral pressure; Critical care

Peer reviewer: Dr. Juan Antonio Llompart-Pou, Service of Intensive Care Medicine, Hospital Universitari Son Espases, Hospital Universitari Son Espases, 07010 Palma, Spain

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INTRODUCTION

Since the time of the Edwin Smith Papyrus's, and undoubtedly before, physicians have employed hypothermia (HT). HT has been used for treatment of cancer pain, induction of electrocerebral silence in surgery, tetanus, traumatic brain injury (TBI), and even status epilepticus (SE)[1-6]. It is unquestionably the greatest tool for neuroprotection in surgical cases requiring circulatory arrest and the standard of care for ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest (CA)[7-9].

Temple Fay, Claude Beck, and Charles Bailey ushered in the modern era of HT in the 1930s and 1940s with their work on TBI and circulatory arrest for cardiac surgery[6]. Fays work demonstrated the absence of irreversible neurologic change in humans refrigerated to as low as 26 ℃[10]. In this era and into the 1960s, patients were often cooled over 24 h, and to temperatures below 28 ℃. With increased awareness of the numerous cardiac, pulmonary, and infectious side effects, interest waned[11-17]. These side-effects were a function of the duration and depth of HT, and the state of intensive care unit (ICU) care at the time. Interest in HT again developed in the 1990s, when data from TBI, stroke, and CA animal models demonstrated mild to moderate HT (30-35 ℃) for 2-24 h produced sizeable improvements in outcome[18-21].

Modern ICU protocols for HT follow a "one temperature fits all" mentality. Rather than augmenting HT based on brain metabolism or surrogate markers, most centers cool to 32-34 ℃. While the appropriateness of this strategy is a matter of debate, evidence now supports the use of HT in the ICU setting. The most impressive current data comes from the CA literature where the number needed to treat for a good outcome from an out-of-hospital ventricular tachycardia/fibrillation is 5-6[8,9].

A growing body of evidence is building favoring maintenance of "normothermia" in the critically ill[22,23].

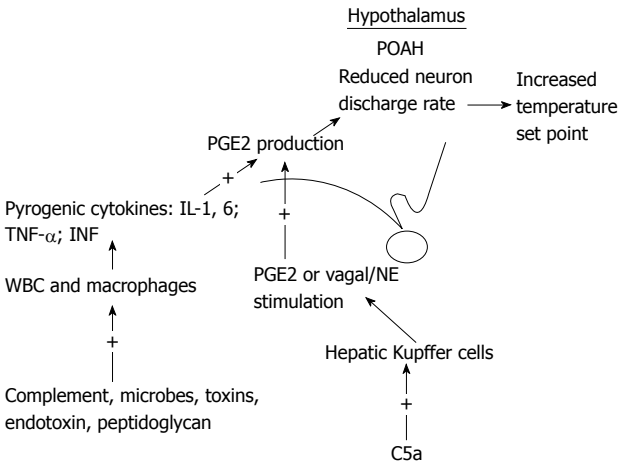

Figure 1 Schematic of fever production. POAH: Pre-optic area of the anterior hypothalamus; IL: Interleukin; TNF: Tumor necrosis factor; INF: Interferon; WBC: White blood cell; PGE2: Prostaglandin E2; NE: Norepinephrine.

This use of cooling techniques to maintain temperatures in the HT to normothermia ranges has prompted a new nomenclature, targeted temperature management (TTM)[24]. This review with briefly summarize the proposed mechanisms by which TTM is thought to work, identifys the disease processes with the strongest evidence for use in adults to-date, and addresses the logistics of TTM delivery.

PHYSIOLOGY OF TTM

Role of fever in critical illness

Is fever bad? This ubiquitous response to infections, lesional, or toxic exposure alerts clinicians that "something is wrong." Potentially blunting this response could be deleterious. Patients with community-acquired pneumonia, *Escherichia coli* bacteremia, and *Pseudomonas aeruginosa* sepsis have improved survival if they develop fever[25-27]. Yet, the development of fever in the medical ICU (MICU) portends poor outcome[28]. In the neurocritical care unit (NCCU), fever occurs in 60%-91% of this population, and 20%-33% of fevers in the NCCU are unexplained[29,30]. In this population, the presence of fever, regardless of etiology [stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), TBI, SE], is associated with increased morbidity and mortality[30-33]. In CA, HT may be a desired target[8,9].

As data accumulates, fever increasingly appears to play a deleterious role in the ICU population. Fever results from neurons in the preoptic anterior hypothalamus (POAH) decreasing their rate of discharge (Figure 1). This may result from pyogenic cytokines [i.e., interleukin 1 (IL-1), 6; tumor necrosis factor α (TNF-α)] producing prostaglandin E2 (PGE2), which then acts upon the POAH. Stimulation hepatic Kupffer Cells by complement also increase PGE2 production. Temperature elevations increase proinflammatory cytokines and lead to the accumulation of neutrophils in damaged tissue, increasing inflammation[34-40]. The development of fever increase neuronal excitotoxicity and glutamate release, accelerating free radical production[41,42]. Fever also causes a variety of physiologic derangements including weakening of the blood-brain barrier (BBB), hemodynamic instability, and cardiovascular dysfunction[43]. The unanswered question remains, how should fever be treated? Should clinicians control the expression of fever, or control the humors responsible for its development?

Physiology of thermoregulation

Humans rigorously regulate core body temperature. Heat loss occurs as the result of convection, conduction, radiation, and evaporation. Sensation of temperature change is largely controlled by the transient receptor potential (TRP) family of ion channels[44,45]. TRPs are expressed by sensory neurons and activated at various temperatures. Information from these channels in the skin and core organs eventually arrives at the hypothalamus. Behavioral and autonomic responses then effect change to alter temperature. Behavioral defenses play less of a role in the ICU. The autonomic response controls the amount of heat the core organs will expose to outer world through precapillary sphincters, vasodilation, vasoconstriction, shivering, and sweating control[46,47].

Contracting near 37 ℃, arteriovenous shunting occurs largely in the hands and feet *via* special connections between arterioles and veins[48]. These shunts have a profound effect on core temperature, and are the first line of thermoregulation. Another means limiting heat loss is through vasoconstriction[49]. Should these mechanisms be insufficient, shivering is typically initiated a degree below the shunting threshold[50]. Signals originating in the POAH descend, eventually reaching the α-motor neurons of the spinal cord. Motor neuron groups are recruited, beginning with the γ motor neurons and ascending to the α motor neurons. Shivering increase metabolism, but loses efficacy with age and prolonged duration[51].

These differences are paramount in understanding TTM. As it does little to address shunting of blood flow to core organs, paralysis is only minimally effective in reducing the febrile response, and thus is of limited benefit in TTM[52-55]. When shivering occurs, effective treatments include sedation and focal hand and face warming, with or without surface warming[56-59]. Reducing the shivering threshold may abate much of this problem from occurring. However, the largest obstacle in controlling the fever response is the arteriovenous shunts and systemic vasodilation/vasoconstriction[49,60-62]. Interventions that relax sphincters or produce vasodilatation (i.e., magnesium, propofol) result in superior heat transfer[62]. Arguably, the fastest method of heat exchange would be to directly cool the core organs.

Protective physiology

Injury to the brain and spinal cord occurs in two phases. In the peri-insult period, neuronal membranes become disrupted *via* insufficient energy, metabolic disturbance, and/or excitotoxicity, heralding necrosis. In the h to d

Table 1 Potential therapeutic effects of hypothermia

Effect	Mechanism	Onset and duration of effect
Improved energy balance	Reduced cerebral metabolism for O_2 and glucose. O_2 consumption reduced 5%-6%/1 ℃ between 22-37 ℃ and ATP hydrolysis decreased by a similar rate	Hours to d. Metabolism may begin to increase after 24 h
	Reduced ATP demand and promotes glycolytic production of ATP. Net increase ATP	
	Decreased mitochondrial dysfunction	
	Improved recovery of high-energy phosphate compounds upon improvement of perfusion demand and following rewarming	
Anti-epileptic effect	Attenuation of $[K^+]_{ex}$ increases with resulting decrease in Ca^{2+} influx. Temps between 31%-33% have demonstrated decreased duration, amplitude, and frequency of ictal discharges	Hours to days. This anti-epileptic effect may continue for a period of time following rewarming
	Increased duration between depolarizations with slowing return of membrane potential	
	Decreased synthesis, reuptake, and release of excitatory neurotransmitters including glutamate	
Neuro-protective	Reduced CNS edema-Improves BBB and energy reserve for membrane pumps via better energy balance	Hours to days
	Prevent/reduce apoptosis-Hypoxia/ischemia can induce apoptosis and calpain-mediated proteolysis. HT mitigates the initiation of these processes.	Hours to weeks
	Intracellular alkalinization	Hours to days
	Less Excitotoxicity-Ca^{++} accumulation precedes neuronal damage in sensitive brain regions. Excessive pre-synaptic release of glutamate activates NMDA and non-NMDA post-synaptic receptors with resulting Ca^{++} entry and release of intracellular Ca^{++} stores. This $[Ca^{++}]_{in}$ increases activates Ca^{++} dependent enzymes producing cell injury. Decreased release of glutamate may reduce mitochondrial dysfunction, DNA damage, and decreased activation of kinases and excitotoxic cascades	Minutes to 72 h
	Anti-oxidant effects-30%-40% decrease in Krebs cycle metabolites with shunting to Pentose Phosphate Pathway occurs. This shunting of metabolites may result in increased NADPH/NADH, improved glutathione reduction, peroxide detoxification, and reduced membrane peroxidation	Hours to days
	Suppression of inflammatory reaction and impaired leukocyte function	First hour to first week
	Improved microcirculation, improving CBF and reducing cerebral edema	Hours to days

Adapted from references 69, 73, 74, 92, 146, 207. Number in right column refer to numbered entry in "mechanisms" column. ATP: Adenosine triphosphate; BBB: Blood-brain barrier; HT: Hypothermia; NADPH: Nicotinamide adenine dinucleotide phosphate; CBF: Cerebral blood flow.

following injury, programmed cell death occurs. Thus, the role for TTM can be grossly divided into two therapeutic time windows: Early/ischemia and late/reperfusion. Early mechanisms revolve around improving energy balance, reducing metabolic demand, and reducing membrane and mitochondria injury[63-65]. Later mechanism involve the consequences of reperfusion injury including suppression of spreading depression and epileptic discharges, reducing inflammation, reducing cerebral edema, bolstering the BBB, and reducing apoptosis (Table 1).

Although TTM offer an array of potential therapeutic actions, yet the, specific targets to focus this therapy remains largely unknown. For example, the metabolism suppressive roles of TTM are intuitively important for a disease process like stroke, but may be less important for a disease such as ICH (Figure 2)[66-68]. In ICH, the reduction of cerebral edema and suppression of inflammation may play a larger role[68,69]. Thus, the role of TTM may vary depending on the disease.

Early phase protective physiology

Membrane and mitochondrial effect: Within seconds of interrupted blood supply, the high energy phosphate compounds adenosine triphosphate and phosphocreatine (ATP and PC) plummet[70]. These reductions cause the tissue to transition from aerobic to anaerobic metabolism; increasing intracellular levels of inorganic phosphate, lactate, and H^+. This leads to an intracellular increase in calcium (Ca^{2+}). With failure of ATP dependent Na^+ and K^+ pumps, the excess Ca^{2+} causes mitochondrial failure, activation of intracellular kinases and proteases, and neuronal depolarization[71,72]. These depolarizations lead to accumulation of glutamate and excitatory neurotransmitters, leading to more Ca^{2+} influx *via* glutamate receptor stimulation, producing a maelstrom of cellular destruction. This disruption of ionic balance leads to cell swelling and rupture, exposing the interstitial tissue to excitatory neurotransmitters.

Evidence from animal models of global hypoxic-ischemia (HI) and TBI demonstrate inhibition of glutamate release, and suppression of reactive oxygen species (ROS) formation between the temperatures of 30 ℃-33 ℃[73]. The decreased synthesis, reuptake, and release of excitatory neurotransmitters, including glutamate, are thought responsible[74-76]. Temperature influences the membrane permeability of K^+, Na^+, and Ca^{2+} with secondary effects on cerebral energy state[73,77]. Animal models of focal and global ischemia demonstrate mild-to-moderate HT is as-

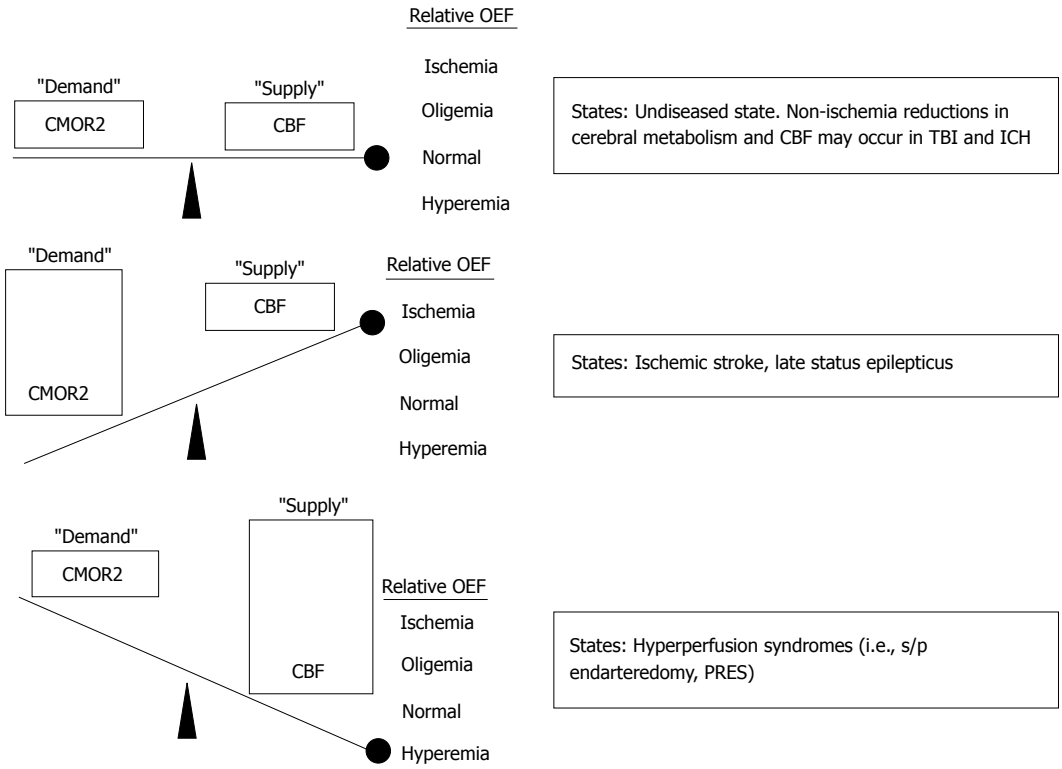

Figure 2 Metabolic pattern of common neurocritical care unit disease. CBF: Cerebral blood flow; TBI: Traumatic brain injury; ICH: Intracerebral hemorrhage.

sociated with attenuation of the initial rise of extracellular K^+ (K_e) and delayed terminal depolarization[78,79]. Less neuronal loss after reperfusion in animals treated with HT suggests the temperature dependent influx of Ca^{++} could be linked to changes in K^+ efflux, raising the link between HT and suppression of intracellular Ca^{2+} accumulation[77].

Post reperfusion, the mitochondrial electron transport chain generates free radicals[80-88]. This is referred to as ischemic-reperfusion (IR) injury. Compounds including peroxynitrite (NO_2^-), hydrogen peroxide (H_2O_2), superoxide (O_2^-), and hydroxyl radicals (OH^-) may damage cells *via* membrane and nucleic acid peroxidation, triggering apoptosis[76,89-91]. HT limits the production of free radicals, with lower temperatures appearing to be more effective[89,92].

Energy balance: Central to TTM is the supply-side economics tenant of supply and demand. Specifically, HT reduces metabolic demand for oxygen and glucose, improving the supply of ATP[93]. HT decreases brain consumption of oxygen approximately 5%-6%/1 ℃ between 22-37 ℃, with commensurate reductions in ATP hydrolysis and CO_2 production[67,70,93,94]. In a study of 10 patients with severe TBI (defined at GCS < 7), HT between 32-33 ℃ decreased $CMRO_2$ by 45% without changes in cerebral blood flow (CBF)[95]. This suggests that HT may produce a state of relative hyperemia. HT attenuates, but does not stop, ATP and PC depletion, and pH reduction, in HI models[42,73,96]. The development of acidosis, known to increase cell loss, is controlled in part by slowing the rate of high energy phosphate consumption[73].

In the post ischemic period, hypothermic animals and humans demonstrated faster recovery of pH[97]. Studies with magnetic resonance spectroscopy (MRS) have suggested HT attenuates the development of acidosis in long-term ischemia and decreases the decline of high energy phosphates approximate 5% per 1 ℃[98,99]. Although lactate levels still increase, HI animal models treated with HT demonstrate faster clearance of lactate, improved glucose utilization, resolution of pH, and quicker recovery of high-energy phosphates compared with normothermic (NT) controls[73].

An approximate 30% decrease in Krebs cycle and glycolytic intermediates, except glucose-6-phosphate, occurs with a marked decrease of Krebs cycle activity during HT[93]. Experimental work with MRS in moderate HT (31 ℃) has demonstrated a 30%-40% decrease in cortical and hippocampal metabolism, with shunting of intermediates to the pentose phosphate pathway (PPP). This corresponds to increases in nicotinamide adenine dinucleotide phosphate (NADPH)[73,93]. One could hypothesize that increase shunting to the PPP could reduce oxidized-glutathione, increase peroxide detoxification, and limit oxidative stress. HT causes intracellular alkalinization, promoting glycolysis[93]. Glycolysis may help to increase ATP levels during HT in conjunction with ebbing demand[93]. In piglet model studies with phosphorus MRS, after and during circulatory arrest at NT (37 ℃) and HT (15 ℃), HT animals displayed slower decay rate of high energy phosphate compounds, improved recovery

of ATP and PC, and improved recovery of intracellular pH[100]. This suggests HT ameliorates injury independent of phosphate compound stores. High energy phosphate compounds are depleted with ischemia in both HT and NT; however, tissue recovers ATP and other high energy phosphate compounds faster if occurring during HT[101]. Gerbils treated with HT (34 ℃) during bilateral carotid artery occlusion experienced a 10%-20% improved metabolic recovery during reperfusion compared to NT controls, displaying less histopathologic evidence of neuronal damage in the cerebral cortex and hippocampus. Animals treated with HT during ischemia demonstrated less cytotoxic edema, as noted by diffusion-weighted imaging and apparent diffusion coefficient on magnetic resonance imaging, than NT controls[20,102].

Cerebral blood flow: While metabolic reductions are clearly demonstrated, evidence for changes in CBF is variable. During cooling, $CMR_{glucose}$ and CBF are directly proportional to intrinsic flow and metabolic rate with reductions normally in the most metabolically active areas[103]. In the uninjured brain, animal data routinely demonstrates CBF and $CMRO_2$ are closely coupled from 33 ℃-35 ℃, with reduction in CBF nearly parallels that of $CMRO_2$ with an 8% decrease per ℃[104]. This relationship is inconsistently coupled from 28 ℃-33 ℃, and below 28 ℃ studies report the development of both ischemic and hyperemic states[77]. The cerebral vasculature retains its responsiveness to CO_2 even at reduced temperatures. Given relatively small differences between α-stat and pH-stat for temperatures ≥ 32 ℃, the low end of the typical target range in the ICU setting, it is unlikely that either acid-base measure would effect brain physiology[104].

However, in the diseased state, this coupling may not hold. Review of experiment literature demonstrates increases, no change, or decreases in CBF[21,77,105,106]. Clinically, TBI studies have demonstrated similar findings[95,107]. The clinical data for other disease states is even less clear. Studies in high grade SAH patients (World Federation of Neurosurgical Societies Grade Ⅳ or Ⅴ) cooling to 35 ℃, then 33 ℃ over two d, have demonstrated $CMRO_2$ and CBF reductions to a greater degree on the side ipsilateral to the ruptured aneurysm[108]. Using a similar protocol, another report demonstrated relative hyperemia ipsilateral to the site of aneurysm rupture, suggesting less autoregulation coupling in the most traumatized tissue[109]. Work in stroke patients has demonstrated early in HT, the decrease in CBF is greater than the commensurate decrease in $CMRO_2$, resulting in relative ischemia[110]. Again, the loss of autoregulation appears to play a role.

Late phase protective physiology

Inflammation: In the h to first week following injury or ischemia the inflammatory response develops. Mediated initially by astrocytes, microglia, and endothelium, the release of TNF-α and IL-1 stimulates leukocyte activation and allow for crossing of the BBB[70,111]. Concurrently, adhesion molecules on leukocytes and endothelium emerge. Activation of complement pathways further aid the accumulation of neutrophils, and later monocytes-macrophages, in damaged tissues. This leukocyte infiltration and cytokine production exacerbate injury[111-113]. HT suppresses this inflammatory reaction through attenuating adhesion molecule upregulation and inflammatory cytokine release[36,114-118]. Further, the function of neutrophils and macrophages are impaired, particularly at temperatures < 33 ℃. Experimental stroke models have demonstrated genes for inflammation are suppressed with TTM[119]. However, similar findings are not seen with TBI and CA, once again suggesting the role of TTM will vary with the disease[120-122].

Blood-brain barrier and edema: Following ischemia-reperfusion or trauma, the BBB often becomes disrupted, potentiating cerebral edema[123-125]. Cerebral edema has been implicated in delayed neurological deterioration, and worse outcome, through the elevation of intracerebral pressure (ICP)[126]. Elevations in ICP reduce the ability of blood to reach the brain, exacerbating the injury and producing ischemia. In ICH the formation of perihematomal edema contributes to approximately 75% of total volume change[127]. Animal models of ICH demonstrate a large perihematomal area that undergoes neuronal death characterized by increased water content and inflammation[128]. TTM may be an effective means to limit cerebral edema[68,129].

TTM reduces the disruptions in the BBB caused by IR injury and trauma[123-125]. TTM decrease the extravasation of hemoglobin following TBI[34]. Following IR injury or trauma, regional production of endothelin (ET-1), thromboxane A2 (TxA2) and prostaglandin I2 (PGI2), become altered, affecting endothelium[130,131]. ET and TxA2 act as vasoconstrictors, and PGI2 as a vasodilator. These injurious conditions typically favor vasoconstriction, and platelet aggregation *via* TxA2, promoting regional hypoperfusion. Animal data in TBI suggest the imbalance between TxA2 and PGI2, and excessive ET-1 production, are mitigated by TTM[132,133]. Further, reductions in inflammation and improved membrane integrity further contribute to reductions in cerebral edema[63]. Finally, reduced temperatures limit the activity of matrix metalloproteinases limiting BBB breakdown[134,135].

Cortical spreading depression and epileptic discharges: Clinical evidence has demonstrated TTM to be effective in treating refractory SE[2,136,137]. Another neuro-electrical phenomenon, cortical spreading depression (CSD), has been correlated to the development of ischemia in TBI and stroke[63]. TTM has demonstrated suppression of CSD[33,102,138]. HT diminishes and slows axonal depolarizations, limiting the release of glutamate and attenuating the development of spreading depression[33,102,138,139]. Further, HT (31-33 ℃) HT decreases the duration, amplitude, and frequency of ictal discharges; lengthens the duration between depolarizations; slows the return of membrane

potential; and is associated with decreased $CMR_{glucose}$[140-145]. Thus with decreasing temperature an inverse relationship to cerebral electrical activity develops[2,142,146,147].

Electroencephalogram (EEG) provides a consistent and reproducible means of qualifying cerebral metabolic rate[148-150]. EEG activity correlates directly with cerebral metabolism and indirectly with neuroprotection[148]. Both animal and human studies demonstrate an abrupt change in EEG activity between 30-33 ℃[150-152]. Low amplitude Δ activity is noted as the predominant pattern at around 30 ℃[149,152]. When concerned about neuroprotection, cooling to a specific temperature may not be advisable as systemic temperatures are not indicative of brain temperature or metabolism[148,149].

Apoptosis: Beginning in the 48-72 h after an ischemic or traumatic injury, HT interrupts the activation and propagation of apoptosis[153-158]. HT attenuates release of cytochrome c, up-regulation of *Fas* and *Bax*, and caspase activation[159-161]. Further, HT increases *p53* expression, promoting tissue repair[162]. The anti-apoptotic signaling pathways for *Erk1/2* and *Akt* are activated too[163-166].

INDICATIONS FOR TTM

Despite nearly 3600 years of use, and a plethora of experimental data, remarkably few clinical indications exist for TTM[65]. To date, the strongest evidence for use in adults is in out-of-hospital pulseless ventricular tachycardia/ventricular fibrillation (VF/VT) CA, ICP control, and fever control in the NCCU population[24,65].

Cardiac arrest

TTM at 32-34 ℃ for 12-24 h in patients comatose after out-of-hospital cardiac arrest (OHCA) with initial rhythms of VF or pulseless VT has become the standard-of-care[8,9,24]. In this population, the number needed to treat for an outcome of good or minimal disability is 5 to 6. Both of these landmark studies demonstrated improved outcomes, and the larger trial demonstrated a reduction in mortality, with TTM[8,9]. Evidence suggests TTM in this population is well tolerated, with no neurocognitive deficits associated with therapy[167]. With respect to patients with cardiogenic shock or requiring primary coronary angiography, TTM can be delivered safely, improving outcomes and not significantly increasing "door-to-balloon" times[9,168,169].

Despite the evidence favoring TTM for OHCA in VT/VF, consensus is not unanimous. A recent meta-analysis of 5 randomized controlled trials of TTM in CA totaling 478 total patients concluded there was a lack of firm evidence for benefit[170]. The authors cite a number of criticisms. The HT after Cardiac Arrest (HACA) study, recruited only 8% of screened patients, and was stopped for slow recruitment[8,170]. This study lacked a predefined power calculation too. Decisions regarding withdrawal of therapy cannot be standardized, and may have influenced the outcomes. The smaller Bernard trial and colleagues evaluated outcome at discharge, finding good outcomes (discharge to home or rehab) in 49% of HT patients and 26% of controls[9,170]. There was no difference in mortality. This differed from the HACA trial that measured outcomes at six mo, using the Pittsburgh- Glasgow Cerebral Performance Category.

In spite of these differences, the strength of these findings has made TTM for OHCA from VT/VF the standard-of-care. However, fewer than 20% of patients with CA fulfill the inclusion criteria for these studies[171]. Regarding the use of TTM with in-hospital CA and pulseless electrical activity (PEA)/asystole (AS), a recent consensus report of five different critical care professional societies concluded the evidence was insufficient to make any recommendations regarding PEA/AS[24]. Similarly, this group could not make a recommendation for or against the use of TTM for in-hospital VT/VF arrest. Therefore, TTM plays more a supportive role in the story of CA.

What about PEA/AS and in-hospital VT/VF arrest make it different than out-of-hospital VT/VF arrest? PEA/AS tend to have a longer time to ROSC[172,173]. In-hospital VF/VT CA is generally a very different entity caused by acute respiratory distress, distributive shock, electrolyte anomalies, or pulmonary embolism[174]. With the advent of "rapid-response" and "pre-code" teams, in-hospital arrest is becoming less common[175]. Regarding PEA/AS, a large, retrospective review demonstrated despite similar percentages of treatment with TTM, patients with out-of-hospital PEA/AS treated with TTM demonstrated only a 15% good outcome compared to 44% with VT/VF[172]. Those treated with TTM in the PEA/AS cohort had a longer delay to receiving basic life support, and a longer time to return of spontaneous circulation (ROSC), than those not receiving TTM. Perhaps, it is time to ROSC, not initial rhythm, clinicians should concern themselves with?

Once TTM has been initiated, what are the best prognostic tools? How does TTM change these? The 2006 American Academy of Neurology (AAN) guidelines on prognosis following CA are largely developed from studies prior to the TTM era. In sum, the absence of motor reaction to noxious stimuli, loss of brain stem reflexes, presence of myoclonic SE, bilateral absence of cortical somatosensory evoked potentials (SSEP) N20 responses, and serum neuron specific enolase (NSE) > 33 mg/L in the first 3 d following CA predict poor outcome[176]. Since these guidelines have been published TTM has been increasingly used for CA. Reports of patients with NSE levels > 33 mg/L, absent N20 SSEP response, and myoclonic SE recovering have been made suggesting our current prognostic tools need re-fitting[177-179].

First, does treatment with HT delay waking, potentially resulting in premature withdrawal of artificial organ preservation therapies? A recent retrospective review of 227 patients attempted to answer this question[180]. One hundred and twenty-eight patients treated with, and 99 patients not treated, with TTM were analyzed comparing

time to awakening. It is important to note that patients not treated with TTM had rhythms other than VF or were in-hospital CA. Further, this center employs a strict sedation protocol to minimize the confounding effect of these drugs on neurologic examination. Patients who survived regained consciousness at a median of 2 d (range 2-8 d) in the TTM group, and at 2 d (range 1-7 d) in the non-TTM group[180]. Thus, TTM appears to not delay awakening following CA.

Next, in the TTM era, what clinical or paraclinical findings predict outcome? Regarding the neurologic assessment, reports are variable. A recent prospective study of 111 CA survivors treated with TTM demonstrated status myoclonus, absent motor response to pain, and incomplete brain stem reflexes did not predict poor outcome in all patients[181]. In fact, this study found a motor score on the Glasgow Coma Scale (GCS) $\leqslant$ 2, or decerebrate/extensor posturing, has a false-positive prediction of mortality of 24% at 36-72 h. However, the specifics of type, amount, and duration of sedatives were not reported in this study, complicating its interpretation. These motor findings have been previously reported in smaller studies[182,183]. In another study comparing predictors of recovery in CA patients treated with and without TTM at a single center, of 14 patients with a motor score $\leqslant$ 2 at day two, 2 survived with a good or moderate outcome as scored by the Cerebral Performance Categories Score (CPC)[184].

Brainstem reflexes offer no clearer insight. In the aforementioned study, patients treated with TTM did not recover if pupillary response to light and corneal reflexes were absent up to 5 d[184]. Similar findings have been previously reported[182]. Notably, Fugate *et al*[184] reported no patient with a spontaneous downward gaze survived. While the absence of cranial nerve reflexes and purposeful motor responses at day 2-3 are concerning, they are not conclusive of final outcome. A recent study reported absence of one or greater brainstem reflexes had a false positive rate (FPR) of 4% when measured between 36 and 72 h in predicting mortality[181]. However, the effect of sedation in this study is uncertain and complicates many studies in TTM.

Do biomarkers offer a better prognostic option? The 2006 AAN guidelines, NSE was reported to have a 0% FPR for predicting poor outcome between 24 and 72 h following CA if > 33 mcg/L[176]. The increased use of TTM in CA calls into question reliance of the absolute value of this benchmark[184,185]. NSE between 24 and 48 h in patients randomized to TTM or no-TTM found higher values in the TTM group[185]. This suggests TTM may affect the normal clearance of NSE. Of note, a study evaluating serial NSE levels in CA patients treated with TTM suggest a downward trend of NSE values portend good outcome, suggesting TTM affects the normal clearance of NSE[184].

Recently a prospective, observational study looked at the patterns of various prognostic markers in patients still comatose three d following HT for CA[186]. The authors note NSE levels > 33 mg/L demonstrated extensive diffusion weighted MRI changes, in all patients. Of patients who underwent SSEP studies, all died who had NSE values of > 27 mg/L and bilateral loss of N20 peaks. All patients lacking pupillary light reflex or corneal reflex and having an NSE > 33 mg/L died. In fact, no patient with a NSE > 27 mg/L made a recovery.

Table 2 Qualitative description of Electroencephalogram pattern

Malignant EEG Patterns	Benign EEG Patterns
Non-reactive background	Generalized slowing
Burst-suppression associate with generalized epileptic activity	Mixed α-theta frequencies
Diffuse periodic complexes on a non-reactive background	Reactive background
Generalized suppression to < 20 mV	Continuous rhythm
Status epilepticus	

EEG: Electroencephalogram.

What role do electrodiagnostic studies play in prognostication? SSEP use is limited by inter-observer variability and sensitivity of system noise[187]. Despite this, SSEPs in the 2006 AAN guidelines reported a FPR of 0.7% for poor outcome when N20 responses were absent bilaterally[176]. A recent retrospective review of 36 patients treated with TTM for CA, and demonstrating bilaterally absent or minimally present N20 response at day 3, reported recovery of consciousness and cognitive function in 2 patients[178]. This suggests these studies may not be as useful in the setting of TTM.

Electroencephalography may provide a means of prognostication, particularly when complimented by other biomarkers or exam findings. Although a universally accepted classification system is lacking, a few patterns are generally accepted as benign or malignant (Table 2). When correlating to NSE, a continuous EEG pattern demonstrated lower NSE levels compared to a burst-suppression, or flat and non-reactive, background[186]. Recent studies have demonstrated the ability of EEG to identify patients with a poor prognosis based on malignant patterns and good prognosis based on benign patterns[184,188,189]. Patients presenting in a burst-suppression pattern at either initiation of EEG or normothermia, or in SE at normothermia did not regain consciousness.

If a continuous EEG pattern was present at either initiation or normothermia, 29/32 and 54/64 patients regained consciousness respectively. The positive predictive value of this was 91%[188]. Examining this dynamic testing further, a study of post-CA comatose patients receiving continuous EEG, the background activity to repetitive vocal, visual, and nociceptive stimuli correlated to in-hospital mortality and neurologic outcome at 2 mo[189]. Survivors in this cohort never demonstrated a non-reactive background to stimulation, epileptiform discharges, or prolonged periods of flat EEG. Recently, two patients treated with TTM having continuous EEG were reported who demonstrated a continuous α pattern that

attenuated to verbal or noxious stimuli[190]. These changes occurred both during and after cooling. Both patients made an excellent recovery.

Increased intracerebral pressure

HT decreases ICP, but how[24]? In the uninjured brain, CBF and cerebral metabolic rate are closely coupled from 33-35 ℃; with that coupling becoming inconsistent between 28-33 ℃[67,93,103,191-194]. The 2011 consensus review of TTM in critical care contends the uncertainty of the mechanism of action for ICP reduction in TTM precludes an affirmative recommendation. Are the elevations of ICP a marker of disease severity or a target where treatment will improve outcome? During TTM, ICP most likely falls secondary to a pleiotropic mechanism. HT decreases brain consumption of oxygen ($CMRO_2$) approximately 5%-6%/1 ℃ between 22-37 ℃ and slows ATP hydrolysis by nearly the same rate[77]. In a study of 10 patients with sever TBI (defined at GCS < 7), HT between 32-33 ℃ decreased $CMRO_2$ by 45% without changes in CBF[95]. This suggests that HT may produce a state of relative hyperemia. However, this study also reported $CMRO_2$ may start to increase after 24 h of cooling[95]. It is notable that post-cooling normothermia values for $CMRO_2$ remained approximately 15% below baseline values. Similar to $CMRO_2$, reductions in $CMR_{glucose}$ and CBF are found to be directly proportional to intrinsic flow and metabolic rate with the highest reductions in the normally most metabolically active areas[103]. While metabolic reductions may contribute to lower ICP, this is likely not the full explanation.

Although recent meta-analysis of TTM in stroke found current evidence too heterogeneous to recommend TTM in stroke patients, some findings are noteworthy[24,195]. Previous work with TTM to a goal temp of 33 ℃ for 48-72 h found ICP elevation positively correlated to the rate of rewarming and were associated with poor outcome[196]. A larger study found slowing the rate of rewarming lead to a statistically significant reduction in mortality of patients with large MCA strokes treated with surface delivered TTM to 33 ℃[197]. This suggests *something* with cooling is rewarming rate dependent. Although different disease mechanisms, clinical studies in TBI found continued reduction in brain metabolism persisting after rewarming, suggesting the elevations in ICP found upon warming are not likely the result in changes in cerebral metabolism[95,196].

A recent study with endovascular delivered TTM compared eighteen patients[129]. Seven patients were deemed, "effectively cooled" or below 34.5 ℃ within 8 h of therapy initiation. This group maintained a temperature of 33.5 ℃ ± 0.6 ℃ for 12-24 h. Eleven patients were not effectively cooled, maintaining a temperature of 35.7 ℃ ± 0.7 ℃ for 12-24 h. All patients had CT scans at admission, at 36-48 h, and at 30 d post stroke. CSF volume at these three time points served as indirect markers of cerebral edema. Specifically, a larger CSF volume presumed less cerebral edema. The authors found a statistically

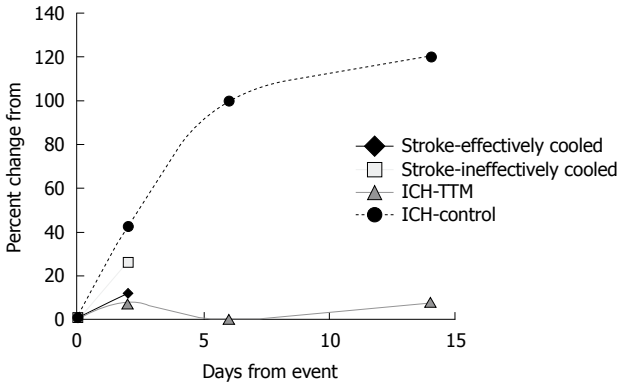

Figure 3 Approximate percent increases in cerebral edema, over time, in stroke and intensive care unit patients treated with and without targeted temperature management. Changes between stroke patients effectively and ineffectively cooled, and changes between intensive care unit patients receiving targeted temperature management (TTM) and controls not receiving TTM, are significant. Stroke patients day two measurements are between 36-48 h. ICH: Intracerebral hemorrhage.

significant difference in the CSF volume of those effectively cooled, compared to the 11 not so, at this second measure suggesting less cerebral edema (Figure 3)[129].

This edema reducing phenomenon may not require cooling to the same degree as for CA. A recent study of 12 patients with > 25 mL of ICH who were cooled to 35 ℃ for 10 d reported reduced cerebral edema (Figure 3)[68]. Perifocal edema was measured on CT. These volumes were compared to cohort of 25, uncooled patients from a local database. In the HT group, edema volume remained stable. The uncooled cohort demonstrated significantly increased cerebral edema. These increases were both in terms of absolute volume and as a ratio of ICH volume[68].

Reductions in cerebral edema, and cerebral metabolism, may not be the only means by which ICP is reduced. The growing evidence for the use of TTM in acute liver failure/hepatic encephalopathy suggests another mechanism. As the development of hyperammonemia overtakes the astrocytes ability to export organic osmolytes to compensate for accumulating glutamine, cerebral edema develops[198]. As serum ammonia levels approach 150 mmol, the risk of elevated ICP increases[199]. To briefly review, glial cells release glutamine, which is metabolized into glutamate in the presynaptic terminals by glutaminase. Glutamate can also be produced by transamination of 2-oxoglutarate, an intermediate in the Citric acid cycle. Experimental evidence has demonstrated TTM to the range of 32-33 ℃ attenuates the uptake of extracellular glutamate[200]. Glutamate levels can be further reduced by a shunting of nearly 1/3 of Krebs Cycle intermediates into the Pentose Phosphate Pathway[201]. This could potentially improve the cell's ability to resist damage from membrane peroxidation.

A series of studies by Jalan and colleagues have noted the beneficial effects of TTM to 32-33 ℃ in patients with HE. One study of 14 comatose patients with elevated ICP reported average ICP reductions from 36.5

to 16.3 mmHg[202]. However, in six patients the results were not sustained requiring intermittent mannitol bolusing. Five patients responded, and one patient succumb to herniation. Yet 13 of these patients went on to successful orthotopic liver transplantation and full neurologic recovery. Another report of five patients with elevated ICP, TTM was maintained through surgery[203]. This strategy improved cerebral perfusion and abated the ICP spikes noted during dissection.

What is the clinician to make of this? The aforementioned consensus review by five international critical care societies ruled the evidence for ICP control by TTM, as it pertains to outcome, is insufficient for an affirmative recommendation at this time[24]. The heterogeneous reporting of ICP, and inconclusive outcome data, between studies lead to this recommendation. As for specific disease process, no recommendation for TTM can be made. As previously noted, evidence for stroke and ICH remains largely at the proof-of-concept and safety stage. Recently, the National Acute Brain Injury Study: HT Ⅱ (NABIS: H Ⅱ) findings were reported[204]. NABIS: H Ⅱ was a randomized, multicenter trial of patients with non-penetrating TBI with ≤ 3 other injured organ systems enrolled within 2.5 h of injury. Patients were cooled to 33 ℃ or 37 ℃ in controls. Primary outcome was 6 mo Glasgow Outcome Scale (GOS) score. This study found no difference at 6 mo GOS score. Citing futility, this study was stopped at the interim analysis of the first 97 patients. Subgroup analysis of patients with evacuated hematomas found those treated with HT had better outcomes compared to the normothermia group. However, this represented only 28 patients. Thus, at least for TBI, HT does not appear to improve outcome.

Normothermia

Nearly 70% of patients in the NCCU experience fever in the first two weeks following injury[205]. The etiology goes unexplained in 1/5 to 1/3 of these patients[29]. The presence of fever increases the risk of poor outcome[23,206,207]. For the NCCU population specifically, after controlling for illness severity and diagnosis (ICH, stroke, or SAH) fever was independently associated with longer ICU stay, higher mortality, and worse outcome[23]. However, is fever causing the miserable outcome or is the miserable outcome heralded by fever?

Attempting to answer this question, one must first inquire what a safe and effective means to do so is. Acetaminophen effectively lowers temperature, but only by approximately 0.2 ℃[195]. Use of endovascular and newer surface cooling systems effectively lowers the fever burden safely, at no increased risk to some patient populations[22,208,209].

The NCCU data represents a mixed population. Certain disease processes may benefit more from TTM targeted at normothermia than others. The development of delayed cerebral ischemia (DCI) after SAH has been associated with a higher fever burden, portending higher morbidity and mortality[210-213]. A recent single center study of 40 consecutive febrile SAH patients maintained at 37 ℃ with a surface cooling hydrogel device (Arctic Sun) during their first 14 d after SAH were matched to 80 SAH patients who underwent conventional fever control (CFC) between 1996 and 2004[214]. The authors found patients undergoing normothermia had a longer ICU stay (19 ± 7 d *vs* 14 ± 8 d, $P = 0.001$) but a similar overall hospital length of stay as compared with CFC patients (28 ± 13 d *vs* 28 ± 21 d, $P = 0.9$). Although a higher proportion of cooled patients underwent tracheostomy and had a higher rate of pneumonia, the proportion of poor outcome at 14 d among cooled patients was no different than among control patients (83% *vs* 85%, $P = 0.7$). However, TTM patients had a statistically significant lower rate of poor outcome at 12 mo (21% TTM *vs* 46% CFC, $P = 0.03$). When entered into a multivariable linear regression model adjusting for age, cooling was associated with improved outcome at 12 mo after SAH, suggesting elimination of fever with TTM may be associated with improved outcome after SAH.

Regarding stroke, the association of fever to poor outcome is strong, but the association of intervention to improved outcome is not so herculean. The 2009 Cochrane review of cooling therapy in acute stroke found no statistically significant effect of pharmacologic or physical temperature-lowering therapy in reducing the risk of death or dependency[195]. However, the pooled data represented a heterogeneous amalgamation of small, phase I trials and acetaminophen studies lacking protocol similarity.

Even murkier is the evidence for fever reduction in the non-NCCU populations. A recent meta-analysis pooled studies representing NCCU, surgical ICU, general ICU, liver-transplant ICU, post-operative ICU, and trauma ICU populations[215]. This found current intravascular and hydrogel cooling systems significantly better at reducing fever burden than traditional cooling blankets and cooling baths. However, these studies were markedly heterogeneous. Concerning was the trend ($P = 0.06$) that hospital mortality for these newer cooling technologies, compared to traditional cooling, was higher at 25.4% *vs* 18% in the pooled analysis.

When comparing the effectiveness of pharmacologic, antipyretic treatments (i.e., NSAIDs, acetaminophen), the authors analysis demonstrated core body temperature reductions favored continuous, dosing rather than blousing, of these medications[215]. Earlier use of these medications at 38.5 ℃, with cooling blankets above 39.5 ℃, demonstrated a significant 1.09 ℃ reduction in mean daily temperatures when compared to more permissive interventions (no intervention until 40 ℃)[216]. As noted with the newer generation of intravascular and hydrogel cooling technology, this earlier use of acetaminophen and surface cooling demonstrated a trend toward increased mortality with $P = 0.09$. Given the motley findings of studies looking at TTM for normothermia, it is not surprising that the American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine,

Society of Critical Care Medicine, and Societe de Reanimation de Langue Francaise offer this observation: Regarding fever, it is a generic response to so many pathologic processes that no recommendation can currently be made for or against TTM. If a RCT is considered, focus should probably include severe fever unrelated to infection[24].

LOGISTICS OF DELIVERY

What features of TTM can be manipulated, if any, to improve efficacy and outcome? Is the efficacy of TTM determined by the duration, depth, and cooling-rate of therapy? Currently, TTM for CA is a "one size for all" approach. The target is typically a temperature of 32-34 ℃ for 12-24 h. Would titrating to a biomarker improve efficacy? Given the paucity of evidence, a biomarker targeted approach can not as of yet be advocated. Given the numerous pathways TTM affects, and the variable pathophysiology of diseases present in the ICU, determining which pathway at which time to focus monitoring is difficult. For example, data from TBI suggests cerebral metabolic rate starts to actually increase, approaching pre-hypothermic values, after 24 h of TTM[95]. Evidence from stroke patients treated with TTM demonstrates early in cooling, a state of relative ischemia develops, later replaced by a state of relative hyperemia[110].

Experimental evidence suggests increased duration of HT could improve efficacy. A recent cardiac arrest animal study varied the time from ROSC to the onset of HT, and the duration of HT[217]. Normothermic animals were controls. Good outcomes, as assessed by a standardized behavioral scale, occurred significantly more frequently in animals cooled within 4 h of ROSC. Survival was also significantly improved. When looking at a histological marker, the surviving neuron counts in animals cooled longer (48 h) was significantly greater than in animals cooled for a shorter period (24 h), or not at all[217].

Do these findings clinically translate? Could variation therapy duration improve the clinical outcome? Clinical evidence is lacking. Any effort to extend duration of therapy must weigh the increased risk of infection inherent to prolonged HT duration. Evidence from stroke and TBI patients treated with TTM report increased incidence of pneumonia with TTM times exceeding 48-72 h[197,218]. Recent retrospective review of 421 patients from a single center demonstrated 67% of patients developed 373 infectious complications[219]. These were most commonly pneumonia (85%), bloodstream infections (9%), and catheter-related infections (3%). Gram-negative bacteria were the most frequent isolated agents, occurring nearly 2/3 of isolates. Infected patients were most commonly treated with TTM, and of a longer duration. However, infection did not impact mortality or favorable neurologic outcome.

If prolonged duration of therapy is precarious, could changing the rate of cooling improve efficacy? The question of cooling rate and its effect on patients is understudied. The Bernard and HACA trials achieved a goal temperature typically within 2 h, at a median of 8 h after ROSC[8,9]. An observational study of OHCA, including PEA and AS, have not shown time to initiation of TTM, or time to reach goal temperature, as having an effect on outcome[220]. However, the protocols for HT were not standardized in this review. A recent study in 49 consecutive patients with OHCA (VT/VF, PEA, AS) with ROSC within 60 min of arrest and GCS $\leqslant$ 8 after CPR were prospectively followed. Predictors of good outcome included youth, early CPR, and a faster rate of cooling[221]. Not surprising, larger body surface area slowed the rate of cooling.

Anesthesia literature in patients receiving intra-operative HT for neuroprotection during circulatory arrest for thoracic aorta procedures provides some insight. Electroencephalography was used as a qualitative marker of cerebral metabolic activity[149]. The development of periodic complexes, burst suppression, and electro-cerebral silence patterns were chosen as qualitative markers of decreasing cerebral activity. Previous work has demonstrated reductions in EEG activity during HT to correlate to cerebral metabolism[148,150]. The authors found an association between rate of cooling and EEG endpoints. Specifically, prolonged time to cool to any EEG marker portended prolonged time to cool to reach the next marker[149]. Further, lower temperatures required for a marker were associated with lower temperatures required for subsequent markers. Said another way, a slower rate of cooling required a lower absolute temperature to obtain the necessary cerebral metabolic endpoint. Larger body surface area and increased hemoglobin concentration were found to directly correlate with times needed to reach burst suppression and electrocerebral silence respectively.

As uncertainty remains regarding the duration, depth, and targeting of TTM, could the type of device used effect outcome? Although firm answers are missing, some provocative findings are reported. In a head-to-head, single center, observational comparison of 167 patient receiving either the CoolGard (Zoll Circulation, Chelmsford, Massachusetts) or Arctic Sun (Medivance, Louisville, Colorado) systems, no significant differences were found in the rate of cooling, ICU stay, duration of mechanical ventilation, survival to discharge, survival at 6-12 mo, of neurologic outcomes[222]. Of note, more hypomagnesemia was observed in the endovascular group. The surface-cooled patients had more episodes of hyperglycemia. Of note, a recent prospective, observational, registry-based study of 22 U.S. and European hospitals demonstrated sustained hyperglycemia was associated with increased mortality[220,223].

While the device itself may not change outcome, many practical issue can affect the success of TTM protocols. A Google search demonstrates a number of devices that are commercially available for induction and maintenance of TTM and range from surface and endovascular cooling catheters, cooling helmets, immersion devices, and intranasal device. A recent prospective study of fifty ICU

patients requiring TTM evaluated the rate of cooling, and the variation above/below target temperature during the maintenance phase of TTM[224]. Five commercially available devices were evaluated which included a water circulating external cooling device (Blanketrol Ⅱ, Cincinnati Sub Zero, The Surgical Company), an air circulating external cooling device (Caircooler CC1000, Medeco), a gel-coated adhesive system (Arctic Sun, Medivance), an endovascular cooling system (Icy-catheter, Alsius CoolGard 3000), or conventional cooling with cold saline bolus and surface cooling with ice. This was a mixed group consisting of OHCA, TBI with elevated ICP, or patients with SAH requiring normothermia. The cohorts of 10 per device were well matched for APACHE Ⅱ, age, and BMI. In sum, the water-circulating blankets, endovascular cooling, and gel-adhesive devices provided the fastest rate of cooling. As for maintenance, the endovascular system provided the most reliable temperature control, drifting out of target range < 5 ± 5% of the time. The next closest device was the gel adhesive device, with a variance of approximately 40% ± 20%. Further, the endovascular and gel adhesive systems rated well with ICU nurses regarding maintenance work-load and hygiene, with endovascular cooling also scoring well in reported ease of patient monitoring[225].

CONCLUSION

Despite nearly 3600 years of medical use, the role of TTM remains ill defined. Currently, the strongest evidence for the use of TTM, in adults, is for HT in OHCA for VT/VF, ICP control, and for normothermia in the neurocritical care population. However, even in these disease processes, a number of questions exist. Data on disease specific therapeutic markers, clinical pathophysiology, and therapeutic depth and duration are limited. Further, for disease processes like HE, stroke, refractory SE, and ICH much of the clinical evidence reported is only at the safety and proof-of-concept stage. In sum, though intuitively appealing, TTM remains enigmatic in the ICU. More work is needed to define targets and goal directed therapies before a final "yeah or nea" can be given to this therapy.

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