Clinical Applications of Targeted Temperature Management

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Targeted temperature management (TTM) has been investigated experimentally and used clinically for over 100 years. The initial rationale for the clinical application of TTM, historically referred to as therapeutic hypothermia, was to decrease the metabolic rate, allowing the injured brain time to heal. Subsequent research demonstrated the temperature dependence of diverse cellular mechanisms including endothelial dysfunction, production of reactive oxygen species, and apoptosis. Consequently, modern use of TTM centers on neuroprotection following focal or global neurologic injury. Despite a solid basic science rationale for applying TTM in a variety of disease processes, including cardiac arrest, traumatic brain injury, ischemic stroke, neonatal ischemic encephalopathy, sepsis-induced encephalopathy, and hepatic encephalopathy, human efficacy data are limited and vary greatly from disease to disease. Ten years ago, two landmark investigations yielded high-quality data supporting the application of TTM in comatose survivors of out-of-hospital cardiac arrest. Additionally, TTM has been demonstrated to improve outcomes for neonatal patients with anoxic brain injury secondary to hypoxic ischemic encephalopathy. Trials are currently under way, or have yielded conflicting results in, examining the utility of TTM for the treatment of ischemic stroke, traumatic brain injury, and acute myocardial infarction. In this review, we place TTM in historic context, discuss the pathophysiologic rationale for its use, review the general concept of a TTM protocol for the management of brain injury, address some of the common side effects encountered when lowering human body temperature, and examine the data for its use in diverse disease conditions with in-depth examination of TTM for postarrest care and pediatric applications.

CHEST 2014; 145(2):386–393

Abbreviations: CPT = Current Procedural Terminology; GCS = Glasgow Coma Score; HIE = hypoxic-ischemic encephalopathy; ICP = intracranial pressure; NABISH = North American Brain Injury Study; Hypothermia; OHCA = out-of-hospital cardiac arrest; PCAS = postcardiac arrest syndrome; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation; STEMI = ST segment-elevation myocardial infarction; TBI = traumatic brain injury; TTM = targeted temperature management

Targeted temperature management (TTM) has been intermittently used for over 100 years but has only recently achieved a mainstream role in clinical practice. In the early 1900s, Russian clinicians placed snow on patients in cardiac arrest in an attempt to achieve return of spontaneous circulation (ROSC).¹ In 1937, Fay² applied refrigeration to patients with cancer and observed tumor shrinkage and devascularization. In 1958, Williams and Spencer³ published a case series of patients resuscitated from intraoperative arrest, demonstrating better neurologic outcomes when patients received TTM. The guideline for heart-lung resuscitation by Safar,⁴ published in 1964, recommended the initiation of hypothermia if there was no sign of neurologic recovery within 30 min of arrest. These

early implementation attempts did not translate into widespread clinical use, and it was not until 2002 that major clinical trials were published readdressing the efficacy of TTM in postarrest patients.^{5,6}

Current clinical indications for TTM as a neuroprotective therapy include adult patients with postcardiac arrest syndrome (PCAS) and neonates with hypoxic-ischemic encephalopathy (HIE); success in these conditions, coupled with lessons learned from early failures in the implementation of TTM, has motivated investigators to reconsider this therapy for other disease processes, including ischemic stroke, traumatic brain injury (TBI), hepatic encephalopathy, septic shock, and acute myocardial infarction. These entities will be further examined in this review of clinical TTM use.

TTM can provide neurologic protection to some patients who have suffered brain injury. Although numerous potential injury pathways are affected by TTM, it remains to be determined which of these are causally related to neuroprotective effects of TTM. Using cardiac arrest as an example, there are three distinct phases of injury: intraarrest ischemic injury resulting from a no-flow state, immediate reperfusion injury (beginning with ROSC and lasting about 20 min), and delayed postreperfusion injury (beginning several hours after ROSC and lasting for several days) (Fig 1). The first phase of injury is characterized by energy failure, ischemic depolarization of cell membranes, release of excitatory amino acids, and cytosolic calcium overload. These events can cause irreversible injury if ischemia is prolonged, and they set the stage for further injury if reperfusion is achieved. With ROSC, the cascade of injury initiated during ischemia is amplified: Resumption of oxidative phosphorylation is associated with reactive oxygen species production, mitochondrial calcium overload, and mitochondrial permeability transition triggering cell death signaling. The later stages of reperfusion are characterized by secondary neuronal calcium overload, activation of pathologic proteases, and altered gene expression and inflammation, among other mechanisms.⁷ Each of these three separate phases of injury is a potential target for TTM, and their corresponding therapeutic windows will likely vary with different organs and mechanisms of injury. Applying TTM within the therapeutic window allows injured cells time to recover and regain function.

In TBI and spinal cord injury, many of the mechanisms by which TTM is likely to be effective are similar to those of brain ischemia; however, the therapeutic window and optimal duration of therapy might differ.

This could be particularly true for mechanisms such as excitotoxicity, blood-brain-barrier disruption, and inflammation. In addition, injury mechanisms unique to trauma, such as mechanical axonal injury, might also be attenuated by hypothermia in ways that are distinct from other forms of brain injury.

Reducing a patient's body temperature provides multimodal protection. Hypothermia decreases metabolism 6% to 7% per 1°C decrease in temperature,⁸ protecting the brain from further injury during the early timeframe postanoxic injury.⁹ Hypothermia also affects the two major pathways for apoptotic cell death: the intrinsic pathway, under mitochondrial control, and the extrinsic pathway, signaled by an extracellular receptor.¹⁰ Furthermore, inflammation and free radical production are attenuated by hypothermia.¹¹ Reperfusion injury can produce decreased blood-brain-barrier integrity and increased vascular permeability, resulting in brain edema, both treatable by TTM.^{12,13}

PROTOCOLS AND ADVERSE EVENTS

TTM is best implemented as a protocol-driven therapy.^{14,15} Various methods can be used to induce and maintain hypothermia.¹⁶ Surface cooling devices include ice packs, cooling blankets, and wraps. Core-cooling devices include endovascular catheters, heart-lung bypass machines, and hemofiltration devices. Continuous core-temperature monitoring with a feedback mechanism is essential to prevent overshoot.¹⁷ Preferred methods include esophageal or bladder temperature probes.¹⁸ For other clinical indications, protocols may differ in the depth (target temperature) and duration of temperature management.

Regardless of the clinical condition being treated, there are three commonly recognized phases to TTM: induction, maintenance, and rewarming (Fig 2). The induction phase extends from initiation of active cooling to when the patient reaches target temperature, which, in patients with PCAS, is typically between 32°C and 34°C. The maintenance phase extends from arrival at goal temperature until rewarming begins. For patients with PCAS, the maintenance phase ranges from 12 to 24 h. Depending on the indication for TTM, the patient may be maintained at target temperature for several days. The rewarming phase is the period during which the patient is gradually rewarmed to normothermia. After rewarming, normothermia should be maintained because pyrexia is associated with adverse outcomes in various forms of brain injury.¹⁶

Phase-specific side effects can be anticipated. During the induction and rewarming phases, defined by active transitions in core body temperature, shivering is frequently observed as the hypothalamus tries to maintain thermoregulatory control. Shivering increases

Manuscript received December 17, 2012; revision accepted July 31, 2013.

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DOI: 10.1378/chest.12-3025

FIGURE 1. Time course of neuronal injury mechanisms during and after cardiac arrest and the different phases during which injury occurs. The shapes of the individual curves schematically depict the severity and duration of injury during each phase. ROSC = return of spontaneous circulation.

metabolic demand, producing a large amount of heat. Control of shivering with neuromuscular blocking agents, sedatives, magnesium, or opioids protects the brain and facilitates temperature transition. During the maintenance phase, mild hypothermia can cause various physiologic disturbances, including bradycardia, hyperglycemia secondary to increased insulin resistance, and polyuria. Mild hypothermia has been associated with a relative coagulopathy, secondary to decreased platelet function, and a mild decline in platelet count. At lower temperatures, abnormalities in the coagulation cascade can be anticipated. Potassium shifts intracellularly, and renal reabsorption of electrolytes including magnesium is inhibited, all of which can contribute to cardiac arrhythmias during TTM. Additionally, hypothermia affects the cardiovascular system by lowering the heart rate and increasing myocardial contractility.⁷ TTM can also predispose patients

FIGURE 2. Phases of targeted temperature management (TTM). An example of a temperature curve for a patient undergoing TTM postcardiac arrest, demonstrating initiation of cooling shortly after ROSC, temperature drop during the induction phase, slight variability around target temperature during the maintenance phase, and gradual increase in temperature during controlled rewarming phase. The patient was a 69-year-old woman who had an out-of-hospital ventricular fibrillation arrest treated with defibrillation and epinephrine with ROSC 16 min after arrest. She was comatose on arrival and a rapid decision was made to initiate therapeutic hypothermia. T = temperature. See Figure 1 legend for expansion of other abbreviation.

to infection, as hypothermia inhibits leukocyte migration and phagocytosis, which becomes more relevant in patients cooled for longer durations; however, increased infection has not correlated to worse outcomes.⁷ During the rewarming phase, hypothermia-induced vasoconstriction decreases, and hypovolemia with associated hypotension can be observed (Fig 3).

CLINICAL APPLICATIONS OF TTM

Postcardiac Arrest Syndrome

For adult patients with PCAS, after out-of-hospital cardiac arrest (OHCA) from a shockable rhythm, TTM is standard of care.^{19,20} Bernard et al⁵ found that 49% of patients who received TTM (33°C, 12 h) had favorable neurologic outcomes at hospital discharge vs 26% of patients receiving standard postarrest care ($P = .046$). The Hypothermia After Cardiac Arrest Study Group reported that at 6 months after hospital discharge, 55% of patients who received TTM (range, 32–34°C, 24 h) had a favorable neurologic outcome vs 39% of patients receiving standard postarrest care ($P = .009$).⁶ Multiple subsequent investigations have suggested comatose survivors of nonshockable rhythms may benefit from TTM as well.^{21–24}

Most widely used algorithms for postarrest TTM adhere closely to the protocols used in the two landmark trials but various details are being actively investigated. Animal studies suggest that more rapid induction of TTM after arrest results in better neurologic outcomes.²⁵ However, in human studies, time to target temperature has been associated with conflicting outcomes.^{26,27} The appropriate duration of TTM is also being studied, as animal studies have shown improved outcomes when the cooling duration was 48 h vs 24 h.²⁵ Traditionally, TTM has been reserved for patients who have ROSC but investigators have also conducted a randomized controlled trial of intraarrest, transnasal cooling, demonstrating that the technique was feasible, safe, and decreased time to goal temperature. In a post hoc analysis of patients receiving early resuscitation (within 10 min of collapse), the intraarrest cooling group had a higher proportion of neurologically intact survivors vs the post-ROSC cooling group (43.5% vs 17.6%, $P = .03$).²⁸

Adult TBI

TBI produces a large burden of disease in adults, with 51,000 deaths and 90,000 patients suffering significant neurologic injury annually in the United States.²⁹ Brain edema and increased intracranial pressure (ICP) are associated with poor neurologic outcomes. Adult TBI trials have used TTM for neuroprotection and to decrease ICP with mostly disappointing results.

FIGURE 3. TTM-induced physiologic changes and resuscitation opportunities. Phase-specific physiologic findings have been observed in patients undergoing TTM and reported in multiple studies. These physiologic changes provide resuscitation opportunities but also may be detrimental to the patient's outcome if not anticipated and appropriately managed. See Figure 2 legend for expansion of abbreviation.

In 1997, Marion et al³⁰ divided patients into two cohorts based upon initial Glasgow Coma Score (GCS) (3-4 vs 5-7), then randomized each cohort to TTM (32-33°C) vs controlled normothermia (37-38.5°C). Patients in the GCS 5-7 TTM cohort had improved neurologic outcomes. Subsequent studies have failed to reproduce these results. In the North American Brain Injury Study: Hypothermia (NABISH)-I, Clifton et al³¹ randomized 392 patients with TBI to controlled normothermia (37°C) vs TTM (33°C) initiated within 6 h of injury and maintained for 48 h. There was no difference in 6-month postdischarge GCS between the two groups. A possible signal of benefit in patients who reached target temperature early informed the study design for NABISH-II, which investigated the efficacy of very early cooling for patients with TBI.³² However, NABISH-II was stopped after an interim analysis showed no possibility of benefit. An international trial (Eurotherm3235) is underway to evaluate the efficacy of TTM (32-35°C, ≥ 48 h) in patients with TBI with ICPs > 20 mm Hg resistant to initial ICP-lowering therapies.³³ In summary, currently TTM cannot be considered standard of care for TBI but may be used as part of a multimodal, stepwise approach.

Ischemic Stroke

Stroke is the third leading cause of death in industrialized countries but $< 10\%$ of all patients who suffer stroke are eligible for thrombolytic therapy.³⁴ Various neuroprotective strategies aimed at reducing the size of the ischemic penumbra have demonstrated significant benefit.³⁵ An early trial by Guluma et al,³⁶

showed the feasibility of TTM (33°C, 24 h) in awake, nonintubated stroke patients. Schwab et al³⁷ applied TTM (33°C, 48-72 h) to stroke patients with middle cerebral artery occlusion and were able to manage elevated ICP while producing few side effects. A randomized controlled trial (EuroHYP-1) evaluating the efficacy of TTM (34-35°C, 24 h) in ischemic stroke has completed enrollment but preliminary data are not yet available.³⁸

Cardioprotection

In animal models, TTM reduces myocardial infarct size when initiated prior to reperfusion.³⁹ These findings have proven difficult to translate to humans. Ly et al⁴⁰ published a pilot study showing that surface cooling was safe and feasible in patients who had ST segment-elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI). Similarly, Dixon et al⁴¹ found that endovascular cooling could be performed safely alongside PCI. Adequately powered clinical trials evaluating the efficacy of TTM in STEMI are needed. An initial trial, Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention (Part 1) (ICE-IT-1) showed no significant difference with respect to door-to-balloon times or infarct size in patients who had STEMI treated with PCI and randomized to TTM vs normothermia.⁴² Additional studies are ongoing in the United States and Europe.

Sepsis

TTM is used as an organ-protective strategy and has been used for fever management with the goal of

neuroprotection. These insights have led investigators to examine the utility of TTM in sepsis. Beurskens et al,⁴³ in a rat model of pneumococcal pneumonia, demonstrated that TTM did not affect the rate of bacterial growth but reduced bacterial dissemination and lung injury, perhaps by altering mitochondrial respiration. Léon et al⁴⁴ induced sepsis in a cecal ligation rat model, demonstrating that TTM resulted in increased duration of survival and hemoglobin-oxygen binding capacity. In a human trial, Schortgen et al⁴⁵ randomized vasopressor-dependent patients in septic shock to standard temperature management vs TTM (36.5-37°C) via surface cooling. They demonstrated the feasibility of surface cooling in patients in septic shock, lowering mean temperature from 39°C to under 38°C in < 2 h. Vasopressor dependence at 12 h was reduced twofold from the standard care group to the TTM group, and 14-day mortality decreased from 34% to 19% ($P = .01$). These provocative preliminary findings need further validation in a study where the primary end point is 28-day mortality.⁴⁵

Acute Respiratory Distress Syndrome

In 1993, Villar and Slutsky⁴⁶ published a pilot study investigating TTM for refractory ARDS. Nineteen patients were randomized to conventional therapy vs TTM (32-35°C, up to several days), and mortality was lowered from 100% to 67%.⁴⁶ This study has several limitations, including small sample size, enrollment in pre-low tidal volume ventilation era, and excess overall mortality; therefore, it can only be considered hypothesis generating. Additional trials are needed to investigate the potential for TTM as either a preventive or therapeutic strategy in patients with ARDS.⁴⁶

Hepatic Encephalopathy

Hepatic encephalopathy is often complicated by increased ICP, and the potential of using TTM to lower ICP has been explored. In three case series (36 patients total), clinicians have demonstrated the feasibility of using TTM to lower ICP and provide a bridge to transplant.⁴⁷⁻⁴⁹ Randomized controlled trials are needed before this can be considered standard of care.

Pediatric Cardiac Arrest

The 2010 American Heart Association (AHA) recommendation for TTM in pediatric cardiac arrest states⁵⁰:

Therapeutic hypothermia (32°C to 34°C) may be considered for children who remain comatose after resuscitation from cardiac arrest. It is reasonable for adolescents resuscitated from sudden, witnessed, out-of-hospital VF cardiac arrest.

This statement is, in large part, extrapolated from adult data.

Two additional retrospective studies compared TTM to normothermia in children successfully resuscitated from cardiac arrest.^{51,52} Doherty et al⁵¹ performed a study across five centers, three of which used TTM, in a cohort where 88% had underlying heart disease and 94% of the arrests were in-hospital. After controlling for multiple variables, there was no difference in outcomes between the two groups. In a markedly different patient population (single center; 8% with underlying heart disease; 91% OHCA), Fink et al⁵² evaluated TTM for primarily asphyxia-associated cardiac arrests. No significant difference in outcome was observed but patients who received TTM, on average, suffered more severe injury (eg, longer ischemic time; higher total epinephrine doses).⁵² These studies provide important initial assessments of TTM following pediatric cardiac arrest but are limited by their retrospective approach and lack of standard protocols. To address these shortcomings, a multicenter randomized clinical trial (Therapeutic Hypothermia After Pediatric Cardiac Arrest [THAPCA]) is underway comparing TTM (32-34°C) to controlled normothermia (36-37.5°C).⁵³

Hypoxic Ischemic Encephalopathy

TTM has been rigorously studied in the neonatal population following birth asphyxia. Shankaran et al⁵⁴ randomized moderately or severely encephalopathic neonates to hypothermia (33.5°C, 72 h) vs usual care. Forty-four percent of patients who received TTM had a poor outcome (death or disability at 18-22 months) vs 62% of control patients (relative risk, 0.72 [95% CI: 0.54, 0.95], $P = .01$).⁵⁴ Another study compared selective head cooling (34-35°C, 72 h) vs usual care for neonates with moderate or severe encephalopathy, stratified based on amplitude EEG recordings obtained within 5.5 h of birth. Fifty-five percent of patients who received TTM had a poor outcome (death or disability at 18 months) vs 66% of control patients ($P = .1$).⁵⁵ An a priori subgroup analysis of patients with moderately abnormal EEG background patterns showed fewer poor outcomes for the TTM cohort vs usual care (48% vs 66% [OR, 0.47; 95% CI: 0.22, 0.8; $P = .009$]). Most recently, a third trial, randomizing 325 infants with HIE to TTM or usual care, demonstrated no difference in the primary outcome of severe disability or death.⁵⁶ Despite these somewhat conflicting findings, TTM is considered standard of care for the treatment of HIE.

Pediatric TBI

TBI is the leading cause of morbidity and mortality in children. In the United States, approximately 475,000 children under the age of 14 years sustain TBI annually. Three early-phase clinical trials showed

TTM to be feasible⁵⁷ and safe^{58,59} in pediatric TBI, but none was powered for efficacy. Subsequently, a randomized controlled trial of TTM (32–33°C) vs normothermia for pediatric patients with severe TBI demonstrated no difference in neurologic outcomes and a trend toward higher mortality in the TTM group.⁶⁰

BARRIERS TO USE OF TTM

Despite significant advances in the understanding and application of TTM and demonstration of its efficacy in a few disease states (cardiac arrest; neonatal ischemic encephalopathy), there are significant barriers to its implementation in diverse clinical settings, limiting its clinical effectiveness.⁶¹ In a 2006 survey of critical care, cardiology and emergency medicine physicians, Merchant et al⁶² found that 74% of US physicians had never used TTM for a patient with PCAS. Physicians cited “not enough data,” “not part of Advanced Cardiac Life Support guidelines,” and “too technically difficult to use” as reasons for not using TTM. However, these findings were published prior to inclusion of TTM in the 2010 AHA guidelines for PCAS management. In 2011, Kremens et al⁶³ administered a telephone survey to all critical care physicians in one US state regarding the use of TTM in patients with PCAS and found that only 17 of 27 hospitals (63%) caring for patients with PCAS used TTM. Physicians cited lack of resources and the cost as reasons for its limited use. In October 2012, the American Medical Association held the annual Current Procedural Terminology (CPT) Code Editors’ Meeting, where two CPT codes were approved for accurate billing of TTM. The new CPT codes will allow for the billing of either total body hypothermia (0260T) or selective head hypothermia (with CPT codes 0260T and 0261T).

CONCLUSION

Despite a solid basic science rationale for applying TTM in a variety of disease processes, human efficacy data are limited and vary greatly from disease to disease. Ten years ago, two landmark investigations yielded high-quality data supporting the application of TTM in comatose survivors of OHCA from shockable rhythms, and TTM is now considered standard of care for these patients. However, implementation remains inconsistent, limiting the effectiveness of the therapy. Additionally, TTM has been demonstrated to improve outcomes for neonatal patients with HIE and is standard of care in that population. Trials are currently under way to examine the efficacy of TTM in the treatment of ischemic stroke, TBI, and acute myocardial infarction; the actual breadth and scope of TTM’s clinical applications remain to be elucidated. Systematic, protocol-

driven implementation programs are needed to deliver TTM to the highest percentage of eligible patients for those conditions where it is now standard of care.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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