Review

Therapeutic hypothermia: a state-of-the-art emergency medicine perspective ☆

Joseph Varon MD [a,b,*], Paul E. Marik MD [c], Sharon Einav MD [d]

[a]*The University of Texas Health Science Center at Houston, TX 77030-3209, USA*
[b]*The University of Texas Medical Branch at Galveston, TX, USA*
[c]*Eastern Virginia Medical School, Norfolk, VA, USA*
[d]*Shaare Zedek Medical Center, Hebrew University Medical School, Jerusalem, Israel*

Abstract Therapeutic hypothermia (TH) has gained popularity as a brain-protective strategy for victims of sudden cardiac death in whom return of spontaneous circulation has been achieved but coma persists. Trials have also demonstrated some advantageous effects of lowering core body temperature after stroke and hypoxic-ischemic encephalopathy of the newborn. In a variety of clinical conditions, TH is still being studied (eg, hepatic encephalopathy and traumatic brain injury). This study describes the historical development of TH, its current applications in emergency medicine, and its potential future uses.
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1. Introduction

Hypothermia has been used therapeutically for centuries [1,2]. Over the past 6 decades, quite a few experimental models and human clinical trials performed in a variety of clinicopathologic conditions have demonstrated that lowering body core temperature may confer benefit [3-5]. However, it is only recently that therapeutic hypothermia (TH) was actually shown to increase the likelihood of neurologically intact survival in patients with cardiac arrest [5-7]. As a result of these findings, TH has gained popularity as a brain protective strategy for comatose survivors of sudden cardiac death [5,6,8-10]. Emergency physicians will undoubtedly find the use of this therapeutic technique potentially applicable for more than one acute care medicine

scenario. This study describes the historical development of TH and its current applications in emergency medicine and discusses the potential future uses of this mode of treatment.

2. Definitions

Therapeutic hypothermia is a clinician-driven treatment modality aimed at decreasing core body temperature [2]. There has been some inconsistency in the literature in defining the range of temperature constituting each level of TH. Some define mild TH as a core body temperature of 3234°C to 34°C, moderate TH as 28°C to 31.9°C, deep as 11°C to 28°C, profound as 6°C to 10°C, and ultra profound as 5°C or less [11]. Others consider an induced decrease of body core temperature to 32°C to 34°C as being mild-to-moderate TH [8]. Either way, most authors, as well as the clinical recommendations for TH, currently suggest a target temperature range of 32°C to 34°C when hypothermia is induced for post–cardiac arrest therapeutic purposes [8,12,13].

3. Historical development of TH

Historical descriptions of the use of TH for various illnesses are abundant. In ancient Egyptian times, several references were made regarding the use of cold as local therapy in the Edwin Smith Papyrus, the most ancient medical text known [14]. Tannic acid derived from acacia seeds was used for "cooling the vessels" [8]. Hippocrates [15] advocated the use of cold water for treating "swellings and pains in the joints, ulceration, those of a gouty nature, and sprains" because it "reduces the swelling, and removes the pain." Galen suggested cold affusion for tertian fever and also invented the "Cold Cream," used to this day for cooling the skin after sunburn [16]. The Chinese surgeon, Hua To (circa 200 AD) practiced forced immersion in cold water [17]. Mercurialis provided a personal example for his patients by immersing himself in the cold springs of the river Arnus so as to ease the pain of renal colic [18]. Shortly after the invention of the mercurial thermometer, James Currie documented the first records of human temperatures in health, disease, and experimental conditions. He performed a series of studies on the effect of various methods of cooling upon physiologic parameters of the human body and subsequently used cooling techniques for treating several clinical disorders. It has also been suggested that William Osler lowered the average mortality from typhoid at the Johns Hopkins Hospital from 24.2% down to 7.1% by cooling his patients.

The "Russian method of resuscitation," first described in 1803, consisted of covering the patients with cardiac arrest with snow in the hope of improving survival [1]. During Napoleon's Russian campaign (1812), Larrey attempted to preserve injured limbs by using TH and used the numbing effect of the cold for decreasing pain during limb amputations [19]. He also noted that injured soldiers who were warmed died earlier than those who were not [20].

In November 1938, Temple Fay [21], a Philadelphia neurosurgeon, began inducing systemic hypothermia in patients with cancer to ease intractable cancer pain. Using a laboratory thermometer that enabled measurements lower than normal, the first patient was cooled to 90°F by exposure to the elements and was thus maintained for 18 hours. Rewarming was performed by applying heat to the body surface and performing hot coffee enemas. Overall, 169 patients who desired a respite from intractable cancer pain were treated by Fay with TH [22]. This series of patients was presented at the Third International Cancer Congress in 1939. However, the article forwarded to Belgium for publication was confiscated by the Nazis and later used to justify a series of inhumane experiments, leading to an aversion to this mode of therapy that would take almost 50 years to overcome. In a late report on this series of patients, Fay [23] described a mortality rate of 11.2% and a 95.7% rate of success in pain relief. Fay [24] also developed an induced hypothermia program for patients with severe head injuries and reported that TH improved "the recovery of the conscious state of patients with brain injury." By this time,

nurse refusal to work in the undesirable environment created by this treatment and discontent with the poor quality of temperature control had led Fay to develop the first cooling blanket for clinical use.

World War II brought a halt to the work of Fay on TH, but he sent his newly developed equipment to Claude Beck and Charles Bailey to facilitate their pioneer work on hypothermia in cardiac surgery [23]. A decade later, in the 1950s, Bigelow and McBirnie [3] raised the possibility that inducing hypothermia during cardiac surgery may be brain protective [25] and published a series of studies in canine and monkey models supporting this hypothesis. Shortly after, 2 studies of post–return of spontaneous circulation (ROSC) hypothermia (30°C-34°C) were published [26,27]. In one study, the hypothermic group had a survival rate of 50% (6/12), and the normothermic group had a survival rate of 14% [27]; these results are somewhat reminiscent of those published more than 40 years later [5,6].

Early laboratory studies on hypothermia suggested that the central nervous system manifests a "cold narcosis" equivalent to hibernation that is entirely reversible [28]. By 1960, the association between hypothermia and decreased oxygen consumption and, more specifically, the association between hypothermia and reduced cerebral oxygen consumption [29], intracranial pressure, and brain volume [30] had been discovered. This led to broad use of hypothermia for not only cardiovascular surgery but for head and spinal cord injuries as well [31].

However, the number of complications observed during implementation of hypothermia and rewarming led many clinicians to abandon this technique [32]. Between the 1960s and the 1990s, the use of TH was reported in only a handful of publications [33]. The concern of adverse effects of TH limited the use of this therapeutic intervention. Interest in the beneficial effects of TH after cardiac arrest was rekindled sometime during the 1990s when animal experiments began to clarify the difference between mild-moderate TH and profound hypothermia and demonstrated that the former may improve neurologic outcome [33].

As data supporting the positive effects of TH continued to accumulate, both scientists and clinicians began showing interest in this treatment modality. By 2002 to 2003, the American Heart Association and the European Resuscitation Council recommended TH as a treatment modality for out-of-hospital comatose patients with cardiac arrest with ROSC [12,13,34,35]. This clinical recommendation was based on the results of 2 prospective, randomized, controlled, clinical trials conducted in Europe and Australia [5]. Concerns as to the methodology of these studies have been raised by practicing clinicians. It has been stated that external funding has often hampered research in areas lacking potential marketable pharmaceutical developments; no "single bullet" is expected to improve the outcome of cardiac arrest [4,36]. However, issues surrounding informed consent in resuscitation research remain somewhat problematic in the United States, even despite the Food and

Drug Administration's provided revisions in "the Final Rule" of 1996 [37-41].

The seminal European and Australian studies examined the impact of TH on the outcomes of patients with out-of-hospital cardiac arrest who had achieved ROSC but had a high likelihood of anoxic brain injury. The multicenter study conducted in Europe by Holzer and coworkers [10] enrolled a total of 275 cardiac arrest patients, including patients with an arrest secondary to ventricular fibrillation (VF). The study group (n = 137) was treated with TH, and the control group (n = 138) was kept normothermic [5]. Therapeutic hypothermia was induced by a device circulating cold air combined with the use of ice packs and was maintained at 32°C to 34°C (bladder temperature) for 24 hours. Patients in the TH group had better neurologic outcomes and a lower mortality rate than did controls [5]. The Australian trial, headed by Bernard and collaborators [6], recruited patients with shockable rhythms only and produced similar results using cold packs. In both studies, those assigning the patients to hypothermia and performing the initial cooling procedures were the emergency medicine staff. Later analyses of TH studies demonstrated that the numbers needed to treat were 7 patients to save one life and 5 patients to improve neurologic outcome [42].

4. How does TH help the brain?

After circulatory arrest, a cascade of neurologic events occur. Within the first 10 seconds, there will be loss of consciousness, and after 20 seconds, electroencephalographic activity becomes isoelectric [2,43]. This is followed by anaerobic glycolysis, leading to a decrease in energy stores. Parallel to energy depletion, there is cellular depolarization with loss of the normal Ca^{2+} balance between the extracellular and intracellular compartments [2,43]. Intracellular calcium accumulates and causes premature neuronal death [8,44].

Tissue injury continues even after achievement of ROSC and restoration of blood flow. This reperfusion injury is thought to be secondary mainly to generation of oxygen free radicals [43,45,46]. The postischemic effects worsen when patient temperature increases 0.5°C or more above 37°C [2]. Activation of the *N*-methyl-D-aspartate (NMDA) receptors occur as the core body temperature increases, contributing further to the elevation of intracellular calcium levels [47].

The protective effect of TH was traditionally attributed to a reduction of metabolic rate [48]. Cerebral metabolism (estimated by oxygen consumption, glucose utilization, and lactate concentration) is temperature dependent. Hypothermia has been shown to reduce cerebral metabolism by decreasing all of these parameters [48]. For each 1°C decrease in core temperature, the cerebral metabolic rate decreases by 6% to 7% [2,30,49].

At the cellular level, TH protects the cell wall and maintains the integrity of the lipoprotein membrane [45]. It further decreases enzymatic reactions that lead to cell damage or death. [50-52]. In addition, TH inhibits activation of NMDA receptors [2]. At the tissue level, TH improves oxygen supply to areas of ischemic brain and decreases intracranial pressure [8]. For these reasons, TH is commonly used during surgical procedures in which cerebral blood flow (CBF) needs to be interrupted, such as cardiac and intracranial surgery [31,53].

Therapeutic hypothermia can also reduce intracranial pressure; to this end, TH has been used in patients with traumatic brain injury (TBI) with increased intracranial pressure refractory to medical management [54]. Mild-to-moderate TH (ie, 32°C-34°C) has been shown to decrease CBF due to cerebral vasoconstriction [48]. This protective effect decreases intracranial pressure and may also act as an anticonvulsant [55,56].

5. Other effects of TH

During induction of TH, patients may exhibit a decrease in heart rate and an increase in systemic vascular resistance [4]. By decreasing the heart rate, TH also causes a decrease in cardiac output (approximately 7% for each 1°C decrease in core body temperature) [57]. Despite this drop, mean arterial pressure is usually maintained. If a patient becomes hypotensive during TH, other causes should be considered (eg, intracranial hypertension and intravascular volume depletion).

In the past, concerns were raised that TH might impair the success of defibrillation through a reduction in sodium channel conductance and increased electrical heterogeneity via dispersion in the action potential duration [58]. Induced QTc prolongation (>460 milliseconds), which in itself can cause polymorphic ventricular tachycardia (VT) and VF, has also been suggested to lower the threshold for defibrillation [59]. However, swine experiments demonstrate that the response to defibrillation may actually be improved during moderate hypothermia (33°C), compared with normothermia (37°C) and severe hypothermia (30°C) [60]. The mechanisms underlying this improvement are not quite understood. Temperature-dependent amelioration of ischemic myocardial injury may play a role. However, this mechanism fails to explain the advantage of moderate over severe hypothermia [61].

Defibrillation success or failure depends on the balance between shock-induced extinction and generation of functional obstacles (rotors) [62]. Recent data demonstrating that moderate hypothermia modifies spiral wave dynamics suggest that moderate hypothermia, in particular, prevents reentrant excitations rotating around the rotors responsible for the genesis of VF. Such an effect would lead to an increased likelihood of spiral wave collision, favoring self-

termination of VT and VF [63]. In practical terms, despite cardiac physiologic and electrocardiographic changes suggestive of an decreased fibrillatory threshold, the likelihood of successful defibrillation may actually improve during TH, and defibrillation is safe and effective regardless of the cooling method used (wet or dry) [64,65].

Ventilation requirements are reduced during TH because of the decrease in metabolic rate. In spontaneously breathing patients, ventilation decreases in an attempt to maintain P_{CO_2} within the reference range [4]. The solubility of gases in blood increases as body temperature decreases [4].

Whether blood gas data should or should not be corrected for core body temperature remains controversial even in deep hypothermic circulatory arrest, which has been used for many more years than TH (pH-stat vs alpha-stat). Furthermore, it is not clear that studies involving deep hypothermic circulatory arrest are also applicable in the setting of post–cardiac arrest at 32°C to 34°C TH. The absence of prospective data regarding use of pH-stat vs alpha-stat in mild TH post–cardiac arrest has resulted in a fair degree of equipoise in previously published retrospective studies of acid-base management specifically in this setting [66,67]. The optimal blood gas strategy remains unclear, pending prospective studies specifically in the setting of mild TH, and will likely be contingent to some extent on the clinical entity being treated (elevated intracranial pressure [ICP], post–cardiac arrest, etc).

Increased renal blood flow during mild TH leads to increased diuresis, particularly during the induction phase [57,68]. Also, during this phase, there is increased entry of potassium into the cells, leading to hypokalemia. Correction of this "derangement" can lead to hyperkalemia during rewarming [4,69]. Similarly, TH decreases phosphate and magnesium concentrations, but this does not require correction [70-74].

In most patients undergoing TH, gut motility is impaired [4]. Enteral nutritional support is usually withheld until TH has been completed and bowel motility returns to normal [8]. Therapeutic hypothermia decreases plasma insulin, with resultant hyperglycemia [75,76]. Most patients undergoing TH require exogenous administration of insulin [2,77,78].

Therapeutic hypothermia has unfavorable effects on platelet function. It also prolongs the prothrombin and partial thromboplastin times [11]. Significant bleeding, however, is rarely observed in these patients [8]. An increased incidence of neutropenia and susceptibility to infections, particularly pneumonia, has been reported [4,11].

6. Conventional and innovative cooling techniques

Therapeutic hypothermia can be accomplished in a variety of ways [2,8,64,79-81]. The ideal cooling device does not exist; such a device would induce rapid temperature reductions, preferentially cool the target organ (ie, the brain), be environmentally versatile (lightweight, small, transportable, and sturdy), and be implementable in any setting even during the resuscitation itself [82]. Because no single technique is appropriate for all patients and all settings, emergency clinicians should consider the method of cooling best suited to the individual. In many instances, a combination of techniques is used to induce and maintain TH [2].

The techniques most commonly used to induce and maintain TH are surface and invasive cooling (see Table 1). Surface cooling is most widespread because it is relatively simple to implement. However, achieving the target body temperature with this technique usually takes 2 to 8 hours, a relatively long time [12,13,83]. External cooling is also not a very efficient method of reducing the temperature of target organs (ie, brain and heart). It is therefore often combined with an additional cooling method. For example, decreasing the temperature of the mechanical ventilator circuit will enhance cooling through use of the lung surface as a heat exchanger. The exaggerated shivering response triggered by what surface cooling requires is another major disadvantage with this technique [84]. Expert management is required to prevent this response; the potential increase in oxygen consumption brought about by shivering may counteract the advantages of TH.

Surface cooling can be performed in several methods. Low-cost techniques include ice packing [8] and alcohol baths (usually considered a temporary measure before definitive cooling). Recirculating cold-water blankets or cold air–forced blankets can also be used [80,85-87]. Total body cold-water immersion has been described, but this method may compromise the quality of monitoring and therapy. Devices that control temperature through a feedback mechanism are generally preferable but more expensive. Higher cost methods including, for example, self-adhesive, hydrogel-coated pads that circulate temperature-controlled water under negative pressure are commonly used for external cooling. The mean rate of temperature reduction

Table 1	Cooling techniques
Noninvasive techniques	Invasive techniques
Caps or helmets	Intraventricular cerebral hypothermia
Cooling blankets	Extracorporeal circulating cooled blood
Hydrogel-coated cooling pads	Infusion of cold IV fluids
Ice packs	Peritoneal lavage with cold exchanges
Immersion in cold water	Retrograde jugular vein flush
	Nasal, nasogastric, and rectal lavage
	Nasopharyngeal balloon catheters

IV indicates intravenous.

when using this method was 1.4°C/hour, and the median time to achieve target core body temperatures was 137 minutes [88].

The obvious disadvantages of surface cooling have led to the development of more invasive approaches to cooling. With the exception of one method, all invasive cooling techniques are currently limited to the in□hospital environment; most are rather cumbersome and require setup in a relatively sterile environment. However, endovascular cooling provides better time within the target temperature range, less temperature fluctuation, and better control during rewarming [89]. Invasive cooling methods include cold carotid infusions, single-carotid artery perfusion with extracorporeal cooled blood circulation, ice water nasal lavage, cardiopulmonary bypass, cold peritoneal lavage, nasogastric and rectal lavage, and the infusion of cold intravenous fluids (4°C) [79,80,85]. Among these, only infusion of cold intravenous fluids has been shown to be both manageable and effective in the emergency and prehospital setting [90]. Bernard and coworkers [91] enrolled 22 comatose post-ROSC patients to receive 30 mL/kg of +4°C Ringer's lactate solution intravenously for 30 minutes after initial evaluation in the emergency department (ED). Kim et al [92] treated 17 patients (of the 25 screened patients and of the 285 patients with ROSC) to receive 2 L of 4°C normal saline during a period of 20 to 30 minutes, with an intravenous pressure bag inflated to 300 mm Hg in the ED. In another ED study, Kliegel and collaborators [93] rapidly infused 2 L of cold fluid without untoward adverse effects, allowing more rapid attainment of the target temperature. Kamarainen and coworkers [94] randomized 37 of 44 screened patients to prehospital TH (n = 19) and control (n = 18) groups. Baseline temperatures were similar in the 2 groups. After infusion of an average of 27 mL/kg (+4°C Ringer's acetate, rate ~100 mL/min using a pressure bag) during 37 ± 16 minutes, core temperature was markedly lower in the hypothermia group at the time of hospital admission ($34.1°C \pm 0.9°C$ vs $35.2°C \pm 0.8°C$, $P < .001$). A more recent study demonstrated that prehospital induction of hypothermia decreased core temperature at hospital arrival but did not improve outcome at hospital discharge compared with cooling commenced in the hospital [7].

Endovascular heat-exchange devices have also been developed to this end. These devices circulate cold saline through an indwelling venous catheter placed percutaneously. These multilumen intravascular catheters have 2 to 3 cooling balloons and therefore require insertion into a major vein [83,95]. Several anatomical approaches (ie, femoral, subclavian, and internal jugular veins) may be used [95]. However, the femoral site may be preferable because of the lower likelihood of dysrhythmias.

Researchers continue to investigate alternative techniques to expedite achievement of target TH temperatures safely. Of particular interest are techniques in which the brain alone is cooled, that is, selective brain cooling [96]. These include noninvasive and invasive methods. A variety of cooling caps and helmets have been designed in an attempt to achieve noninvasive selective brain cooling [9]. Invasive methods include retrograde jugular vein flush, femoral-carotid bypass, and intraventricular cerebral hypothermia [97]. Retrograde jugular vein flush has even been used effectively in the ED setting [98].

7. Temperature monitoring

Regardless of the mode of how TH is achieved, reliable temperature measurements are essential [99]. Core body temperature can be measured with a variety of probes: rectal, bladder, vaginal, tympanic, esophageal, or intravascular (eg, a pulmonary artery catheter) [12,13]. The accuracy and precision of pulmonary artery temperature measurements are generally superior to other modes of measurement [100]. Nasopharyngeal and esophageal temperatures correspond to brain temperature with smaller mean differences than temperatures measured in body areas further from the brain and the heart [101]. Tympanic membrane temperature measurement is noninvasive but does correlate well with brain and epidural temperatures [99]. However, readings may be unreliable during head cooling or if the auditory canal is obstructed (eg, earwax) [99,102,103]. Rectal probes should probably be avoided; fecal insulation may impair correlation with intracranial temperatures [8,102].

8. Clinical applications of TH

The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) recommends TH (32°C-34°C) for unconscious adult patients with ROSC after out-of-hospital cardiac arrest (Table 2) [12,13,35]. Although initially recommended for patients with a presenting rhythm of VF, TH has also been suggested

Table 2 The basics of TH

TH	
Ideal candidate	Cardiac arrest with rapid ROSC, VF/VT, hemodynamically stable, unresponsive
How soon?	As soon as possible, may still benefit within 8 h or more after ROSC
How to induce?	Ice packs to groin, axilla, and neck Adjuncts—cold saline boluses (intravascular catheters), cooling blankets, fan mist
Adjunctive medications	Sedation, paralytic agents
Temperature measurement	Continuously monitored Bladder, esophageal, rectal, or PA

PA indicates pulmonary artery.

for patients with cardiac arrest with other presenting rhythms and for in-hospital cardiac arrests [34].

Although not recommended by guidelines, TH is being used in many other clinical scenarios [4]. These include TBI, traumatic cardiac arrest, stroke, neonatal hypoxic-ischemic encephalopathy, near-drowning, hepatic encephalopathy, the acute respiratory distress syndrome (ARDS), bacterial meningitis, and cardiac failure [4,44,99,104-108].

Trials of TH in of TBI have yielded conflicting results [54]. An early randomized clinical trial performed in a single medical center demonstrated improved neurologic outcome when patients were cooled to 33°C for 24 hours after a mean postinjury delay of 10 hours [109]. This finding was later contradicted [110], leading several authors to conclude that the data suggest no survival or neurologic benefit in patients with severe brain injury [111,112] and may even endanger patients [113]. Only recently was the confounding role of poor study design and inconsistency in study protocols understood; studies on TH in TBI can be divided into those with protocols for cooling for a short, predetermined period (eg, 24-48 hours) and those that cool for longer periods and/or terminate based on the normalization of intracranial pressure. A recent Cochrane-style quantitative systematic review of publications on the subject to date concluded that the best available evidence supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI (Glasgow Coma Scale score ≤8). When short-term cooling studies were analyzed separately, mortality and neurologic outcome remained unaffected. However, long-term or goal-directed cooling studies demonstrated considerably reduced mortality (relative risk, 0.62; 95% confidence interval, 0.51-0.76) and a higher likelihood of good neurologic outcome (relative risk, 1.68, 95% confidence interval, 1.44-1.96) [114].

Animal models of TH have been shown to decrease the neurologic sequelae of acute cerebrovascular accidents [115,116]. Over a decade ago, Schwab and coworkers [117] demonstrated that TH reduced intracerebral pressure and levels of some of the extracellular excitatory amino acids in a cohort of 25 patients with an acute stroke of the middle cerebral artery territory. Therapeutic hypothermia for acute ischemic stroke has been evaluated in a few small pilot studies. Induction volumes of cold fluids have recently been demonstrated to be safe after acute stroke [118]. Surface cooling is feasible in awake patients with ischemic stroke, provided that temperatures are only mildly reduced (35°C) [119]. Alternatively, cooling to 33°C is possible, but this was achieved with an endovascular device in the inferior vena cava and a combination of buspirone, meperidine, and cutaneous warming with a heating blanket to suppress shivering [120]. To date, no randomized controlled trials of TH for acute ischemic stroke have been performed. Logistic challenges present an important barrier to the widespread application of hypothermia for stroke and, most importantly, the need for high-quality critical care. With the advent of "stroke units," we are likely at the dawn of a new era of TH trials in stroke [121].

There is strong evidence to support the use of TH in the setting of neonatal hypoxic-ischemic encephalopathy [25,122]. When ILCOR guidelines were last published, the evidence supporting TH in neonatal hypoxic-ischemic encephalopathy included 1 large trial (CoolCap, n = 235), 1 small randomized control trial (n = 67), and several feasibility trials. Since then, several large cooling trials have either reported significant overall improvement in death or disability or have stopped recruitment pending final results. The cumulative data from these trials indicate "a consistent, robust beneficial effect of TH for moderate to severe neonatal encephalopathy, with a mean number needed to treat between 6 and 8" [123].

Therapeutic hypothermia may also be used in patients with fulminant liver failure complicated by hepatic encephalopathy and intracranial hypertension [124]. Although clinical trials have yet to prove the benefit of this treatment, it is rapidly gaining popularity [125,126]. In an experimental animal model, Rose and collaborators [127] showed that mild TH decreased cerebrospinal fluid ammonia, reduced cerebral extracellular concentrations of ammonia, and decreased brain water leading to a decrease in intracranial pressure when compared with normothermic controls. Cordoba and associates [128] in a similar model found that TH prevented ammonia-induced cerebral edema. Therapeutic hypothermia has also been used as a bridge to liver transplantation in selected patients [129].

Therapeutic hypothermia has been shown to reduce hypercapnia, decrease minute volume, improve oxygenation, and minimize barotraumas in patients with ARDS [4,130]. Villar and Slutsky [131] reported a 34% reduction in mortality in a series of patients with severe ARDS treated with hypothermia compared with normothermic controls.

9. Timing and therapeutic window

Experimental and clinical data suggest that TH should be initiated as early as possible after ROSC because the extent of brain damage is related primarily to the length of ischemia [12,13,132,133]. Animal data suggest that the earlier TH is initiated and the earlier the target temperature is reached, the greater the chance of a positive outcome [2,107,134]. These findings emphasize the importance of expert emergency medicine involvement in the management of relevant cases.

In a recent systematic review of the literature on prehospital induction of TH, only 11 studies were included; 4 induced cooling during active cardiopulmonary resuscitation and 7 performed cooling after ROSC. Eight of the studies scored "poor" for quality, and the authors of the metaanalysis noted significant differences in research methodology and outcome measures that did not enable the drawing of any conclusions [135].

However, therapeutic benefit has been reported in clinical studies even when cooling was delayed for several hours [12,13]. The authors reported a case in which TH was delayed for almost 12 hours after ROSC with a good neurologic outcome [44]. However, it remains clear that the earlier TH is implemented, the better, and the emergency medicine practitioner should be aware of this therapeutic option.

The length of hypothermic therapy required to achieve a beneficial effect remains unclear. Guidelines stated in ILCOR suggest maintenance of TH for 12 to 24 hours [12,13]. In some cases, a longer period of TH may be beneficial; in the presence of ongoing but potentially reversible intracranial hypertension, more prolonged therapy may be required.

A summary of the positive and negative effects of TH is presented in Table 3.

10. Rewarming

Rewarming should not be performed at a rate faster than 0.5°C per hour to avoid temperature overshoot. This can easily be achieved with heating air blankets [4]. Many institutions rewarm during a period of 24 hours with a target temperature of 36.5°C. During rewarming, shivering should be controlled, and hypotension should be treated with intravenous fluids [2]. In cases where intracranial hypertension is controlled solely with hypothermia, slow rewarming

Table 3   Summary of the negative and positive effects of TH

	Pros	Cons
General	Lowers mortality rates in postresuscitation human studies (NNT = 7) [5,6,11,12,57,91,94]	Requires appropriate equipment and drugs and expert management [2,8,49] May induce shivering (which increases oxygen consumption) [2,8,29]

Brain	Cellular effects [29,30,32,44,45,48,50]:
	  1. Protects cell wall and maintains integrity of lipoprotein membrane
	  2. Decreases enzymatic reactions leading to cell damage/death
	  3. Inhibits activation of NMDA receptors
	Tissue effects [2,29,32,44,54]:
	  1. Improves oxygen supply to areas of ischemic brain
	  2. Decreases intracranial pressure (decreases CBF due to cerebral vasoconstriction)
	Whole-brain effects [29,30,32,45,53,56]:
	  1. Reduces cerebral metabolism (oxygen consumption, glucose utilization, and lactate concentration)
	  2. Anticonvulsant
	Overall [5,6,7,8,10,43]:
	  improves neurologic outcomes in postresuscitation human studies (NNT = 5)
		Has a direct sedative effect (particularly in very low temperatures) [8,43,112]
		Requires sedation (which may interfere with neurologic assessment and/or diagnosis of seizure activity) [2,8]

Cardiac	Improves response to defibrillation[64]	Decreases heart rate (with secondary decrease in CO) [2] Increases systemic vascular resistance [8]
Pulmonary	Reduces ventilatory requirements [2,8]	–
Renal	Increases renal blood flow with increase in diuresis [68]	–
Metabolic	No correction of electrolyte disturbances required [2]	Electrolyte disturbances [58,69] (hypokalemia, hypophosphatemia, hypomagnesemia) Decreases plasma insulin with resultant hyperglycemia. Exogenous administration of insulin is often required [77].
Gastrointestinal		Impairs gut motility. Enteral nutritional support may need to be withheld [2,8,49].
Coagulation	Significant bleeding is rarely observed [8]	Decreases platelet function [2,49] Prolongs prothrombin and partial thromboplastin times [49]
Immune function		Increases incidence of neutropenia and susceptibility to infections, particularly pneumonia [2,8,49]

NNT, number needed to treat.

protocols at a rate of 0.5°C to 1°C per day should be established [4,8,136].

11. Complications and practical considerations during TH

Shivering is an important adverse effect of TH; it increases overall oxygen consumption and should be treated aggressively [12,13]. Shivering must be avoided pharmacologically through appropriate administration of sedation and antishivering agents (eg, meperidine and magnesium) before induction of hypothermia. Midazolam (0.15 mg kg^{-1} h^{-1}) together with fentanyl (2.5 μg kg^{-1} h^{-1}) may be used initially, with adjustment of the doses to facilitate mechanical ventilation [137]. Indeed, a recent survey of the sedation protocols used for TH, midazolam was the sedative used in most (39/68) intensive care units (ICUs) (doses, 5-0.3 mg kg^{-1} h^{-1}) [138]. In our ICU, we prefer propofol with or without remifentanil because of the rapid reversal of their neurologic effects and lack of residual sedation, enabling more accurate neurologic assessment shortly after return to normothermia [139]. In the above-mentioned survey, propofol was used in 13 of 68 ICUs at doses up to 6 mg kg^{-1} h^{-1}. Not all ICUs use analgesics; 18 (26%) of 68 ICUs did not. Fentanyl was the analgesic used the most, in 33 of 68 ICUs, at doses between 0.5 and 10 μg kg^{-1} h^{-1} [138].

Neuromuscular blocking agents may be required in some cases [112,13], particularly if shivering remains uncontrolled. In these cases, it is preferable to use a short-acting agent such as rocuronium (0.5 mg/kg bolus, 0.5 mg kg^{-1} h^{-1} continuous) for similar reasons if possible. Continuous or intermittent electroencephalographic monitoring is recommended to rule out seizure activity if anticonvulsants are not used as part of the sedation protocol [60]. Care should be taken to ensure amnesia throughout TH and full reversal of muscle relaxation at the time of arousal. This is particularly true when pancuronium is used for muscle relaxation. In the multicenter survey, pancuronium was the muscle relaxant most commonly reported as being used (24/68 ICUs), followed by cisatracurium in 14 of 68 ICUs.

Dysrhythmias, hyperglycemia, infections, and coagulopathy have all been reported as complications of TH [33,111]. The role of empiric prophylactic antibiotics during TH in preventing infection remains unclear. The infection most commonly associated with TH in survivors of cardiopulmonary resuscitation is pneumonia, which can easily be attributed to aspiration during the resuscitation itself. An early metaanalysis of TH found a trend toward a higher incidence of sepsis in the hypothermia group, but other complications such as pneumonia, renal failure, or pancreatitis occurred equally often in both groups. Bleeding occurred more often with TH, but this was not statistically significant [10]. A more recent Cochrane Database Review found no significant differences between patients treated and those not treated with TH in all of the following potential complications of treatment: bleeding of any severity, need for platelet transfusions, pneumonia, sepsis, pancreatitis, renal failure/oliguria, hemodialysis, pulmonary edema, seizures, lethal or long-lasting arrhythmias, cardiac complications, hypocalcemia, and hypophosphatasemia [140].

All patients undergoing TH should receive deep vein thrombosis prophylaxis in the form of sequential compression devices at the minimum.

12. Conclusions

Animal and human data demonstrate that TH confers protection against ischemic neuronal injury. Mild TH has proven beneficial for comatose survivors of cardiac arrest with ROSC and for neonates with hypoxic-ischemic encephalopathy. Therapeutic hypothermia has thus become the standard of post–resuscitation care and is likely to become so in neonatal hypoxic-ischemic encephalopathy. Therapeutic hypothermia may also be beneficial in a variety of other clinical conditions (eg, acute liver failure, TBI, and cold-water drowning). To date, combined external and intravascular cooling techniques seem to be most efficient for inducing and maintaining TH, but selective brain cooling also seems promising. Therapeutic hypothermia should be initiated as soon as possible after neurologic injury. A temperature of 32°C to 34°C for 12 to 24 hours is usually recommended. Rewarming must be controlled and gradual.

Acknowledgments

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