Targeted Temperature Management in Survivors of Cardiac Arrest

Ivan Rocha Ferreira Da Silva, MD[a],
Jennifer Ann Frontera, MD[b,*]

KEYWORDS

• Mild therapeutic hypothermia • Cardiac arrest survivors • Hypoxic-ischemic brain injury
• Neurologic prognosis

KEY POINTS

- Evidence supports mild therapeutic hypothermia (MTH) as the fifth link of the life chain, with significant decrease in mortality and improvement of neurologic outcomes in cardiac arrest (CA) survivors throughout the last decade.
- Cardiologist and intensivists must be acquainted with the indications and technique because MTH is the only proven neuroprotective therapy for CA survivors.
- Future research will help define current questions, such as the optimal timing, target temperature, and duration of MTH.

INTRODUCTION

Cardiac arrest (CA) is one of the most challenging situations in medicine because it involves not only reinstituting meaningful cardiac activity, but also minimizing secondary neurologic injuries. It is a major public health issue worldwide and a considerable amount of resources are spent in research yearly to understand better pathophysiological mechanisms, as well as therapies, to reduce secondary injuries in survivors. It is estimated that the global incidence of out-of-hospital CA is 82 to 189 cases per 100,000 inhabitants in industrialized countries.[1,2] Data from studies conducted before the widespread use of mild therapeutic hypothermia (MTH) show that only 5% to 20% of CA survivors were discharged from the hospital with good neurologic outcomes.[3–5] Of all the numerous randomized controlled trials (RCTs) that tested therapies to improve neurologic outcome after CA, the only ones with positive reproducible results were studies using MTH.[6] This article focuses on MTH as the main strategy for post-CA care.

RATIONALE FOR THE USE OF MTH AFTER CA

Hypoxic-ischemic brain injury is a well-known consequence of CA. Brain injury and cardiovascular instability are the major determinants of survival after CA.[7] It is estimated that the cost of care during the first 6 months after a CA for a patient severely disabled or in a vegetative state can be as high as $300,000.[8]

HISTORICAL PERSPECTIVE

The use of hypothermia for clinical purposes has been suggested for thousands of years. Hippocrates advocated the packing of wounded soldiers in snow and ice in 400 BC.[9] Baron Dominique Jean

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[a] Neurocritical Care Unit and Stroke Department, Hospital Copa D'Or, Rio de Janeiro 22031-011, Brazil;
[b] Cerebrovascular Center, Neurological Institute, Cleveland Clinic Lerner College of Medicine, 9500 Euclid Avenue S80, Cleveland, OH 44195, USA
* Corresponding author.
E-mail address: frontej@ccf.org

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Larrey, surgeon-in-chief of the Napoleonic armies, observed that the wounded soldiers lying closer to the campfire died sooner than those in more remote, colder areas did.[10] Clinical interest in hypothermia was revived in the 1930s and 1940s with observations and case reports describing successful resuscitation of drowning victims who were hypothermic.[11] Subsequently, scientific reports of its use after CA[12–14] and in patients with traumatic brain injury[15] were published in the 1950s and 1960s.

In 1964, the legendary anesthesiologist and intensivist Peter Safar[16] recommended in his historic "first ABCs of resuscitation" that hypothermia be used in patients who remain comatose after successful restoration of spontaneous circulation.

At that time, no consensus was reached about the ideal duration and goal temperature, or the ideal candidates for induced hypothermia. Due to adverse effects observed at very low temperatures, and difficulty efficiently and safely inducing and maintaining hypothermia, interest in this treatment modality declined precipitously. Approximately 30 years later, laboratory studies using animal models demonstrated the benefit of mild hypothermia after CA.[17,18] These were followed by several pilot trials of MTH in humans showing improved neurologic function compared with historic controls, as well as safety and feasibility.[19–21] Those studies set the foundation for the seminal RCTs,[22,23] which ushered in a new era in the post-CA care, culminating in 2003 with a statement from the International Liaison Committee on Resuscitation that "unconscious adult patients with spontaneous circulation after out-of-hospital CA should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation."[24] In 2005, induced hypothermia was included in the American Heart Association chain of survival.[25]

Pathophysiology of Brain Injury in CA

The brain receives approximately 25% of the cardiac output and is a strict aerobic organ with very high demand for glucose and very limited energy storage. Thus, it is extremely vulnerable to ischemic insults. Studies using animal models demonstrated that after 10 minutes of induced brain ischemia brain concentrations of glucose, glycogen, adenosine triphosphate, and phosphocreatine are virtually nonexistent.[26] This is usually followed by loss of transmembrane electrochemical gradients and consequent failure of synaptic transmission,[27] release of glutamate leading to excitotoxic cell death,[28] neuronal necrosis, and apoptosis.[29] Although the restoration of brain perfusion will reestablish energy stores, further injuries can ensue in a process known as reperfusion injury. Some of the studied mechanisms of reperfusion injury include lipid peroxidation, generation of oxygen reactive species, continued glutamate neurotoxicity, activation of calcium-dependent systems, and neuronal damage mediated by inflammatory cells.[30] **Box 1** summarizes some of the known mechanisms of neuronal injury associated with CA.

Protective Effects Associated with MTH

Since the 1950s, animal studies have shown that induced hypothermia can decrease the cerebral blood flow and cerebral metabolic rate of oxygen

Box 1
Mechanisms of anoxic-ischemic brain injury

Immediate

1. Cellular energy depletion, with anaerobic metabolism
2. Collapse of transmembrane sodium and potassium gradients
3. Failure of synaptic transmission, axonal conduction, and action potential firing
4. Intracellular acidosis
5. Hypercalcemia
6. Glutamate release, with neuronal hyperexcitability
7. Activation of intracellular enzymatic systems (protein kinase C and B, calcium/calmodulin-dependent protein kinase II, mitogen-activated protein kinases, phospholipase A2, C and D).
8. Mitochondrial dysfunction
9. Reperfusion, with generation of reactive oxygen species and lipid peroxidation
10. Elevated production of nitric oxide and peroxynitrite
11. Blood-brain barrier dysfunction
12. Loss of cerebral autoregulation

Delayed

1. Release of proinflammatory mediators (eg, tumor necrosis factor-α and interleukin-1)
2. Inflammatory cells recruitment
3. Complement activation
4. Caspase activation with apoptosis
5. Coagulation activation

Data from Refs.[27,133–135]

consumption as much as 6% to 7% for each 1°C reduction in brain temperature.[31,32] Recent studies using transcranial Doppler ultrasonography showed a significant decrease in the mean velocities of flow of the middle cerebral artery during MTH, but no changes in jugular venous oxygen saturation, showing a preserved metabolic coupling without further ischemia.[33,34] Additionally, MTH inhibits the release of glutamate and dopamine[35] and induces the release of brain-derived neurotrophic factor,[36] which further inhibits glutamate. A decrease in oxidative stress, free radical generation,[37,38] and cell-death secondary to apoptosis has also been observed.[39] Hypothermia suppresses the inflammatory cascade triggered after CA[40–42] and reduces early hyperemia, delayed hypoperfusion, blood-brain barrier disruption and cerebral edema.[43,44] **Box 2** summarizes the protective mechanisms of MTH.

Box 2
Protective mechanism of therapeutic hypothermia

Early

1. Decrease of cerebral metabolism
2. Decrease in mitochondrial injury and dysfunction
3. Improve ion pump function, decrease intracellular influx of calcium
4. Improve cell membrane leakage, decrease intracellular acidosis
5. Decrease production of reactive oxygen species
6. Decrease formation of cytotoxic edema

Late

1. Decrease of local production of endothelin and thromboxane A2, increase generation of prostaglandins
2. Improve tolerance for ischemia
3. Decrease neuroinflammation
4. Decrease apoptosis
5. Decrease cerebral thermo-pooling
6. Decrease vascular permeability
7. Activation of protective genes
8. Suppression of cortical spreading depression
9. Suppression of seizure activity
10. Decrease coagulation activation and formation of microthrombi

Data from Refs.[71,80]

Hypothermia After CA with Initial Shockable Rhythm

Two landmark studies, published simultaneously in 2002, reported significant improvement of neurologic outcomes using MTH in patients with out-of-hospital CA with ventricular tachycardia or ventricular fibrillation (VT/VF) as the initial arrest rhythm.

The Hypothermia After Cardiac Arrest (HACA) trial was a multicenter European RCT that enrolled 275 survivors of out-of-hospital CA with the initial rhythm of unstable VT or VF.[22] Subjects were randomly assigned to MTH, with a goal temperature of 32° to 34°C for 24 hours using cold air as the cooling method (TheraKool, Kinetic Concepts, Wareham, United Kingdom) versus standard treatment with normothermia. The goal was to reach the target temperature (measured with a bladder probe) within 4 hours after the return of spontaneous circulation (ROSC) and, if necessary, ice packs were used as an adjunct method. After 24 hours at the goal temperature, subjects were passively rewarmed, which was expected to occur over a period of 8 hours. Fifty-five percent of the subjects in the MTH group had a favorable neurologic recovery after 6 months (Cerebral Performance Category score 1 and 2, or ability to work with minor deficit and full independent activities of daily living). This was in contrast to 39% of subjects in the control group (risk ratio for a favorable outcome with hypothermia, 1.40; 95% CI, 1.08–1.81) with an absolute risk reduction of 16% and a number needed to treat to achieve a positive neurologic outcome of six. Additionally, a significant reduction in the rate of death at 6 months in the MTH group was observed (risk ratio for death, 0.74; 95% CI, 0.58–0.95), with an absolute risk reduction of 14% and number needed to treat to avoid one death of seven.

Simultaneously, an Australian trial conducted by Bernard and colleagues[23] enrolled 77 survivors of out-of-hospital CA with an initial rhythm of unstable VT/VF. Subjects enrolled on odd-numbered days received MTH, with a goal temperature of 33°C, for 12 hours, using ice packs as the cooling method. Subjects enrolled on even-numbered days received standard treatment with normothermia. Cooling was started by rescue personnel at the scene of the CA using cold packs (CoolCare, Cheltenham, Victoria, Australia). This was continued in the hospital using ice packs. Body temperature monitoring was performed with a pulmonary artery catheter. After 12 hours, subjects were actively rewarmed for the next 6 hours by external warming with a heated-air blanket, with continued sedation and neuromuscular blockade to suppress shivering. Twenty-one of the 43 subjects (49%) who were

treated with MTH survived and had a favorable neurologic recovery (defined as discharged home or to a rehabilitation center) at hospital discharge, compared with 9 of the 34 subjects (26%) treated with normothermia ($P = .05$). The number needed to treat to obtain a favorable neurologic recovery was four. The odds ratio for a good outcome in the hypothermia group compared with the normothermia group, after adjustment by logistic regression for age and time from collapse to ROSC, was 5.25 (95% CI, 1.47 to 18.76; $P = .011$). Though mortality was reduced in the hypothermia group compared with the normothermia group (51% vs 68%), this did not reach statistical significance, likely due to the small sample size in this study.

Hypothermia After CA with Initial Nonshockable Rhythm

In contrast to the studies with VT/VF as the initial rhythm, there are no large RCTs to evaluate the efficacy of MTH in subjects with CA and nonshockable rhythms. Although it would be logical to deduce that the brain injury mechanism could be the same, it is not clear whether other factors influence outcome. Patients with pulseless electric activity or asystole (PEA/asystole) arrest are usually sicker at baseline, and asphyxia and circulatory shock often result in bradycardia or hypotension, or both, before progressing to pulseless CA, during which time additional brain injury may be incurred. Studies from the era before hypothermia showed that subjects with CA and nonshockable rhythms have worse prognosis when compared with VT/VF arrest,[45–48] with the exception of children[46] and subjects with out-of-hospital witnessed CA secondary to a cardiac cause.[49,50]

Some nonrandomized, retrospective and prospective analyses of MTH in nonshockable rhythms have been published. Of these, three studies of out-of-hospital nonshockable rhythm CA found some possible improvement of neurologic outcomes with MTH,[51–53] although one of these showed only a trend for better prognosis but without statistical significance.[53] Another two studies found no benefit of using MTH for out-of-hospital nonshockable rhythm CA.[54,55] The only retrospective study that analyzed in-hospital nonshockable rhythm CA found no benefit for MTH.[56] A meta-analysis including studies before 2010 that tested MTH in nonshockable rhythm CA survivors found that MTH is associated with reduced in-hospital mortality, but no significant neurologic benefit could be found.[57]

Currently, two trials are recruiting subjects to study MTH in nonshockable rhythm CA in-hospital (NCT00886184) and out-of-hospital (NCT00391469). Until further data are available, MTH does not seem to confer any survival or neurologic benefit to CA survivors who present with a nonshockable rhythm.

APPLICATION OF MTH

Indications

MTH is currently indicated for patients who survive CA with VT/VF as the initial rhythm and who are not able to follow commands after being adequately resuscitated. Its use is strongly supported by the American Heart Association guidelines,[58] the European Resuscitation Council guidelines,[59] and the International Liaison Committee on Resuscitation guidelines.[60] Some centers also use MTH in patients with PEA/asystole as the initial rhythm, although evidence for this practice is limited (see previous discussion). The current data support the use of out-of-hospital CA, although it would be reasonable to treat someone with a witnessed CA secondary to a cardiac cause with VT/VF as the rhythm in the inpatient setting. In addition, the largest trial (HACA) did not include subjects who were resuscitated for more than 60 minutes, which seems a reasonable cutoff, unless the cause for the CA was near-drowning in cold water. Recently, the analysis of a large registry of CA care, including several hospitals in the United States, showed that, compared with patients at hospitals in the quartile with the shortest median resuscitation attempts in nonsurvivors (16 min; interquartile range [IQR] 15–17), those at hospitals in the quartile with the longest attempts (25 min; IQR 25–28) had a higher likelihood of ROSC ($P<.0001$) and survival to discharge ($P<.021$).[61]

Induction

Regardless of the method used to induce MTH, it is extremely important to expedite the process because delays in initiation seem to diminish or even abrogate its beneficial effects in animal models.[62,63] It is suggested that goal core temperature (32°–34°C) should be reached as soon as possible and no more than 8 hours after ROSC. The goal is to reach mild hypothermia because severe cardiac complications are usually encountered with temperatures lower than 30°C.

Several cooling methods, including ice packs and infusion of cold saline, as well as devices (intravascular cooling catheters, nasal cooling, helmets, surface cooling), were tested in small trials. The methods are usually divided in surface cooling (eg, cooling pads, ice packs) or core cooling (eg, intravascular cooling catheters, cold saline infusion). **Table 1** summarizes the most commonly used methods, with their advantages and

Table 1
Most commonly adopted cooling methods

Method	Comments
Core cooling	
Infusion of cold fluids	Usually bolus of 30 ml/kg of normal saline solution at 4°C Very rapid method and inexpensive, but no control over temperature goals Should not be used as maintenance, but as an induction adjuvant (even in the prehospital setting) Studies have shown this volume is well tolerated
Intravascular cooling catheters	Provides quick induction (1.5°–4.5°C) and highly reliable maintenance and rewarming Requires invasive procedure with risk of infection, hemorrhage, and venous thrombosis Anecdotal evidence suggests less shivering than surface cooling
Surface cooling	
Ice packs	Easy, inexpensive, can provide fairly rapid induction No control over temperature goals and overshoot is common Should not be used as maintenance, but may be used an induction adjuvant (even in the prehospital setting) Risk of severe skin lesions
Water-circulating cooling blankets	Less expensive than other methods, reusable, but inferior to cooling pads or intravascular catheters[67] Risk of skin lesions
Cooling pads	Most effective are hydrogel-coated water circulating pads Easy to apply, less labor intensive, with fairly fast induction (1.5°–2.0°C) and reliable maintenance and rewarming Risk of skin lesions, particularly with prolonged use at a low water temperature Cooling pads are reasonably expensive, but avoid risks associated with invasive procedures

disadvantages. To date, there is no evidence to determine the most effective method. A retrospective nonrandomized study with 167 subjects compared surface cooling (using cooling pads) with core cooling (using an intravascular cooling catheter) and found no difference in survival or neurologic outcome between groups.[64] These findings were corroborated by another retrospective study.[65] Evidence does suggest, however, that devices with hydrogel cooling pads are much more effective than conventional cooling blankets.[66,67] Finally, pressure bag infusion of 30 to 40 ml/kg of cold saline or Ringer lactate solution (4°C) can decrease the core body temperature by roughly 1°C per liter of fluid infused.[68–70] Some investigators defend that a combination of core cooling with cold saline infusion with surface cooling might be very effective, possibly with less shivering during induction, although this hypothesis has not been tested in trials to date.[71]

The Neurocritical Care Society Emergency Neurologic Life Support (NCS ENLS) suggests a goal temperature of 32° to 34°C, with the concomitant use of cold saline infusion (4°C, 40 ml/kg intravenous bolus) and a surface or core cooling method for MTH induction.[72]

Maintenance

After core temperature goal is reached, it should be maintained with minimal fluctuations (±0.5°C) for 24 hours. Although one of the main positive RCTs used 12 hours for the maintenance phase, most centers currently adopt 24 hours.[72] A recent small, pilot, randomized trial with 36 subjects suggests that MTH with a target of 32°C may yield better protection than cooling at 34°C, resulting in better short-term and long-term outcomes.[73] **Table 2** summarizes tests commonly ordered during MTH.

Rewarming

The rewarming phase should be as slow and controlled as possible. Animal experiments and human clinical observations suggest that rapid rewarming might lead to loss of many of the benefits and neuroprotective effects of MTH.[74–78] Significant decreases in jugular venous oxygen saturation have been reported during rapid rewarming,[77] as well as isolated brain hyperthermia (with normal core temperature),[75] increases in interleukin 6, and activation of the complement cascade.[79] Rebound cerebral edema and further

Table 2
Tests performed during MTH

Type	Frequency	Comments
Complete blood count, international normalized ratio, activated partial thromboplastin time, fibrinogen	Every 12 h	Watch for DIC, hemolysis, platelet dysfunction
Serum electrolytes (sodium, potassium, phosphorus, magnesium, calcium) and renal function	Every 8 h	Intracellular electrolyte shifts can occur during induction and extracellular shifts during rewarming Monitor for hypokalemia during induction and rebound hyperkalemia during rewarming Replete potassium <3.5 mg/dL Watch for ATN
Arterial blood gases	Every 12 h	Oxygen and carbon dioxide can be overestimated and pH underestimated if not corrected to actual body temperature
Glucose	Every 6 h	Insulin resistance commonly seen
Amylase, lipase, liver function	Every 12 h	Elevation of liver and pancreatic enzymes can occur during MTH, but usually do not represent cell injury
Lactate	Every 8 h	Mild lactic academia can be seen in MTH
Chest radiograph	Daily	Observe for infections and volume overload
EEG	Continuous	Patients should be monitored continuously to detect nonconvulsive status epilepticus
Blood cultures	Every 48 h	Some investigators suggest screening cultures to detect occult bacteremia (MTH induces mild leukopenia and fever cannot be detected)

Abbreviations: ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation.

brain injury are the most feared consequences of rewarming too rapidly.

Some investigators suggest a rewarming rate of 0.2° to 0.5°C per hour in patients after CA and an even slower rate of 0.1° to 0.2°C per hour in patients with primary neurologic conditions, such as traumatic brain injury or stroke.[80] Many cooling devices have feedback mechanisms that permit rewarming at specific speeds. When the target temperature of 36° to 37°C is reached, the cooling device should lock the patient at this normothermic goal for the next 24 to 48 hours because rebound hyperthermia is common, and can be extremely detrimental to the brain.[81] A slower rewarming period can also minimize electrolyte shifts and resistance to insulin changes, normally observed during this phase.

Temperature Monitoring

Monitoring core body temperature during MTH is essential. Noninvasive measurements, such as axillary, oral, tympanic, and temporal temperature, were tested in small studies and are completely unreliable.[71,82,83] According to the NCS ENLS, the preferred route of monitoring temperature in approximate order of preference would be endovascular, esophageal, and bladder or rectal.[72] Intracranial monitoring devices, such as intracranial pressure or brain tissue oxygenation monitors, can offer an exquisite opportunity for reliable brain temperature monitoring, although the device should not be primarily placed for temperature monitoring. Worth mentioning, bladder temperatures in anuric patients might differ considerably from brain temperatures.[84] In the context of anuria, an esophageal, intravascular, or rectal temperature probe is preferred.

COMMONLY ENCOUNTERED PROBLEMS DURING MTH

Table 3 discusses commonly encountered clinical complications during MTH.

Shivering

One of the most problematic challenges when inducing MTH is the triggering of the human body's

Table 3
Most commonly observed physiologic changes and complications during MTH

Physiologic Changes and Complications by Systems	Comments
Cardiovascular	
1. Hypovolemia	Normally secondary to cold diuresis during induction
2. Heart rate	Patients usually develop bradycardia, but matched with decreased body metabolism Malignant bradycardia and decreased stroke volumes normally only seen with temperature <30°C (patients should be rewarmed because atropine is usually ineffective) Care with use of dexmedetomidine
3. EKG changes	Increase in PR, QT, and QRS intervals Arrhythmias normally seen in temperature <30°C (atrial fibrillation and ventricular arrhythmias) Rewarming is the most effective treatment in this situation Osborn waves normally noted only in cases of severe accidental hypothermia
Renal and electrolytes	Intracellular electrolyte shifts can occur during induction and extracellular shifts during rewarming Rapid induction and slow rewarming usually minimize changes ATN only observed in case of accidental hypothermia with temperature <28°C
Endocrine	Insulin resistance with hyperglycemia commonly seen Goal is normally serum glucose of 140–180 mg/dL Insulin requirements may increase during induction and maintenance phases and decrease during rewarming Insulin drips are the preferred therapy
Infections	MTH can increase the chances of developing infections, particularly pulmonary infections due to decreased airway ciliary clearance Some investigators suggest surveillance blood culture every 48 h, to detect occult bacteremia (MTH induces mild leukopenia and fever cannot be detected) Decrease in the temperature used by cooling device to maintain a constant body temperature can be an indirect sign of fever
Blood and coagulation	MTH can induce mild leukopenia, as well as mild coagulation cascade and platelet dysfunction, but without significant clinical impact DIC is mostly commonly observed in accidental hypothermia
Thermoregulation:	Shivering markedly increases brain and body metabolism, mitigating most of the protective effects of MTH Rapid induction can minimize shivering, and the shivering response is blunted with temperature <34°C (see **Box 3**)
Gastrointestinal	
1. Motility	Patients can develop ileus and delayed gastric emptying Effective bowel regimen should be prophylactically prescribed
2. Pancreas and liver	Liver metabolism is markedly decreased and mild increases in liver function enzymes can be observed, but usually of no significance Amylase and lipase can also be mildly elevated, but without representing cell injury Pancreatitis has been described in patients with severe accidental hypothermia
3. Drug metabolism	Due to liver function decrease, drug metabolism is usually compromised and half-lives of drugs primarily cleared by the enzymatic system may be prolonged
Nutrition	Patients should be fed during MTH, but metabolic requirements should be corrected to body temperature

(*continued on next page*)

Table 3
(*continued*)

Physiologic Changes and Complications by Systems	Comments
Skin	Patients are in high risk for bedsores, due to skin vasoconstriction, immobilization and immune suppression Careful observation should be exerted in patients wearing cooling pads
Respiratory and blood gases	Oxygen and carbon dioxide can be overestimated and pH underestimated if blood gas analyses are not corrected to actual body temperature, due to gas solubilization Patients in MTH tend to have low actual PCO_2, due to decreased metabolism It is controversial whether pH and PCO_2 values management should be guided by corrected arterial blood gases (alpha-stat vs pH-stat theories) The authors believe that a combination of corrected arterial blood gases aiming for PCO_2 levels mildly lower than normal (around 35 mm Hg) could avoid cerebral ischemia secondary to extremely low PCO_2 or hyperemia (with increased intracranial pressure) due to high actual PCO_2 levels
Neurologic	Neurologic examination can be extremely blunted during MTH and obscured after rewarming due to decreased drug metabolism Patients should be monitored with continuous EEG because nonconvulsive status epilepticus is not rare following anoxic brain injury

Abbreviations: ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation.

thermoregulatory defenses. Shivering and vasoconstriction are physiologic reactions to a decrease in the core body temperature to values lower than the physiologic range. With any minimal decrease of the skin temperature, vasoconstriction ensues. If the core body temperature drops below 35.5, shivering with vigorous muscle contractions to generate heat occurs.[85] Shivering not only decreases the effectiveness of MTH, but can also be harmful because it activates a catecholaminergic response with consequent hypertension, tachycardia, and severe hemodynamic stress. Shivering is associated with increased oxygen consumption and metabolic rate, excess work of breathing, and increased myocardial oxygen consumption.[71,80] In the surgical literature, shivering is strongly associated with cardiac events,[86–89] and animal models of MTH have shown that shivering can negate its neuroprotective effects.[90,91] In a study with neurocritical subjects with traumatic brain injury, shivering was associated with significant lowering of brain tissue oxygenation levels,[92] indicated ischemia and metabolic distress. The Bedside Shivering Assessment Scale (BSAS) is a simple and reliable tool for evaluating the metabolic stress of shivering. It was validated in a study in which it was compared with indirect calorimetry.[93] **Box 3** describes the BSAS.

Most of the autonomic response to a lowering of the core body temperature is derived from hypothalamic centers; however, it is estimated that skin temperature contributes about 20% to

Box 3
The BSAS

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

Adapted from Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. Stroke 2008;39(12):3243; with permission.

control of vasoconstriction and shivering.[85] All candidates for MTH will be intubated and on mechanical ventilation, so blunting the physiologic responses of the central nervous system to hypothermia with sedation is a natural choice. Propofol is one of the preferred drugs because of its short half-life. Other options include opiates, such as fentanyl infusions or meperidine. The authors typically use meperidine for shivering only in conjunction with continuous electroencephalogram (EEG) monitoring because it has a substantial risk of lowering the seizure threshold. Recently, α2-receptor agonists (dexmedetomidine and clonidine) have received some interest as options for shivering control. Several other drugs with different mechanisms of action have been studied, such as buspirone, nefopam, doxapram, ketanserin, physostigmine, tramadol, ondansetron, and dantrolene, but with mixed results.[85] Magnesium sulfate was shown to lower the shivering threshold in some studies.[78,94–96] Small bolus doses of muscle paralyzers can be used in severe shivering, but repeated or continuous use should be discouraged owing to the risk of development of neuromuscular complications.

Nonpharmacologic approaches can be extremely helpful to combat shivering. Counterwarming of the skin was shown to be feasible and effective in some studies[97–99] because each 4°C increase in mean skin temperature reduces the thresholds for vasoconstriction and shivering by 1°C and 50% of thermal comfort is determined by skin temperature.[85,100] Though skin counterwarming may seem paradoxic, such skin rewarming typically does not affect core body temperature when advanced cooling devices are used.[71,85] Finally, fast induction to goal core temperature might also decrease the incidence of shivering because the shivering response often ceases completely at temperatures below 33.5°C.[15,71,101] **Table 4** summarizes the

Table 4
Most commonly used strategies to combat shivering

Therapy (Frequently Adopted Sequence)	Comments
Fast induction of hypothermia	Shivering tends to be minimized after temperature <35°C is reached
Counterwarming	Fairly effective and safe Use of air-warmed blanket Some hand and feet warming devices have been found to cause thermal burns
Buspirone	Usual dose 30–60 mg po every 8 h Might take 24 h to start acting Contraindicated in cases of severe renal or liver dysfunction Not useful in patients with ileus related to MTH
Magnesium sulfate	Bolus 2–4 g, intravenous, with goal of serum magnesium >2 Continuous drips of 12–16 g/24 h can be used Caution in patients with renal dysfunction Safe in pregnant patients
Meperidine	Bolus of 10–25 mg, intravenous, every 2–3 h Not very sedating Seizures can be observed especially in patients with renal dysfunction
Fentanyl	Bolus of 50–100 μg and drip 25–100 μg/h Watch for hypotension
Dexmedetomidine	Continuous infusion at 0.1–1.4 μg/kg/min May cause hypotension and bradycardia Clonidine is another option with alpha-2 agonism
Propofol	Bolus of 30–50 mg, maintenance drip 20–200 μg/kg/min Watch for hypotension, bradycardia, hypertriglyceridemia, propofol infusion syndrome
Benzodiazepines	Sometimes preferred in patients with hemodynamic instability or seizures
Muscle paralyzers	Very effective, but reserved as last option, due to neuromuscular complications related to prolonged use Bolus administration might decrease incidence of adverse effects Use compromises neurologic examination evaluation

most commonly used drugs and techniques to suppress shivering.

Associated Cardiologic Conditions

Cardiac conditions are the leading primary cause for out-of-hospital CA in the general population; therefore, those patients frequently need further aggressive cardiac care after recovery of spontaneous circulation. Multiple small studies have reported the feasibility and safety of using MTH in patients with cardiogenic shock[102–104] and the application of MTH in combination with emergent percutaneous coronary intervention (PCI),[105–112] as well as the adjunct use of fibrinolytic therapy.[113,114] One multicenter randomized study, Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients with Acute Myocardial Infarction (COOL-MI), with subjects with acute myocardial ischemia (but no CA) showed that is safe and feasible to perform endovascular core cooling in conjunction with PCI.

Prognostication

The advent of MTH in CA helped improved the neurologic prognosis in survivors, but also created the uncertainty on how to prognosticate outcome in patients who do not follow commands after rewarming. Several studies have tested neurologic examination findings, MRI with diffusion-weighted imaging, somatosensory-evoked potentials (SSEP), EEG, and neuron-specific enolase (NSE) with some interesting results. No definitive guidelines currently exist on how to interpret the test results, but most of the studies have shown that the previous data derived from CA survivors who did not receive MTH do not fully apply to those who receive MTH. The current guidelines of the American Academy of Neurology for prognostication after CA[115] (without MTH) are heavily based on the seminal paper of Levy and colleagues[116] in the early 1980s, which relied on neurologic examination 72 hours after CA. Some current studies with subjects who received MTH showed that the neurologic examination is not a totally reliable tool in this setting. The current experience in most specialized centers indicate that, in addition to the neurologic examination, MRI, EEG, SSEP, and NSE might be interpreted together, with no test alone being more accurate than the others. Moreover, most specialists believe that a longer observation time (at least >72 h but probably >5–7 days) is needed to prognosticate more accurately because some patients can have a remarkable recovery later in the course and elderly patients may take longer to metabolize drugs with central nervous system action because of decreased liver function secondary to hypothermia. One clear problem with the existing literature regarding outcomes after CA with MTH is that most studies are retrospective, unblinded, and confounded by withdrawal of life-sustaining therapy. A rigorous, prospective, and blinded approach to understanding predictors of outcome is needed. **Table 5** summarizes the most relevant evidence on prognostication after CA and MTH.

CURRENT OUTCOME TRENDS AFTER CA IN THE HYPOTHERMIA ERA

Recent large population studies in the United States showed a consistent trend of decreased mortality after CA in the last decade,[3,117–119] which can be partially attributed to the more widespread use of MTH. Girotra and colleagues[118] analyzed all adults who had an in-hospital CA between 2000 and 2009 at 374 hospitals in the Get with the Guidelines-Resuscitation registry. They reported that risk-adjusted rates of survival to discharge increased from 13.7% in 2000 to 22.3% in 2009 ($P<.001$), and that rates of clinically significant neurologic disability among survivors decreased over time, with a risk-adjusted rate of 32.9% in 2000 and 28.1% in 2009 ($P = .02$). Worth mentioning, this study also included subjects with an initial rhythm of PEA/asystole and the exact percentage of subjects who received MTH is not known. The same trend for improved mortality after the implementation of MTH was observed in Dutch, Japanese, and Finnish studies.[120–122] Some studies also indicated an increased use of MTH in the United States and Europe throughout the last decade.[123–127] Some investigators defend that CA survivors should be transferred to CA centers[128] for higher level of care, with some studies showing that it is feasible and might help improve outcomes.[123,125,128–132]

Hyperthermia

Fever after surviving a CA is deleterious and has been shown to impair brain recovery. The exact cause is not fully understood, but evidence shows that activation of inflammatory cytokines occurs after CA, resembling the systemic inflammation seen in septic patients.[111,112] Small studies and case series have disclosed that there is a strong association between poor survival outcomes and a body temperature greater than 37.8°C.[60,113–115] Moreover, fever is directly associated with worse prognosis in stroke and neurocritical patients.[116–121] To date, no RCT has evaluated induced normothermia versus conventional temperature management with the use of antipyretics in CA survivors. The authors suggest an intensive

Table 5
Relevant current evidence on prognostication after CA in patients treated with MTH

Study	Investigators	Conclusion
Retrospective chart review of 37 consecutive adults treated with MTH	Al Thenayan et al,[136] 2008	A motor response better than extension by day 3 was not prognostically reliable after therapeutic induced mild hypothermia for comatose cardiac arrest survivors None of the patients who lost pupillary or corneal reflexes on day 3 or developed myoclonic status epilepticus recovered awareness
Prospective, observational study with 111 subjects treated with MTH	Cronberg et al,[137] 2011	All 17 subjects with NSE levels >33 ng/l failed to recover consciousness In the >33 ng/l NSE group, all 10 studied with MRI had extensive brain injury on diffusion-weighted images, 12/16 lacked cortical responses on SSEP, and all 6 who underwent autopsy had extensive severe histologic damage
Prospective study with 111 subjects treated with MTH	Rossetti et al,[138] 2010	Three clinical variables, assessed within 72 h after CA, showed higher false-positive mortality predictions in MTH compared with the AAN guidelines: incomplete brainstem reflexes recovery (4% vs 0%), myoclonus (7% vs 0%), and absent motor response to pain (24% vs 0%) Unreactive EEG background was incompatible with good long-term neurologic recovery and strongly associated with in-hospital mortality The presence of at least 2 independent predictors out of 4 (incomplete brainstem reflexes, myoclonus, unreactive EEG, and absent cortical SSEP) accurately predicted poor long-term neurologic recovery (positive predictive value = 1.00); EEG reactivity significantly improved the prognostication
Prospective study with 34 subjects treated with MTH	Rossetti et al,[139] 2010	Continuous EEG monitoring showing a nonreactive or discontinuous background during MTH is strongly associated with unfavorable outcome in subjects with coma after CA
Retrospective study with 6 subjects with PSE treated with MTH	Rossetti et al,[140] 2009	Subjects with PSE and preserved brainstem reactions, SSEP and EEG reactivity may have a favorable outcome if their condition is treated as status epilepticus Subjects with nonconvulsive PSE showed a better prognosis than subjects with myoclonic PSE ($P = .042$)
Multicenter prospective cohort study with 391 subjects treated with MTH	Bouwes et al,[141] 2012	53% had a poor outcome Absent pupillary light responses (FPR 1; 95% CI, 0–7) or absent corneal reflexes (FPR 4; 95% CI, 1–13) 72 h after CPR, and absent SSEPs during hypothermia (FPR 3; 95% CI, 1–7) and after rewarming (FPR 0; 95% CI, 0–18) were reliable predictors Motor scores 72 h after CPR (FPR 10; 95% CI, 6–16) and NSE levels were not reliable predictors

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Study	Investigators	Conclusion
Retrospective study with 185 subjects treated with MTH	Leithner et al,[142] 2010	Of 36 subjects with bilateral absent SSEP N20 responses, 35 (97%) had poor outcome One subject had prolonged high amplitude peripheral SSEP, but bilaterally absent N20 3 d after CA and regained consciousness with normal cognitive functions and reproducible N20 responses One subject had minimally detectable N20 at day 3 and recovered consciousness and normal N20 responses on follow-up
Prospective study with 90 subjects treated with MTH	Oksanen et al,[143] 2009	In multiple logistic regression analysis, age, NSE at 48 h, and increase in NSE levels were predictors of poor outcome Cut-off points with 100% specificity in predicting poor outcome were 33 microg/l for NSE at 48 h and a change of 6.4 microg/l from baseline NSE at 24–48 h
Prospective study with 192 subjects (103 hypothermic, 89 nonhypothermic)	Fugate et al,[144] 2010	The absence of pupillary light responses, corneal reflexes, and an extensor or absent motor response at day 3 after CA remained accurate predictors of poor outcome after therapeutic hypothermia (P<.0001 for all) Myoclonic status epilepticus was invariably associated with death (P = .0002) Malignant EEG patterns and global cerebral edema on head computed tomography were associated with death in both hypothermic and normothermic subjects (P<.001) NSE >33 ng/ml levels measured 1–3 d after CA remained associated with poor outcome (P = .017), but had a false-positive rate of 29.3%
Prospective study with 97 subjects who received MTH compared with 133 maintained in normothermia	Steffen et al,[145] 2010	NSE serum levels were significantly lower under MTH compared with normothermia in univariate analysis Recommended cutoff levels for NSE 72 h after ROSC (>33 ng/l) do not reliably predict poor neurologic outcome in CA subjects treated with MTH
Prospective study with 83 subjects treated with MTH	Wijman et al,[146] 2009	Based on MRI: the percentage of brain volume less than an ADC[a] cutoff of 650–700 $\times$ 10(-6) mm^2/s best differentiated between survivors and subjects who died or remained vegetative The percentage of brain volume less than ADC 400 to 450 $\times$ 10(-6) mm^2/s best distinguished between survivors with good vs impaired neurologic outcome at 6 mo Quantitative DWI at this threshold resulted in a 38% absolute increase in sensitivity for predicting poor outcome compared with the neurologic examination while maintaining 100% specificity

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Study	Investigators	Conclusion
Prospective study with 61 subjects treated with MTH	Rossetti et al,[147] 2012	Serum NSE and EEG findings were strongly correlated (Spearman rho = 0.45; $P<.001$) Median NSE peak values were higher in subjects with unreactive EEG background ($P<.001$) and discontinuous patterns ($P = .001$) All subjects with nonreactive EEG died 5 survivors (3 with good outcome) had NSE levels >33 μg/L
Retrospectively analysis of 227 subjects (128 subjects received MTH)	Fugate et al,[148] 2011	Median day of awakening was day 2 for both groups and most (91% hypothermic and 79% nonhypothermic) awakened within 3 d
Retrospective study with 54 subjects treated with MTH	Crepeau et al,[149] 2013	EEG features correlating with poor outcome included seizures, nonreactive background, and epileptiform discharges

Abbreviations: AAN, American Academy of Neurology; ADC, Apparent Diffusion Coefficient; FPR, false-positive ratio; N20, response recorded at 20 ms during SSEP; PSE, postanoxic status epilepticus.

[a] Measures the magnitude of diffusion of water molecules within cerebral tissue; areas with cytotoxic brain injury are darker on an ADC map compared to healthy tissue.

Data from Refs.[136–149].

control, aiming for a core body temperature around 37°C, for at least the first 48 hours after completion of a standard MTH protocol for VF/VT CA.

FUTURE PERSPECTIVES AND ONGOING TRIALS

MTH after CA is still new and, in the near future, some questions still must be answered, such as the optimal goal temperature, duration of MTH, optimal device for MTH, and better ways of prognosticating outcome for these patients. Trials evaluating intra-arrest MTH (NCT00886184) and out-of-hospital initiation of MTH with cold saline (NCT00391469), as well as for in-hospital arrests (NCT00886184), are currently recruiting subjects. Moreover, a trial that will compare surface cooling to core cooling (NCT00827957) and another that will compare MTH at 36°C versus 33°C (NCT01020916) will try to resolve some of the current questions.

SUMMARY

A growing body of evidence supports MTH as the fifth link of the life chain, with significant decrease in mortality and improvement of neurologic outcomes in CA survivors throughout the last decade. The cardiologist and the intensivist must be acquainted with the indications and technique because MTH is, so far, the only proven neuroprotective therapy for CA survivors. Future research will help better define current questions, such as the optimal timing, target temperature, and duration of MTH.

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