




Targeted Temperature Management for Treatment of Cardiac Arrest

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Abbreviations *IHCA* In-hospital cardiac arrest · *OHCA* Out-of-hospital cardiac arrest · *PEA* Pulseless electrical activity · *VT* Ventricular tachycardia

Abstract

Purpose of review Cardiac arrest is a common condition associated with high mortality and a substantial risk of neurological injury among survivors. Targeted temperature management (TTM) is the only strategy shown to reduce the risk of neurologic disability cardiac arrest patients. In this article, we provide a comprehensive review of TTM with an emphasis on recent trials.

Recent findings After early studies demonstrating the benefit of TTM in out-of-hospital cardiac arrest due to a shockable rhythm, newer studies have extended the benefit of TTM to patients with a nonshockable rhythm and in-hospital cardiac arrest. A target temperature of 33 °C was not superior to 36 °C, suggesting that a lenient targeted temperature may be appropriate especially for patients unable to tolerate lower temperatures. Although early initiation of TTM appears to be beneficial, the benefit of prehospital cooling has not been shown and use of intravenous cold saline in the prehospital setting may be harmful.

Summary There is substantial risk of neurological injury in cardiac arrest survivors who remain comatose. TTM is an effective treatment that can lower the risk of neurological disability in such patients and ideally delivered as part of a comprehensive, goal-directed post-resuscitation management by a multidisciplinary team in a tertiary medical center.

Introduction

More than 650,000 adults experience a cardiac arrest each year in the USA [1]. Although survival for both in-hospital and out-of-hospital cardiac arrests has improved in recent years [2, 3], overall survival continues to remain low. The mean survival for out-of-hospital cardiac arrest (OHCA) is nearly 10% [4], while mean survival for in-hospital arrest (IHCA) is approximately 25% [5, 6]. Among patients who survive, there is a substantial risk of neurological disability and poor quality of life [7]. Efforts for improving resuscitation care quality have largely focused on improving the timeliness and quality of acute resuscitation (e.g.,

bystander cardiopulmonary resuscitation, timely defibrillation). However, there is overwhelming evidence that neurological injury continues to occur in patients even after return of spontaneous circulation. To date, targeted temperature management (TTM) is the only treatment that has been shown to improve survival and reduce the risk of neurological disability in patients surviving cardiac arrest. In this article, we provide a comprehensive review regarding the role of TTM in patients resuscitated from cardiac arrest with a focus on randomized controlled trials of TTM (summarized in Table 1).

Mechanism of neurological injury and prevention with hypothermia

The brain is highly sensitive to hypoxic injury [17]. Within minutes of cessation of cerebral flow, cerebral ATP is depleted, which leads to loss of structural integrity of membranes, disrupts calcium homeostasis, and results in mitochondrial damage. This is followed by release of excitatory neurotransmitters (e.g., glutamate) which can trigger cellular necrosis [18]. If the period of anoxia is sufficiently long, neurological injury may continue to occur even after restoration of circulation likely due to a complex interplay of impaired cerebrovascular autoregulation, cerebral edema, and postischemic neurodegeneration caused by excitotoxicity, calcium overload, oxygen free radical formation, protease activation, and necrotic and apoptotic pathway activation [19–22]. These pathways are enacted within hours and may continue for several days even after achievement of ROSC [23]. Impaired reflow can also cause neuronal damage due to microvascular occlusions caused by intravascular thrombi [24]. Hyperemia is common in the initial reperfusion phase [25], which has been associated with an increase of reactive oxygen species and mitochondrial injury that can further potentiate neuronal injury [26]. The risk of neuronal injury may be further exacerbated by metabolic abnormalities such as hyperglycemia, acid-base disturbances, inflammatory responses, and occurrence of seizures [27, 28].

Lowering central body temperature protects against neuronal injury through several mechanisms which include blunting the inflammatory cascade, decreasing the release of excitatory neurotransmitters, and limiting the intracellular processes that trigger apoptotic cell death [29]. Moreover, hypothermia significantly reduces cerebral metabolism and brain edema, which occurs following anoxic brain injury thereby reducing intracranial pressure and improves oxygen supply-demand mismatch [30].

Historical background

The earliest mention of therapeutic hypothermia (TH) dates back to early 3500 BC when it was used as a strategy to treat head wounds [31]. The first modern

Table 1. Table displays important randomized control trials studying the use of TTM for OHCA and IHCA surviving patients

Authors	Study size	Study design	Year	Study population
The Hypothermia after Cardiac Arrest Study Group [8]	275	RCT	2002	OHCA due to a shockable rhythm
Bernard et al. [9]	77	RCT	2002	OHCA due to a ventricular fibrillation
Bernard et al. (RICH trial) [10]	234	RCT	2010	OHCA due to ventricular fibrillation
Nielsen et al. (TTM trial) [11]	939	RCT	2013	OHCA with a presumed cardiac cause
Kim et al. [12]	1359	RCT	2014	OHCA with either VF or nonshockable rhythms
Deye et al. (ICEREA trial) [13]	400	RCT	2015	OHCA, presumed cardiac cause
Kirkegaard et al. [14]	355	RCT	2017	OHCA, presumed cardiac cause
Lopez et al. (FROST-I trial) [15]	150	RCT	2018	Witnessed OHCA with shockable rhythms
Lascarrou et al. (HYPERION trial) [16]	581	RCT	2019	OHCA and IHCA with nonshockable rhythms

Authors	Intervention vs. control	Primary outcome	Major findings
The Hypothermia after Cardiac Arrest Study Group [8]	TTM 33 °C versus normothermia (37 °C)	Favorable neurologic outcome at 90 days	Significantly lower death rate and higher favorable outcome in hypothermia group
Bernard et al. [9]	TTM at 33 °C versus 37 °C	Survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility	Hypothermia group (33 °C) had higher rates of survival with favorable neurological outcome
Bernard et al. (RICH trial) [10]	Cool IV fluids en route to hospital versus standard of care	Survival to discharge	No significant difference in survival to discharge
Nielsen et al. (TTM trial) [11]	TTM at 33 °C versus 36 °C	All-cause mortality through the end of the trial (mean period of 256 days)	No significant differences between the groups
Kim et al. [12]	Prehospital cooling with 2 L of 4 °C normal saline versus standard care	Survival to hospital discharge and neurologic status at discharge	No improvement in survival or neurological outcomes
Deye et al. (ICEREA trial) [13]	TTM with endovascular versus "basic" external cooling methods	28-day survival with favorable neurologic outcome	No significant difference
Kirkegaard et al. [14]	TTM at 33 °C for 24 h versus 48 h	6-month neurologic outcome	No significant differences between the groups
Lopez et al. (FROST-I trial) [15]	TTM at 32 °C, 33 °C, and 34 °C	Favorable neurologic outcome at 90 days	No significant difference between study groups
Lascarrou et al. (HYPERION trial) [16]	TTM at 33 °C versus normothermia 37.5 °C	Survival with a Cerebral Performance Category (CPC) of 1 or 2 at 90 days	Significantly improved outcomes of hypothermia group versus normothermia group (10.2% vs. 5.7%)

description of use of therapeutic hypothermia for post cardiac arrest care was an uncontrolled case series of 4 patients who suffered in-hospital cardiac arrest [32, 33]. All patients underwent open cardiac massage with prompt restoration of circulation. Cooling was initiated with a water-cooled mattress with a target temperature of 30–33 °C. All patients survived to discharge and 3 (75%) had complete neurological recovery. These observations were subsequently confirmed in a case series of 19 patients who experienced perioperative cardiac arrest, of whom 12 (63%) patients were treated with hypothermia. Hypothermia was associated with a marked increase in survival (50% vs. 14%). Although both these studies were nonrandomized, they suggested that hypothermia may be a promising intervention to reduce the marked neurological injury due to cardiac arrest. Unfortunately, randomized controlled trials to evaluate its efficacy were not conducted until the end of the century, and the clinical use of hypothermia remained uneven during this period.

Early trials

In 2002, two landmark randomized controlled trials—one from Europe and another from Australia—were simultaneously published in the *New England Journal of Medicine* that demonstrated the efficacy of therapeutic hypothermia in improving neurological survival in OHCA patients with an initial shockable rhythm who were comatose after return of spontaneous circulation. The Hypothermia After Cardiac Arrest (HACA) study included 274 patients from 9 centers across Europe and found that hypothermia with a target temperature of 32–34 °C improved survival to discharge with a good neurological outcome (55% vs. 39%; RR, 1.40; 95% CI 1.08–1.81) as well as 6-month mortality (41% vs. 55%; RR, 0.74; 95% CI 0.58–0.95). [8]. Similar findings were also demonstrated in the study by Bernard et al. that included 77 OHCA patients who were successfully resuscitated ventricular fibrillation. Treatment with hypothermia to 33 °C within 2 h of return of spontaneous circulation improved rates of survival to discharge with a good neurological outcome (49% vs. 26%; adjusted odds ratio 5.25; 95% CI 1.47–18.76; $P = 0.011$) [9].

The promising findings of the aforementioned randomized controlled trials led to a rapid incorporation of TH as a Class I recommendation for post-arrest care in the guidelines, especially for OHCA due to a shockable rhythm. However, there were several limitations of both these early trials, which merit further discussion. First, both trials were small in size (274 and 77 patients, respectively). Second, treating physicians were not blinded and protocols for neuroprognostication and withdrawal of care were not standardized, raising concerns that premature withdrawal of care in patients treated with normothermia may have exaggerated the observed benefit. Third, in the HACA study, the mean temperature in the normothermia group was 37.5 °C, which raises the concern whether survival difference was driven in part by increased neurological injury from fever in the control group. Finally, it remained unclear whether the benefit of hypothermia could be extrapolated to patients with nonshockable rhythms or in-hospital cardiac arrest.

Targeted temperature management trials

To address some of the above limitations, the TTM trial, an international multicenter trial, was designed. A total of 950 unconscious adult cardiac arrest survivors

were randomized to a targeted temperature of 33 °C vs. 36 °C [11]. Patients were adults with at least 20 min of cardiopulmonary resuscitation during an OHCA [11] and included patients with both shockable and nonshockable rhythms, except patients with asystole who had an unwitnessed arrest. Ice-cold fluids, ice packs, intravascular temperature management devices, or surface cooling temperature management devices were all used at the discretion of each research site. A key strength of the TTM trial was that neuroprognostication was standardized across both treatment arms. In particular, early withdrawal of care was strongly discouraged for at least 72 h after return of normothermia in both groups. Importantly, neurological assessment was performed by a physician who was blinded to the treatment strategy. At 180 days, all-cause mortality was not significantly different between patients randomized to 33 °C vs. 36 °C (50% vs. 48%; $P = 0.51$). Rates of death or survival with poor neurological function at 6 months was also similar (54% vs. 52%; $P = 0.78$).

The findings of the TTM trial suggests that targeting a lower body temperature of 33 °C does not confer any additional benefit compared with a higher body temperature of 36 °C. However, it is important to emphasize that body temperature was actively managed in both treatment arms in the TTM trial using similar cooling techniques and the study did not compare “no cooling” with active cooling. However, real world data from the national registries found that immediately following the publication of the TTM trial, there was an abrupt decrease in clinical use of TTM from 52.5% in the last quarter of 2013 to 46.4% in the first quarter of 2014, raising concerns that the findings of the TTM may have been misinterpreted in clinical practice [34].

In contrast to the TTM trial, FROST-I was a randomized controlled trial of three different target temperatures—32 °C, 33 °C, or 34 °C—and found no difference in the primary end point of survival with good neurological outcomes at 90 days in OHCA patients with a shockable rhythm [35]. However, it is difficult to draw meaningful conclusions as the trial only enrolled 150 patients and was likely underpowered. Taken together, these trials suggest that TTM using a lower temperature threshold is not superior to a more lenient temperature. Moreover, a target temperature of 36 °C has many practical advantages compared with more stringent hypothermia in post-arrest patients who are often hypotensive and may not tolerate lower body temperatures.

Nonshockable rhythms

Until recently, evidence from RCTs for cardiac arrest due to a nonshockable rhythm remained limited. While the HACA and the Bernard study excluded patients with an initial nonshockable rhythm, the representation of nonshockable OHCA in the TTM trial was only 20%. And yet, these rhythms represent a majority of cardiac arrest patients—> 75% of OHCA and > 80% of in IHCA patients in the USA—and have an initial rhythm of asystole and pulseless electrical activity (PEA). The HYPERION trial studied the efficacy of TTM with targeted temperature 33 °C versus targeted normothermia (37 °C) in comatose patients admitted to an ICU after a cardiac arrest due to an initial nonshockable rhythm. The study included patients with OHCA and IHCA. The incidence of the primary end point of survival with a favorable neurological outcome at 90 days was significantly higher in the hypothermia group (10.2%) compared with 5.7% in the targeted normothermia

group (95% [CI], 0.1 to 8.9, $P = 0.04$) [36], but there was no significant difference in overall mortality between groups (81.3% vs. 83.2%). Although this is the first RCT to demonstrate a benefit of TTM for nonshockable cardiac arrests, concerns were raised regarding the wide confidence interval of the overall effect estimate such that the occurrence of 1 additional event in the control arm would have resulted in the loss of statistical significance (i.e., a fragility index of the trial was 1) [35]. Moreover, there were systematic differences between the treatment and control arms with regard to neuroprognostication, which may have impacted the incidence of the primary endpoint. Current guidelines already recommend use of TTM as a Class I indication for patients with a nonshockable rhythm (level of evidence, C) [36], which is likely to remain unchanged in light of the HYPERION trial.

In-hospital cardiac arrest

There are a number of reasons why the efficacy of TTM may differ in IHCA patients, which precludes a direct extrapolation of TTM studies focused on OHCA patients to management of IHCA. First, response times in patients who arrest in a hospital are much shorter compared with OHCA, thus limiting the period of “no-flow” to the brain and other vital organs. Moreover, resuscitation in hospitalized patients is performed by highly trained medical professionals, and the risk of neurological injury post arrest may be smaller. However, hospitalized patients are also sicker at baseline, have more comorbidities, and have a higher incidence of asystole or PEA, which may increase the risk of death and neurological injury. Therefore, understanding the benefit of TTM in patients with IHCA is critically important.

To date, the only dedicated randomized controlled trial that evaluated the efficacy of TTM was conducted in children [37], which found no improvement in survival with the use of TTM. Among adults, until recently, the best evidence came from an observational study that did not find TTM to be associated with improved survival and neurological outcomes in IHCA patients [38]. Although the study used a rigorous methodology, the potential for confounding due to indication cannot be excluded from an observational study. In the aforementioned HYPERION trial, the overall benefit of TTM on improving neurological survival in patients with a nonshockable rhythm was consistent in the 25% of the cohort that had IHCA. In fact, the magnitude of benefit of TTM was larger in the IHCA group compared with OHCA (absolute difference in survival in favor of TTM: IHCA: 10.6% vs. OHCA: 2.4%). However, the interaction was not significant likely due to the small size of the trial [36].

Methods of cooling

A number of methods for cooling have been employed in prior studies. These include infusion of cold intravenous saline, application of external gels pads applied on the skin that circulate chilled water, or an intravascular device that circulates cold saline through the balloons of a catheter placed in the inferior vena cava that cools the blood as it passes over the catheter. The infusion of cold intravenous saline for initiation of cooling has typically been in the prehospital setting and is no longer recommended as discussed in the next section [12]. The ICEREA randomized trial compared surface cooling with an intravascular

cooling device manufactured by ZOLL in patients presenting after an OHCA [13]. Overall, there was no significant difference in the incidence of survival without major neurological damage at 28 days (OR, 1.41; CI, 0.93–2.16; $P = 0.107$). However, there was a trend towards improvement of neurological outcome at day 90 in the endovascular group ($P = 0.07$). Moreover, the overall time ICU nurses spent monitoring the cooling system was significantly reduced with the intravascular catheter, which could be used for other aspects of clinical management of post-arrest patients. Similar findings were also demonstrated in the post hoc analysis of the TTM, which also found that when compared with surface cooling methods, cooling with an intravascular catheter was associated with better control of target temperature with fewer deviations but was not associated with survival or adverse events [39].

Timing of cooling initiation

Several observational studies have examined the association of timing of attainment of target temperature with survival outcomes and showed inconsistent results [40–42]. In a recent post hoc analyses of the Continuous Chest Compression trial, investigators found that early attainment of target temperature was associated with improved survival (OR: 1.56; 95% CI: 1.02–2.38). Accordingly, multiple RCTs have been conducted to confirm this hypothesis. The largest of these studies was conducted by Kim et al. who randomized 1359 patients to receive prehospital infusion of cold intravenous saline (4 °C) by paramedics versus hypothermia induction upon arrival to the hospital [12]. Although patients who received infusion of cold saline achieved target temperature a median of 1 h earlier compared with the control group, there were no significant differences in survival to discharge or neurologic outcomes. Further, the incidence of rearrest in the field, pulmonary edema, and use of diuretics was higher in the intervention arm. These findings were consistent with that of the smaller RCTs that also did not find any improvement in clinical outcomes with prehospital initiation of cold IV fluids [10, 43]. Accordingly, the current AHA guidelines recommend against prehospital initiation of cooling with rapid infusion of cold intravenous saline.

It is possible that the lack of benefit in the above trials was due to the deleterious hemodynamic effects of cold saline itself and may have counterbalanced a benefit of early attainment of target temperature. The concept of achieving rapid prehospital cooling using an intranasal device that delivers a mixture of oxygen and a liquid coolant to the nasopharynx was investigated in the PRINCESS trial in patients with bystander witnessed OHCA. [44]. Although the median time to reach a target temperature less than 34 °C was shorter with transnasal cooling device, survival with a favorable neurologic outcome did not differ significantly between groups (16.6% vs. 13.5%; $P = 0.25$).

Thus, to date, evidence from RCTs to support prehospital initiation of cooling to achieve target temperature more rapidly is lacking.

Duration of cooling

In a majority of studies, TTM was implemented for 24 h of TTM, and it remains unknown whether a longer duration of cooling could benefit cardiac arrest

survivors. A recent randomized control trial compared whether TTM at 33 °C for 48 h compared with the standard of 24 h improved survival with a good neurological outcome at 6 months in patients with OHCA [44]. Overall, the trial found no significant difference in the primary outcome between groups (69% vs. 64%; $P = .33$). Mortality was also not significantly different between groups. There was a higher incidence of adverse events in the 48 h arm compared with the 24 h arm ($P = 0.03$), and patients had longer ICU stays (151 vs. 117 h; $P < 0.001$). Based on these findings, a strategy of cooling beyond 24 h does not improve survival outcomes and may be associated with an increased risk of adverse events and ICU length of stay. The ICECAP trial, which is investigating whether TTM for a shorter duration (e.g., 12 h) leads to better outcomes, is currently underway [45].

Current guidelines

Current American Heart Association guidelines recommend TTM with goal temperature 32–36 °C (Class I, B-R) for at least 24 h (Class IIa, C-EO) for comatose OHCA victims having survived VT/VF (Class I, B-R) and upgraded the recommendation to survivors of IHCA and OHCA with nonshockable rhythms (Class I, C-EO) [36, 46].

Practical considerations

Multiple clinical trials during the last two decades have confirmed that TTM is beneficial for treatment of cardiac arrest patients who remain comatose following achievement of ROSC. While the definition of comatose has varied across studies, we suggest considering patients to be eligible for TTM if they do not respond meaningfully to verbal commands. Contraindications for TTM include presence of intracranial hemorrhage due to concerns of worsening coagulopathy with cooling. In addition, patients with marked hemodynamic compromise or severe sepsis may also be considered ineligible as cooling can exacerbate hypotension and the reduce ability to fight infections.

At our institution, all patients undergo a computed tomography of the brain to rule out hemorrhage. Following placement of an intravenous cooling catheter, TTM is initiated with the goal of achieving target temperature over the course of 3–4 h. The choice of target temperature (33 °C vs. 36 °C) is based on patient factors. Once a target temperature is attained, the temperature is maintained for a period of 24 h, and the goal is to minimize temperature fluctuations. Shivering is controlled with the use of neuromuscular blocking agents especially if a target temperature of 33 °C is chosen. In addition, sedatives (e.g., lorazepam) and analgesics (e.g., fentanyl) are used for ensuring adequate sedation and comfort. All patients treated with TTM are monitored on telemetry and have periodic 12-lead electrocardiograms due the risk of QT prolongation with hypothermia [47] and possible heightened risk of VT/VF [48].

Treatment with TTM should occur in the setting of comprehensive post-resuscitation care in an intensive care unit with a multidisciplinary team with broad expertise in critical care, cardiology, neurology, and infectious disease, among others. Patients require close monitoring and optimization of hemodynamics, oxygenation, ventilation, metabolic parameters, and neurological

function. Hypothermia often leads to hypotension, and patients who are hemodynamically unstable on multiple pressors may not tolerate hypothermia. Bradycardia can also occur especially at a lower target temperature and usually does not require treatment unless associated with hypotension. We target a mean arterial pressure of >75–80 mmHg to ensure adequate cerebral perfusion. Placement of a Swan Ganz catheter for invasive hemodynamic assessment to guide therapy and mechanical circulatory support devices may be considered in individual patients. All patients treated with TTM are on a ventilator and require optimization of arterial oxygenation with strict avoidance of both hypoxia and hyperoxia—the latter has been associated with increase in risk of neurological injury. Likewise, appropriate ventilation to ensure normocarbia is also important. Metabolic parameters such as glucose, electrolytes, lactate, and serum pH also need to be closely monitored. Seizures may occur during the post-resuscitation phase, which can further exacerbate neurological injury, but may not be recognized due to use of sedatives and neuromuscular blocking agents. Neurological expertise is critical for management of post-arrest patients including consideration of continuous electroencephalography (EEG) monitoring to identify subclinical seizures. Infections are common as hypothermia can compromise the body's ability to fight infections. Therefore, there is a low threshold to start empiric antibiotics in patients treated with TTM.

After 24 h of TTM, passive rewarming may be initiated with a goal rate of 0.25 °C per hour until the patient reaches a normal body temperature. Once normothermia is achieved, efforts to avoid fever should be continued using pharmacological or nonpharmacological means. Neuroprognostication should be withheld for at least 72 h (preferably longer) to ensure that the sedative effects of medications used during the cooling phase have abated and adequate time for neurological recovery to occur. Close communication with patient's family is also important to address questions and manage expectations.

Over the past decade, many centers have developed highly specialized teams that deliver high-quality post-resuscitation care, and published data suggest that care from such teams may improve cardiac arrest survival [49]. It is also important to emphasize that post-resuscitation care is resource-intensive and the expertise may be available only at a few medical centers. Accordingly, professional societies have recommended that post-resuscitation care be regionalized in centers of excellence [50]. Based on recent evidence that has found large variation in post-resuscitation survival across US hospitals [51], there is an urgent need to identify best practices for high-quality post-resuscitation care.

Future directions

TTM is a relatively safe and effective strategy to confer neuroprotection in patients with a cardiac arrest who remain comatose after achievement of ROSC. After the initial trials demonstrating benefit in shockable OHCA, newer evidence has shown efficacy of TTM in nonshockable rhythms. Despite a strong recommendation from current guidelines for IHCA patients, use of TTM in IHCA patients remains variable likely due to persistent uncertainty regarding its benefit. While the recently published HYPERION trial found a similar benefit of TTM in both IHCA and OHCA, limitations of the study would support need for additional evidence of TTM in IHCA patients. Ongoing trials would also

address whether TTM for a shorter duration (12 h) vs. 24 h would provide a similar benefit.

Summary

TTM is a relatively safe and effective strategy that can improve neurological outcomes in patients who remain comatose after achieving ROSC from a cardiac arrest. Following the initial trials that demonstrated its efficacy in shockable OHCA, newer evidence has emerged regarding its efficacy in OHCA due to a nonshockable rhythm and possibly adult IHCA also. Current evidence supports a broad range of TTM from 33 °C to 36 °C and should be maintained for 24 h. Although TTM should be initiated as early as possible, prehospital initiation of cooling has not been shown to improve survival outcomes. Finally, TTM should be administered in the context of high-quality post-resuscitation care guided by a multidisciplinary team with sufficient expertise and experience in intensive management of these critically ill patients.

Compliance with Ethical Standards

Conflict of Interest

T. P. Rasmussen declares that he has no conflict of interest. T.C. Bullis declares that he has no conflict of interest. S. Girotra declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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