

REVIEW

Advances in Cardiopulmonary Resuscitation: Hypothermia versus Normothermia in Survivors of Out-of-Hospital Cardiac Arrest*

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ABBREVIATIONS

CPR = cardiopulmonary resuscitation
ICU = intensive care unit
MTH = mild therapeutic hypothermia
OOHCA = out-of-hospital cardiac arrest
PCI = percutaneous coronary intervention
ROSC = recovery of spontaneous circulation
TTM = targeted temperature management (trial)
VF = ventricular fibrillation

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ABSTRACT

Despite high levels of public awareness, the widespread use of automatic external defibrillators and the ongoing education of doctors in advanced life support seminars, the percentage of victims who arrive at the hospital after out-of-hospital cardiac arrest (OHCA) is small. Of those who reach the hospital, the main cause of death in two thirds of the cases is persistent neurologic disability. The only therapy that has so far seemed to positively affect the neurological outcome of patients after cardiac arrest is mild therapeutic hypothermia (MTH). However, the application of MTH is also known to be associated with a number of potential adverse effects, and recent trials report on an increasing rate of stent thrombosis. If the results are confirmed, safe levels of temperature regulation would need to be defined. Recently, a study was published that takes a critical approach to MTH. Hypothermia was compared to targeted temperature management near normothermia. After the end of the study period, there was no statistically significant difference regarding the survival to discharge and the neurological prognosis at 180 days. The authors stress that in both groups the temperature was actively controlled to avoid temperatures over 37 degrees Celsius. There followed few more publications with similar findings. The most important message from these trial is that even if the aggressive regulation of temperature with the form of hypothermia may seem unjustified, this does not mean that fever should be left untreated. Normothermia is a goal that can be achieved rather easily and can also save the lives of many patients.

INTRODUCTION

Cardiac arrest is a major health problem in Western societies. Every year there are approximately 450,000 cardiac arrest victims in the USA¹ and 325,000 in Europe.² Despite high levels of public awareness, the widespread use of automatic external defibrillators and the ongoing education of physicians in advanced life support seminars, the percentage of victims who arrive at the hospital is small. The main cause of death in two thirds of cases that are admitted to hospital is persistent neurologic disability.³

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In recent years it has been recognized that the treatment of victims of cardiac arrest does not end after the return of spontaneous circulation (ROSC), because post-cardiac arrest syndrome, a complex metabolic and pathophysiological process that results from the ischemia-reperfusion injury, demands a multidisciplinary approach through well-organized bundles of care.⁴ One of the cardinal manifestations of the syndrome is persistent brain damage, with mild therapeutic hypothermia (MTH) being the main form of treatment.

POST CARDIAC ARREST SYNDROME

Post-cardiac arrest syndrome is the result of pathophysiological mechanisms that follow the cessation of circulation for a certain amount of time and subsequent reperfusion. The first observations of this clinical syndrome were made by Negovsky who named it "postresuscitation disease".⁵ Today, post-cardiac arrest syndrome is defined as the unique and complex combination of pathophysiological processes including: 1) brain dysfunction 2) myocardial dysfunction 3) systemic ischemia, and 4) unresolved precipitating pathology.⁶ The most significant aspect of this syndrome and that with the most clinical implications is brain dysfunction.

The pathophysiology of brain dysfunction is not completely understood. In animal models, even relatively small periods of global ischemia are enough to cause degeneration in certain areas of the brain, such as the hippocampus, cerebellum, corpus striatum and the cerebral hemispheres.⁷ Bottiger et al showed that in mice, five minutes of reversible ischemia was enough time to observe neuronal DNA fragmentation and the expression of particular genes that lead to apoptosis of neural cells of the hippocampus.⁸

Today it is recognized that disorders of calcium homeostasis, free radicals, brain edema, the no-reflow phenomenon and inflammation, all play an important role in the generation of neural injury. In short, after a period of ischemia lasting at least five minutes, there is ATP depletion resulting in neuronal membrane depolarization, opening of calcium and sodium channels and the influx of calcium ions into the cell. This process triggers the secretion of excitatory neurotransmitters as well as kinase/phosphatase activation resulting in the expression of genes that induce apoptosis. The production of free radicals as well as the inflammatory cascade that begins a few minutes after reperfusion and develops for hours or days, contribute to oxidative stress, lipolysis, proteolysis and eventually lead to cellular destruction. After inducing reversible ischemia in mice, Hosman et al observed that in all specimens there were areas of no-reflow positively correlated to the duration of ischemia. Low-flow can also be caused by the compression of the small vessels from brain edema, as well as by microthrombosis.

MILD THERAPEUTIC HYPOTHERMIA

The only therapy that has so far appeared to positively affect the neurological outcome of patients after cardiac arrest is mild therapeutic hypothermia (MTH). Preliminary studies on animals have shown that hypothermia slows the biochemical cascade caused by the abrupt cessation and return of cerebral blood flow. The effects of hypothermia go beyond the traditional theory of decreased brain metabolism. Research has proven that hypothermia attenuates the disorders of calcium homeostasis and the resulting neuroexcitatory cell injury.⁹ At the same time, hypothermia reduces free radical production and lessens apoptosis. Hypothermia also attenuates the inflammatory reaction and might have beneficial effects on preserving the integrity of the blood brain barrier.

The first two landmark studies that applied MTH to humans were published in 2002.^{10,11} The first study was conducted in Australia and enrolled 77 patients with out-of-hospital cardiac arrest.¹⁰ In order to be eligible for the study, patients had to have ventricular fibrillation (VF). Patients were assigned to the MTH group if they were admitted on odd-numbered days, and to the control group if they were admitted on even-numbered days. Of the 43 patients in the MTH group, 21 were discharged with a good neurological outcome, compared to only 9 of the 35 control patients. The second study was a multicenter study conducted in Europe, which also exclusively enrolled patients with VF after out-of-hospital cardiac arrest.¹¹ Randomly assigned patients received MTH of 32 - 34 degrees Celsius for 24 hours, compared to the control group. Seventy-five of the 136 (51%) patients receiving MTH had a good neurological outcome, in contrast to 54 of 137 (39%) of the control group. That study also found that people in the MTH group had an increased rate of survival at 6 months. The authors concluded that for every 6 patients that receive MTH, a life is saved.

The results were confirmed by a meta-analysis that included 5 studies with 481 patients in total.¹² Although different cooling methods were used in these studies, the results were consistent in demonstrating that MTH increases survival with a good neurological prognosis. The authors concluded that patients in the hypothermia group were more likely to reach a satisfactory neurological outcome, defined as cerebral performance category (CPC) 1 or 2 during hospital stay and were more likely to survive to hospital discharge compared to standard post-resuscitation care.

However, MTH is only one aspect of a broader supportive post-resuscitation strategy. All victims of cardiac arrest should be admitted to an intensive care unit (ICU) because they will need mechanical ventilation, hemodynamic support, continuous hemodynamic monitoring, as well as reliable core body temperature measurements. Before the induction of MTH, patients should be sufficiently sedated. Analgesia prevents patient discomfort and paralysis is used to avoid the

detrimental effects of shivering that increases metabolism, as well as heart rate and induces patient ventilator dyssynchrony. There are different methods for performing MTH, which can be categorized as invasive or non-invasive. One of the simplest approaches is ice packs, which offer a slow cooling rate of 0.9 degrees Celsius per hour. There are also cooling blankets, as well as more sophisticated methods of non-invasive cooling, such as nasopharyngeal evaporative cooling. As for the invasive methods, the simplest technique is the infusion of cold fluids. There is also the insertion of specialized intravascular cooling catheters. Based on the studies that have been conducted so far, the outcome is similar irrespective of the cooling method.¹³

The application of MTH is also known to be associated with a number of potential adverse effects. One study which was conducted in 22 hospitals and enrolled 765 MTH patients found that pneumonia occurred in 48% of patients, electrolyte disturbances in 5-37%, seizures in 24% and arrhythmias (mainly bradyarrhythmias) in 7- 14%. Through multivariate analysis, hyperglycemia and seizures were found to be the major causes of mortality in these patients.¹⁴ MTH is also associated with thrombocytopenia and coagulation disorders. The first studies examining the feasibility of MTH with percutaneous coronary intervention (PCI) procedures focused on bleeding diathesis which was not statistically significant.¹⁵ A recent study compared the pharmacodynamics of the newest platelet adenosine diphosphate (ADP)-P2Y12 receptor inhibiting drugs in the setting of cardiac arrest, and found that victims of cardiac arrest had significantly increased platelet reactivity, indicating a worse response to dual antiplatelet therapy.¹⁶ Another recent study reports on the rate of stent thrombosis in the setting of PCI after cardiac arrest. They retrospectively examined all patients who were admitted with acute myocardial infarction and received PCI in their institution. Repeated angiography was not performed routinely, but only in the case of clinical instability. Six out of 55 patients (10.9%) in the hypothermia group had a definite stent thrombosis, compared to three out of 153 (2.0%) p=0.01, in the control group.¹⁷ The authors concluded that despite the fact that cardiac arrest victims were not adequately premedicated with dual antiplatelet therapy, MTH could also be implicated.

MTH is considered a standard practice according to resuscitation guidelines for comatose victims of out-of-hospital cardiac arrest presenting with a shockable rhythm.¹⁸ Although MTH has been proven to have beneficial effects, there are still questions regarding its applications. First, even though the guidelines recommend the application of MTH to comatose victims of cardiac arrest with non-shockable rhythms, the benefits of this practice have not been confirmed by research. Second, although most centers follow the protocols set by the landmark trials, basic components of MTH are not yet well-known, such as the onset and the rate of cooling, the duration of hypothermia, and the re-warming rate. Third, as was mentioned before, myocardial dysfunction is a basic component

of post-cardiac arrest syndrome. The application of coronary angiography and PCI is becoming common practice as evidence grows. The initial studies that combined PCI with MTH showed that hemorrhagic complications were not statistically significant. If the results of the recent trials regarding stent thrombosis are confirmed, there would be major problems with combining these two beneficial forms of treatment or at the very least, safe levels of temperature regulation would need to be defined.

**TARGETED TEMPERATURE
MANAGEMENT IN SURVIVORS
OF OUT-OF-HOSPITAL CARDIAC
ARREST (OOHCA)**

Recently, the Targeted Temperature Management (TTM) trial was published that takes a critical approach to MTH.¹⁹ The authors based their hypothesis on the fact that there are no widely proven criteria for the absolute lowest temperature and on the fact that former studies had small samples. The study was conducted in 36 ICUs in Europe and Australia and its aim was to compare hypothermia to targeted temperature management near normothermia.¹⁹

The primary outcome of the study was survival to discharge and the secondary outcome was a favorable neurological prognosis at 6 months. Victims of out-of-hospital cardiac arrest (OOHCA) without obvious extracardiac cause over 18 years old who remained comatose after sustained ROSC were included in the study, irrespective of the type of the first recorded rhythm. The exclusion criteria for the study were refractory shock, obvious or suspected extracardiac shock, pregnancy, and morbidity that precluded survival at 180 days. The patients were randomly assigned to discrete groups. In the hypothermia group, patients received hypothermia as soon as possible and remained at 33 degrees Celsius for 28 hours, followed by a gradual re-warming period of 8 hours. In the normothermia group, patients received standard care, but their temperature was actively maintained within the normal range. After the 36-hour treatment, both groups received standard care with special care taken to avoid pyrexia. At 72 hours, blinded external physicians performed neurological prognostication in order to withdraw life-sustaining therapy in cases of brain death.

After the end of the study period, the authors concluded that there was no statistically significant difference regarding the survival to discharge and the neurological prognosis at 180 days. Survival to discharge was 50% in the hypothermia group (238 of 473 patients) versus 52% in the normothermia group (241 of 466 patients), p=0.51 and survival with a good neurological prognosis at 180 days was 46% (218 of 469 patients) versus 48% (222 of 464 patients), p=0.78 respectively.¹⁹ A subgroup analysis was conducted to test the effects of hy-

pothemia among 6 different categories which were: gender, age over 65, presence of a shockable rhythm, time to ROSC over 25 minutes, and the presence of shock at admission. The results were consistent among the 6 specified subgroups and the authors stress that hypothermia did not prove to be more beneficial than normothermia in any of the subgroups. Other important findings of the study were that there was no statistical significance in the number of patients with shivering, nor in the number of hours with fever or temperature above 37.5 degrees Celsius.

In another more recent randomized trial, 1359 adults with prehospital cardiac arrest with (n=583) and without VF (n=776), were assigned to standard care with or without prehospital cooling, following ROSC.²⁰ Most patients resuscitated from VF and admitted to the hospital received hospital cooling regardless of their randomization. Survival to hospital discharge was similar among the intervention and control groups among patients with VF (62.7% vs 64.3%; P=NS) and among patients without VF (19.2% vs 16.3%; P=NS). Neurological status was also similar for patients with VF (57.5% of cases had full recovery or mild impairment vs 61.9% of controls; P=NS) or those without VF (14.4% of cases vs 13.4% of controls; P=NS). Overall, the intervention group experienced re-arrest in the field more than the control group (26% vs 21%; P=0.008). The authors concluded that although use of prehospital cooling reduced core temperature by hospital arrival and reduced the time to reach a temperature of 34°C, it did not improve survival or neurological status among patients resuscitated from prehospital VF or those without VF.

Thus, these recent trials have cast doubts on the benefits

and have raised questions about timing and temperature goals of induced hypothermia (Table 1). In another follow-up study of the latter trial, the association of prehospital hypothermia with neurological function at least 3 months after cardiac arrest and survival 1 year after cardiac arrest was assessed in 508 individuals who were discharged alive.²¹ Overall, the neurological status at 3 months, and 1-year survival (87% and 84%) of the two treatment groups were similar (P=NS). One-year survival was excellent for those with good neurological status at discharge, but very poor for those with impaired neurological status. The authors concluded that besides excellent survival, patients who had good neurological function at discharge continued to have good function at least 3 months after the event.

With regards to the timing of cooling, another randomized trial indicated that among 245 patients (123 having intra-arrest MTH and 122 in-hospital cooling) with OOHCA, the rate of patients admitted alive to hospital was not different between groups (33% vs 30%).²² Levels of biomarkers of neurological injury and inflammation were also similar and there was no difference in survival and cerebral performance found at 1 month. The authors concluded that early (intra-arrest) MTH did not affect biological markers of inflammation or brain damage or clinical outcome.

Thus, the traditional concept of performing hypothermia on comatose patients with OOHCA may need to be re-examined. One possible explanation for the discordant results may relate to the fact that in previous studies, the temperature in the control group was not actively controlled and episodes of fever and hyperpyrexia could be the reason for the striking difference in neurological outcome and survival rates. However,

TABLE 1. Randomized studies comparing therapeutic hypothermia versus normothermia in cardiac arrest victims

Study, year	Patients (MTH/NT)	VT/VF	Initiation of cooling	MTH T°/Time to target cooling	Favorable neurologic outcome (RRR)	Death (RRR)	Better (MTH vs NT)
HACA, 2002 ¹¹	275 (137/138)	265	105 min	33°C/480 min	55% vs 39% (40%)*	41% vs 55% (26%)*	MTH
Australian, 2002 ¹⁰	77 (34 / 33)	77	<5 min	33°C/120 min	49% vs 26% (44%)*	51% vs 68% (25%)	MTH
TTM, 2013 ¹⁹	939 (473/466)	752	130 min	33°C/600 min	47% vs 48%	50% vs 48%	Similar
Seattle, 2014 ²⁰	1364 (prehospital cooling)	583	<5-30 min	32°C-34°C/252-330 min	58% vs 62% (VF) 14% vs 13% (no VF)	37% vs 36% (VF) 81% vs 84% (no VF)	Similar
THAPCA-OH, 2015 ²⁴	295 (155/140)	23	354 min	33°C/156 min	20% vs 12%	63% vs 72%	Similar

HACA = hypothermia after cardiac arrest (study); MTH = mild therapeutic hypothermia; NT = normothermia; RRR = relative risk reduction; TTM = targeted temperature management (trial); VF = ventricular fibrillation; VT =ventricular tachycardia

*P <0.05

the latter hypothesis is refuted by a retrospective study of chart review comparing cardiac arrest victims with sustained ROSC who did not receive MTH but never exceeded 37.5°C during the 36 hours postcardiac arrest with patients who received MTH.²³ The study showed significantly more patients in the hypothermia group had a favorable neurological outcome (hypothermia: 256 of 467 or 55% vs normothermia: 69 of 165 or 42%) and survived for >180 days (hypothermia: 315 of 467 or 67% vs normothermia: 79 of 165 or 48%). The authors concluded that MTH was associated with significantly improved neurological outcome and 180-day survival compared to spontaneous normothermia in cardiac-arrest patients.

Finally, the results of the TTM trial by Nielsen et al¹⁹ have just been recently corroborated in the pediatric population by the findings of the Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) trial,²⁴ which compared the efficacy of therapeutic hypothermia (target temperature, 33°C) with that of therapeutic normothermia (target temperature, 36.8°C). Among 260 cardiac arrest victims, there was no significant difference in the primary outcome between the hypothermia group and the normothermia group (20% vs 12%; relative likelihood, 1.54; P=NS). The change in the neurologic status score from baseline to 12 months was not significantly different and 1-year survival was similar (38% in the hypothermia group vs 29% in the normothermia group; relative likelihood, 1.29; P=NS). The authors concluded that in comatose children who survived OOHCA, therapeutic hypothermia and normothermia conferred similar benefit in survival with a good functional outcome at 1 year.

A recent special report published in *Circulation* and addressing this critical issue concluded that for the time being “we should continue to cool most cardiac arrest patients to 32 - 33°C, pending the results of further studies which should compare different temperature levels (32°C, 34°C, and 36°C) and determine optimal duration (24, 48, or 72 hours) of MTH, always with a slow (0.1 to 0.25°C/hour) rewarming rate”, but admitted that “the results of the TTM trial clearly suggest that in some cardiac arrest patients strict fever control is sufficient to mitigate hypoxic injury”.²⁵

ASSOCIATED FACTORS IN IMPLEMENTING THERAPEUTIC HYPOTHERMIA

Despite the initial positive studies and guideline recommendations, MTH utilization appears low in the real-world practice,²⁶ probably due to several practical issues with its application. According to a Bostonian study, few hospitals appeared to perform MTH (47/419, 11.2%), but implementation appeared increasing over the study period (2006 – 2008).²⁶ Even in those cohorts in whom MTH is applied, several factors have been reported to predict outcome. According with a

retrospective analysis of 170 consecutive patients treated with MTH, those 77 (45.2%) who survived to hospital discharge had a significantly lower maximum partial pressure of arterial oxygen (198 mmHg) measured in the first 24 hours following cardiac arrest compared to non-survivors (254 mmHg, $p = 0.022$).²⁷ Multivariate analysis including age, time to ROSC, presence of shock, bystander CPR, and initial rhythm revealed that *hyperoxia* with higher levels of the partial pressure of arterial oxygen was significantly associated with increased in-hospital mortality (odds ratio 1.439, $p = 0.034$) and poor neurologic status at hospital discharge (odds ratio 1.485, $p = 0.033$).²⁷ According with a retrospective analysis performed on 196 consecutive cardiac arrest survivors, presence of *severe acidemia* at initiation of MTH in shockable (but not in non-shockable) patients was significantly associated with poor neurological outcomes.²⁸

Patient admission temperature and use of cooling was assessed in a prospective cohort of 177 comatose cardiac arrest patients treated with MTH (32–34°C, 24 hours) (median age 61 years; median time to ROSC 25 min). *Lower spontaneous admission body temperature* and *longer time of passive rewarming* were associated with in-hospital mortality after cardiac arrest and MTH. The authors concluded that impaired thermoregulation may be an important physiologic determinant of post-resuscitation disease and cardiac arrest prognosis.²⁹

According with a retrospective chart review of 194 consecutive MTH-treated comatose post-cardiac arrest syndrome patients, time to awakening after resuscitation was highly variable and often longer than 3 days. *Earlier awakening* was associated with better neurologic status at hospital discharge.³⁰ The role of target temperature was assessed in 36 cardiac arrest victims (26 shockable rhythm, 10 asystole), who were randomly assigned to 32°C ($n=18$) or 34°C ($n=18$), maintained during 24 hours followed by 12 to 24 hours of controlled rewarming. Eight of 18 patients in the 32°C group (44.4%) had better outcome compared with 2 of 18 in the 34°C group (11.1%) (log-rank $P=0.12$). All patients whose initial rhythm was asystole died before 6 months in both groups. Eight of 13 patients with initial shockable rhythm assigned to 32°C (61.5%) were alive free from severe dependence at 6 months compared with 2 of 13 (15.4%) assigned to 34°C (log-rank $P=0.029$). The authors concluded that a *lower cooling level* may be associated with a better outcome in patients surviving OOHCA secondary to a shockable rhythm.³¹

In a prospective, randomized controlled trial, 234 cardiac arrest victims with an initial cardiac rhythm of VF were assigned to either prehospital cooling by paramedics with a rapid infusion of 2 L of ice-cold lactated Ringer’s solution ($n=118$) or cooling after hospital admission ($n=116$).³² In the paramedic-cooled group, 47.5% patients had a favorable outcome at hospital discharge compared with 52.6% in the hospital-cooled group (risk ratio 0.90, $P=0.43$). The authors concluded that paramedic cooling with a rapid infusion of

large-volume, ice-cold intravenous fluid decreased core temperature at hospital arrival but was not shown to improve outcome at hospital discharge compared with cooling commenced in the hospital.³²

In another study of 80 OOHCA patients, hypothermia was induced after randomization by either invasive or noninvasive surface cooling at 33°C core body temperature for 24 hours followed by active rewarming.³³ Neuron-specific enolase (NSE) levels used as a surrogate parameter for brain damage at 72 hours did not differ significantly between the 2 groups. Neurological and clinical outcome was similar in both groups. Target temperature of 33.0°C was maintained more stable in the invasive group (33 vs 32.7 °C, $p < 0.001$). Bleeding complications were more frequent with invasive cooling (43.6% vs 17.9%; $p = 0.03$). The authors concluded that invasive cooling has advantages with respect to temperature management over surface cooling, however, it did not result in improved outcome. Bleeding complications were more frequent with invasive cooling.³³ In a similar study, 194 witnessed cardiac arrest patients were randomized to intra-arrest cooling with a RhinoChill device ($n=93$) vs standard care ($n=101$).³⁴ A total of 18 device-related adverse events were reported. Time to target temperature of 34°C was shorter in the treatment group. There were no differences in rates of ROSC between the groups (38% vs 43%), in overall survival of those admitted alive (44% vs 31%), or in neurologically intact survival to discharge (34% vs 21%). The authors concluded that prehospital intra-arrest transnasal cooling is safe and feasible and is associated with a significant improvement in the time intervals required to cool patients but no difference in outcomes.³⁴

CONCLUSION

In conclusion, mild therapeutic hypothermia (MTH) is today a well-accepted treatment for victims of cardiac arrest, especially for those presenting with VF. As the amount of research grows, more concerns are arising about the absolute level of temperature control. The most important message from recent trials is that even if the aggressive regulation of temperature with the form of hypothermia may seem unjustified, this does not mean that fever should be left untreated, hence prevention of hyperthermia should be actively pursued. Normothermia is a goal that can be achieved rather easily and can also save the lives and brains of many patients. Finally, the apparent “failure” of MTH in recent trials to confer an improved outcome compared to normothermia, might also be related to the recent advances in all other aspects of life support, which make it even harder to prove or disprove the beneficial effect of a single intervention in a clinical trial (<http://blogs.nejm.org/now/index.php/the-cold-truth-rethinking-temperature-management-after-cardiac-arrest/2013/12/04/>).

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