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Temperature management for out of hospital cardiac arrest- what do the Targeted Temperature Management trial results mean for patient care?

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Abstract

Over 300,000 Americans suffer a cardiac arrest outside of the hospital each year and even among those who are successfully resuscitated and survive to hospital admission, outcomes remain poor. The only intervention that had been reproducibly demonstrated to ameliorate the neurological injury that follows cardiac arrest is therapeutic hypothermia (TH). A number of laboratory studies have shown that TH slows oxidative metabolism, and reduces inflammation, free radical generation, necrosis, apoptosis, cerebral edema, and excitotoxicity that result from ischemia and reperfusion injury. Two landmark clinical trials showed superior survival and neurological outcomes when comparing post-arrest patients treated with TH versus standard care. Recently, the largest randomized controlled trial of TH dosing strategies in post-arrest patients has concluded that targeting a core temperature of 33°C for 24 hours followed by active maintenance of normothermia until 5 days post-arrest is equivalent to 36°C for 24 hours followed by active normothermia. The results of this trial have highlighted the uncertainty concerning temperature management strategies following cardiac arrest. The optimal duration, goal temperature, and target population remain unknown. Current evidence supports aggressively managing and maintaining post-arrest survivors at either 33°C or 36°C and underlines the importance of active maintenance of normothermia thereafter.

Introduction-

Over 300,000 Americans suffer a cardiac arrest outside of a hospital each year, with survival to hospital discharge ranging from 10.4% in adults and 5.4% in children.[1] Approximately

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60% of survivors die as a result of severe neurological injury[2,3] due to the cascade of damage that occurs within minutes of cessation of blood flow to the brain and in the minutes to hours following reperfusion.[4] Targeted interventions improved rates of return of spontaneous circulation (ROSC) including high-quality closed chest cardiac massage[5] and early defibrillation[6] but therapies that specifically address neurological injury post-resuscitation are lacking.

Two landmark trials published in 2002 demonstrated superior neurologic outcomes in adult subjects that suffered an out-of-hospital cardiac arrest (OHCA) with an initial rhythm ventricular tachycardia (VT) or fibrillation (VF) who were treated with 12 to 24 hours of therapeutic hypothermia (TH; 32°C-34°C)[7,8] compared to subjects receiving less aggressive temperature management (37°C). In the wake of these trials, TH was recommended in comatose survivors of VF/VT OHCA[9]. TH was also widely used in comatose cardiac arrest survivors regardless of initial rhythm, age, and arrest location, despite a lack of evidence in these sub-populations. Recently, a third trial, the largest randomized trial of targeted temperature management strategies, called into question both the depth and duration of hypothermia in OHCA survivors.[3] The purpose of this review is to provide a historical background on the use of TH and outline current recommendations for modern post-arrest temperature management.

Experimental and clinical use of hypothermia-

After extensive preclinical work suggesting that TH lowers metabolic rates and oxygen consumption,[10–12] TH began to be used in the operating room for patients undergoing total circulatory arrest during cardiac surgery in the mid 1950's.[13–15] The reasoning behind the use of TH in this setting was that lower tissue oxygen requirements could extend the time a patient could be without circulation, allowing surgeons to perform longer, more extensive cardiac procedures.[13] Improved tolerance to ischemia also suggested the possibility of preserving tissue for solid organ transplantation.[16] Investigation of TH as a therapy for a broader range of neurological injury stemmed from observational reports of preserved neurological function following prolonged cardiac arrest from cold water drowning.[17,18] It was postulated that being hypothermic at the time of insult provided significant neurological protection in these cases, a fact subsequently demonstrated experimentally.[19] In response to these observations, TH began to be utilized in pediatric asphyxial arrest and traumatic brain injury survivors in the late 1970's.[20,21] Despite widespread use, there were no guidelines for TH induction method, depth, or duration owing to an absence of well-controlled clinical trials.

Subsequent animal studies revealed that temperature plays a key role in both protection and exacerbation of ischemic brain injury,[22,23] that TH provides neuroprotection at the cellular level when initiated shortly after ischemic insults,[24,25] and that tissue preservation is observed even when TH is initiated 6 hours after an experimental insult.[26] Additionally TH attenuates a number of injury pathways caused by the ischemia/reperfusion response including, inflammation, oxidative stress, necrosis, apoptosis, cerebral edema, and excitotoxicity.[27] Observational studies in humans found that hyperthermia is associated with

poor outcomes in both adults and children.[28,29] These preclinical and observational studies suggested that TH may be a promising therapy for the post-cardiac arrest population.

Therapeutic hypothermia randomized trials-

Two landmark trials published in 2002 by Bernard et al.[7] and the Hypothermia After Cardiac Arrest (HACA) study group[8] were the first to demonstrate a survival and neurological benefit by cooling OHCA survivors. A summary table of study characteristics is provided (Table 1). The HACA trial was completed to compare survival and neurological outcome of cardiac arrest survivors treated with induced TH versus standard care. Subjects included in this trial suffered a witnessed OHCA with an initial rhythm of VF/VT and were aged 18–75, with initiation of resuscitation by emergency medical personnel within 5–15 minutes of patient's collapse and ROSC within 60 minutes. Consecutive eligible subjects were randomized to either 1) TH maintained between 32°C-34°C for 24 hours followed by passive rewarming or 2) no active temperature management. Both groups received standard intensive care including sedation with midazolam and fentanyl, mechanical ventilation, and paralysis to prevent shivering. The primary outcome of the study was neurological function defined as a Cerebral Performance Category (CPC) of 1 (good recovery) or 2 (moderate disability) at 6 months. Secondary outcomes included survival to 6 months and rates of adverse events during the first seven days of care.

Between 1996 and 2001, 3551 subjects were assessed for eligibility and a total of 275 subjects were enrolled. 138 subjects were treated with TH and 137 received standard care. Mean time to target temperature in the TH treated subjects was 8 hours after ROSC. Subjects treated with TH had improved mortality (Death in standard care 55% subjects vs. TH 41%; p=0.02) as well as have a favorable neurological outcome (Favorable neurologic outcome standard care 39% vs. TH 55%; p=0.009). TH was not associated with rates of serious complications including bleeding, need for platelet transfusion, pneumonia, sepsis, renal failure, or pulmonary edema.

Bernard et al. tested a similar hypothesis: is survival and neurological function in cardiac arrest patients improved with treatment with TH?[7] The investigators enrolled cardiac arrest subjects found with an initial rhythm of VF with persistent coma following ROSC, transport to a study emergency department, and ability to randomize and initiate TH within 2 hours of ROSC. Both groups received the same intensive care bundles including sedation with midazolam, paralysis, protocolized ventilator management, thrombolytic therapy when indicated, lidocaine bolus to prevent recurrent VT/VF, and pulmonary artery catheter insertion for hemodynamic monitoring. Subjects were randomized to either receive TH targeting 33°C or 37°C by passive rewarming. Subjects randomized to the TH group were cooled using ice packs applied to head, torso, and limbs. When the target temperature was reached, ice packs were removed and target temperature was maintained for 12 hours. Subjects randomized to standard care were held at a target temperature of 37°C. The primary outcome was favorable discharge location (i.e. discharge to home or acute rehab vs. discharge to a long-term care facility or death).

Over 33 months, 84 subjects were enrolled, 7 were excluded, and 77 were included in the final analysis. Of the study group, 43 received TH and 34 received standard care. A significant number of patients experienced pyrexia in the standard care cohort. Subjects treated with TH had significantly better discharge dispositions (discharge home or acute rehab) when compared to standard care subjects (standard care good outcome 26% vs. TH 49%; p=0.046). However, there was no difference in survival between groups (standard care mortality 68% vs. TH 51%; p=NS).

Despite the positive results of these two trials, they must be interpreted in light of their limitations. The populations included in these trials were narrow: 13% of OHCA cases have an initial rhythm of VF/VT and 58% of cases are unwitnessed.[30] It was unclear from the results of this trial if TH would be beneficial in other subgroups. Further, a majority of the deaths in both trials were due to withdrawal of life-sustaining therapy. Neither study standardized neurological prognostication, which could have biased the decision to withdraw life support. The additional attention paid to the TH groups in these trials may have introduced a Hawthorne effect, in which unmeasured variables could have changed and thus biased treatment. The control groups in both studies averaged around 37.1–37.7°C during the time the TH group was at 33°C, and due to variability, around 25% of temperatures in both studies in the control group were above 38°C. Such hyperthermia has been associated with poor outcomes in this population.[28,29]

In response to these trials, the International Liaison Committee on Resuscitation revised its post-arrest management guidelines to recommend that OHCA patients should be cooled to 32°C-34°C for 12–24 hours when the initial rhythm was VT/VF.[9] The statement also stated that TH may be beneficial in patients that suffer arrests with other initial rhythms or location.

No subsequent validating randomized controlled TH trials were completed until a decade later. A small pilot trial by Lopez-de-Sa et al., published in 2012, compared two different depths (34°C vs. 32°C for 24 hours) of TH in witnessed OHCA survivors with an initial shockable rhythm and ROSC within 60 minutes.[31] The primary outcome of the trial was good neurologic outcome (CPC 1–2 - good neurologic outcome) at 6 months post arrest. Safety endpoints were rates of bleeding, intracranial hemorrhage, transfusion, infection, electrolyte abnormalities, and arrhythmias.

The investigators screened 72 patients during the study period and randomized 18 subjects in the 32°C group and 18 subjects in the 34°C group. The study groups did not differ in baseline clinical characteristics. The subjects randomized to the 32°C arm of the trial had significantly better survival (32°C mortality − 55.6% vs. 34°C− 88.9%; p=0.03). In a subgroup analysis of subjects with an initial VF/VT rhythm, subjects randomized to the 32°C arm had significantly better neurologic status at 6 months post arrest (32°C CPC 1–2 – 69.2% vs. 34°C– 23.1%; p=0.02). After randomization and treatment, regardless of TH depth, no subjects that suffered an initial asystolic arrest survived to 6 months. The only significant difference in clinical safety outcomes was that the incidence of seizures was higher in the 34°C group compared to 32°C group (32°C – 6% vs. 34°C – 61%; p=0.0002).

This study suggests that the optimal depth of TH for post arrest patients may be lower and proposes the mechanism of seizure suppression as a benefit of deeper hypothermia. Seizures are common after cardiac arrest and associated with worse survival and neurologic outcome.[32,33] While survival and neurological outcome were significantly better in the 32°C group, the trial was small and underpowered to definitively test superiority of 32°C targeted temperature management.

Targeted Temperature Management-

Despite the widespread use of TH for nearly a decade, the evidence that TH improves neurologic outcome was restricted to retrospective and two randomized controlled trials. Through 2011, only 478 subjects had been studied in randomized controlled trials, leading to skepticism of TH's clinical efficacy.[34,35]

The Targeted Temperature Management (TTM) trial by Nielsen et al. was published in December 2013.[3] In contrast to the Bernard and HACA trials, this tested a temperature management protocol aimed to prevent hyperthermia (36°C) versus the intervention temperature depth of the Bernard and HACA trials (33°C). Compared to previous trials, a broader range of patients were included in the TTM trial. Specifically, Nielsen included witnessed OHCA regardless of initial rhythm (i.e. including asystole and pulseless electrical activity). Subjects were randomized to receive 28 hours of TH either 33°C or 36°C with subsequent rewarming to and active maintenance of 37°C. Subjects that remained comatose 72 hours after ROSC underwent standardized neurological prognostication by a physician blinded to the subject's study arm. The primary outcome of the trial was mortality at 180 days. Secondary measures included CPC and Modified Rankin Scale (mRS) at 180 days. Either a CPC of 1 (good recovery) or 2 (moderate disability) or a mRS of 0 (no disability) to 3 (moderate disability) was considered a good outcome.

950 subjects were enrolled in the trial with 476 randomly assigned to 33°C and 474 to 36°C. The study groups did not differ at baseline in demographic characteristics, past medical history, characteristics of the cardiac arrest, or clinical characteristics on admission such as body temperature, serum lactate, presence of ST-segment elevation myocardial infarction, or degree of cortical or brainstem dysfunction. The number of deaths (33°C: 50% vs. 36°C: 48%), neurological function (33°C: CPC 3–5 54% vs. 36°C: CPC 3–5 52%) and motor function (33°C: mRS 4–6 48% vs. 36°C: mRS 4–6 47%) were not statistically different between groups, though much higher proportions of patients were discharged in good functional state compared to patient outcome reports from the United States.[36,37] The cause of death also did not significantly differ between groups. Subgroup analyses failed to identify any subgroups, including those with longer CPR duration and non-shockable rhythm (ie characteristics consistent with increased injury severity) who benefited from 33°C over 36°C.

The results presented by Nielsen and colleagues represent a cohort larger than the combination of all prior randomized hypothermia studies. The HACA and Bernard studies did not include patients with non-shockable initial rhythms and other studies have reported that this group has extremely poor outcomes.[38] The results of Nielsen and colleagues show

that are consistent with prior reports in that subjects with initial asystole or PEA had extremely poor outcomes.

33 or 36°C? Implications for patient care-

With the available evidence, which temperature target should you choose? In response to the results of the TTM trial the International Liaison Committee on Resuscitation released a statement suggesting that temperature management should be set for 33°C per current guidelines[39] but that the decision to cool to 36°C may be accepted as equivalent outcomes were achieved using either treatment strategy.[39,40] This recommendation is not yet reflected in the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, which recommend a target temperature of 32°C to 34°C for 12 to 24 hours.[41]Updated guidelines for 2015 are expected to be released this year and will likely be modified based on the results of the TTM trial.

While we now know that outcomes are similar when treating with 33°C or 36°C, there are many questions remaining regarding temperature management in cardiac arrest survivors. A majority of TH research including the TTM trial has been conducted in OHCA, and Bernard and HACA only included subjects with an initial rhythm of either VT/VF or a cardiac etiology of arrest. These arrests only comprise a small subset of total arrests and arrest survivors. A meta-analysis concluded that patients with non-shockable initial rhythms treated with TH may have a survival benefit[42] but only non-randomized studies were available for analysis. It has not been conclusively shown that patients that arrest in hospital benefit from TH treatment but it is unclear if there is lack of a treatment effect or that TH is utilized less and often less aggressively.[43] The optimal depth and duration of TH remain unknown though a recent study in neonatal asphyxial encephalopathy failed to show benefit for longer or colder TH goals.[44] There may be subgroups of patients that would benefit from deeper and longer durations of temperature management such as at risk of cerebral edema or herniation,[45] present with severe brainstem dysfunction,[46,47] or are suffering or at high risk of developing seizures[32] though at present there is insufficient clinical data to demonstrate such benefit. Future studies are needed to clarify these questions.

A consistent message from these studies[3,7,8,31] has been that a system of care is necessary to optimize outcomes following resuscitation from cardiac arrest. This system should include temperature management, optimization of cardiovascular and pulmonary systems, coronary angiography (when indicated), delayed and standardized neuroprognostication, and aggressive rehabilitation. Specifically, early pyrexia following cardiac arrest remains associated with poor outcomes in patients during the hypothermia era.[48,49] Pyrexia must be avoided including rebound pyrexia following rewarming.[50] Although on its face the difference between a target temperature of 36°C and 37.5°C (the de facto mean of the prior studies' control groups) is seemingly insignificant, it is at present the only clear difference that can be linked to the differences in control group mortality. The increased mortality may be attributable to the small number of patients who trended to the higher end of the temperature range (>38°C) or it may be that the brain experience significantly greater reperfusion injury when kept at 37°C vs 36°C. Passive cooling and use of anti-pyretic

medications may not be enough to ensure pyrexia prophylaxis. Instead, active temperature management (see below) should be considered mandatory.

Current guidelines recommend that all post-arrest patients that do not follow commands be considered for targeted temperature management.[41] Contraindications for targeted temperature management include intracerebral hemorrhage, profound hemorrhage or coagulopathy, severe sepsis, refractory hypotension, and pregnancy.[51] At our institution, we aggressively manage the temperature in all comatose OHCA and IHCA regardless of initial rhythm. We generally induce TH with ice packs placed around the head, axilla, and groin, and/or intravenous infusion of 4°C saline, both of which are readily available regardless of setting. When able, generally after ICU admission, we place an endovascular cooling catheter (e.g Coolgard or ICY catheter, Alsius Corp., USA) or apply surface cooling pads (e.g Arctic Sun, Medivance, USA), which we find to be equally effective, an observation supported by the literature,[52] and superior to ice packs or cooling blankets alone. However, as demonstrated in both the Bernard and HACA studies, in centers that do not have access to such equipment, ice packs and cold saline can be used effectively to achieve and maintain the target temperature of choice.[7,8] Regardless of the particular methodology, we feel that institutional protocols for the initiation and maintenance of TTM are essential to ensure safe, effective, and timely patient care.

During induction and maintenance of TTM, we measure core temperature (bladder, esophageal or rectal) since axillary and oral temperatures often do not reflect core temperature.[53] We maintain TTM, whether 36C° or 33C°, for 24 hours, then rewarm at a rate of no more than 0.25°C/hr to 37°C to prevent secondary brain injury from overly rapid rewarming.[54] Some centers routinely administer continuous infusions of neuromuscular blockers for the duration of TTM to suppress shivering. This has been associated with rapid lactate clearance and decreased mortality.[55] We preferentially use sedation, when sufficient, to treat shivering and for analgesia/sedation, but have a low threshold to use bolus doses of neuromuscular blockers when sedation itself is inadequate, especially in the induction phase of TTM.

Although TTM may be most frequently discussed in the context of cardiac arrest, any bundle of care must include protocols to support patients with multisystem organ failure with the goal of preventing secondary brain injury.[56] We routinely monitor all comatose survivors of cardiac arrest with continuous electroencephalographic (EEG) monitoring, and aggressively treat seizures with anticonvulsants.[32] Hypothermia itself may suppress seizures, so we generally continue monitoring patients through the rewarming process, at the least. Although current guidelines recommend maintaining a mean arterial pressure (MAP) >65mmHg,[41] cerebral blood flow and autoregulation is often impaired after anoxic brain injury and observational data suggest that neurological outcomes may be better when MAPs are higher, regardless of vasopressor use.[57] It is our practice to target a MAP of >80mmHg with vasopressor infusions as needed to promote cerebral perfusion, except if there are individual patient factors that preclude mild hypertension. TTM may cause bradycardia, which is generally not clinically significant and does not impair cardiac output since stroke volume increases in parallel with decreases in heart rate.[58] We rarely need to rewarm patients because of cardiac dysrhythmias or hemodynamic instability. Similarly, we aim to normalize

arterial carbon dioxide (PaCO2) and oxygen (PaO2) to avoid cerebral vasoconstriction or vasodilation and excess oxidative stress, respectively. It is important to remember that many laboratories do not temperature correct the results of the arterial blood gas analysis. A patient's actual PaCO2 is about 2mmHg lower per degree below 37C in a non-temperature corrected blood gas, and PaO2 is about 5mmHg lower per degree below 37C. Familiarity with an institution's standard laboratory assays is necessary. Hypothermia reliably causes intracellular shift of potassium, resulting in apparent hypokalemia in the serum. Since this effect reverses during rewarming, we avoid repletion of hypokalemia above a level of about 4mEq/L during TTM to prevent rebound hyperkalemia.

Conclusions-

The use of TH to prevent and treat brain injury has been studied for the past 60 years. High quality randomized controlled trials support the need to actively manage temperature and avoid pyrexia. The optimal duration of temperature management, goal temperature, and populations that benefit from temperature management remain unknown. Current evidence supports actively managing and maintaining comatose post-arrest survivors at either 33°C or 36°C for 24 hours and underlines the importance of pyrexia prevention thereafter.

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Appendix:

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Table 1:

Study characteristics of therapeutic hypothermia trials.

	Included patient demographics	Patients enrolled	Mortality	Good neurologic outcome	Limitations
HACA	VT/VF survivors, TH induced <60 minutes, 24 hours of TH	TH-138	TH-41%	TH-55%	Pyrexia in control subjects, select study population.
		Control-137	Control-55%	Control-39%	
Bernard	VF survivors, TH induced < 2 hours, 12 hours of TH	TH-43	TH-51%	TH-49%	Small study population, 8% of assessed patients were included in study
		Control-34	Control-68%	Control-26%	
De-Sa	VT/VF survivors, TH induced < 60 minutes, 24 hours of TH	32°C– 18	32°C– 56%	32°C– 69%	Small study population.
		34°C– 18	34°C– 89%	34°C– 23%	
TTM	Cardiac etiology of arrest, TH induced < 4 hours, 28 hours of temperature management	33°C– 476	33°C– 50%	33°C– 54%	Conducted in European and Australian centers, may not reflect other countries outcomes.
		36°C– 474	36°C– 48%	36°C– 52%	