Available Evidence Regarding Targeted Temperature Management (TTM)

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Introduction:
The ability to obtain good neurological outcomes after cardiac arrest is often limited. Interventions during the acute phase of treatment post return of spontaneous circulation (ROSC) are therefore critical. The primary goal of cardiopulmonary resuscitation (CPR) is to optimize coronary perfusion pressure and maintain systemic perfusion in order to prevent neurologic and other end-organ damage while working to achieve ROSC. While the utility of therapeutic hypothermia for preservation of neurologic function post-cardiac arrest had been suggested in the early 1950s and 1960s, the studies were inconclusive, with high complication rates. It was not until the 1990s that studies showed possible benefits to mild hypothermia in animal models. The results of the 2002 trial by the Hypothermia after Cardiac Arrest Study Group were the basis for the inclusion of therapeutic hypothermia in the American Heart Association's post-cardiac arrest care guidelines. Subsequent trials have assessed the difference between therapeutic hypothermia to 33 degrees Celsius (°C) and “targeted temperature management” (TTM) aiming for 36°C, the duration of TTM, the method used to achieve and maintain it, and whether TTM confers a similar neurological benefit for cardiac arrests secondary to non-shockable rhythms; some of these trials will be discussed below and will help us answer the question at hand.

Question: What is the current available evidence on: temperature degree, duration and method of cooling in TTM patients post cardiac arrest?


By the time of the study by Nielsen et al. therapeutic hypothermia was recommended in international resuscitation guidelines but questions still remained as to whether a specific temperature was superior to general temperature regulation. Previous research had shown that fever is associated with worse outcomes and in the Hypothermia after Cardiac Arrest Study Group trial many patients in the control group developed fever, potentially confounding the results.

This international, randomized clinical trial took place in intensive care units (ICUs) in Europe and Australia and involved patients with out-of-hospital cardiac arrest of a presumed cardiac cause, irrespective of arrest rhythm, with a Glasgow Coma Scale (GCS) score of less than 8 after ROSC. Patients were also required to maintain spontaneous circulation for more than 20 minutes after resuscitation. The main exclusion criteria were time from ROSC to screening of more than four hours, unwitnessed arrest with asystole as initial rhythm, suspected or known intracranial hemorrhage or stroke, or an initial core temperature of less than 30°C. Enrollees were then assigned to either TTM of 33°C or 36°C for 36 hours. There was no blinding for the direct care providers, but neurologic prognosis was performed by blinded individuals. There was no standardization of cooling performed and gradual warming was performed after 28 hours. Fever control continued until 72 hours after the arrest in both groups. The primary outcome was death at the end of the trial with secondary outcomes of death at 180 days, and neurological outcome assessed by cerebral performance category and the Modified Rankin scale.

Of the 939 patients enrolled, the majority, approximately 80%, in each group had a shockable rhythm on initial assessment and 75% had bystander CPR performed. For both groups, mean time to basic life support was determined to be one-minute, advanced life support started at 10 minutes, and time to ROSC at 25 minutes. Rates of cardiovascular disease were high and approximately 40% of patients in both groups had an ST-segment elevation myocardial infarction. Both groups had similar initial neurological presentations with median GCS of 3. Intravascular cooling was performed in 24% of patients and surface cooling performed in the remaining 76%.

By the end of the trial, 50% of patients in the 33°C group and 48% of patients in the 36°C group had died. Neurological outcomes by both scales were similar between the groups. The authors also investigated harms in both groups and determined no significant difference in adverse events between both groups. These results suggest that targeting a lower temperature of 33°C confers no additional benefit to targeting 36°C. However, the decade since the original Hypothermia after Cardiac Arrest trial had seen significant advances in pre-hospital, emergency department, and critical care that may have contributed to these outcomes. Additionally, the study leaves unanswered the question regarding the benefits of TTM in certain post cardiac arrest patients compared to non-cooling interventions.


After guidelines began to recommend the use of TTM, many researchers began studying the various logistical aspects of cooling and rewarming. Kirkegaard et al. sought to address the proper duration of hypothermia. The authors cite neonatal protocols for 72 hours of cooling as possible evidence that longer cooling may have benefits. They therefore designed...
a multicenter, randomized, blinded-outcome-assessor trial to compare 24 hours to 48 hours at 33°C. It is not clear from their manuscript why they chose 33°C when they cite in their introduction that there was no difference between 33°C and 36°C in prior studies.

Power analysis led to the enrollment of 355 patients stratified by study site, age, and initial rhythm. Patients were included if their arrest was presumed to be of cardiac origin, either shockable or non-shockable rhythm. Randomization occurred within the first 23 hours after the target temperature had been reached. As they could not blind the treatment teams, they blinded the outcome assessors who collected the six month variables.

When analyzing admission data, there were no significant differences between the two groups, but interestingly the majority of both groups received bystander CPR (82% for the 24-hour group and 84% for the 48-hour group) and were found to have an initial shockable rhythm (86% for 24 and 91% for 48). During the study, it took the 24-hour group significantly longer than the 48-hour group to reach target temperature after ROSC (320 minutes vs. 281 min, p=0.01). More complications (such as severe arrhythmias and pneumonias) occurred in the 48-hour group and more patients had to be rewarmed ahead of schedule, both of which make sense as one would expect more difficulties when keeping patients cooler longer. There was no significant difference between groups with respect to percentage of patients with good functional status (69 vs. 64%, p=0.33) or mortality (27 vs. 34%, p=0.19) at six months. The 48-hour group had a significantly longer length of stay in the ICU and time on mechanical ventilation amongst survivors, both of which were expected since they were kept at target temperature for longer, requiring more resources.

When looking at this study population overall, the authors noted most patients received bystander CPR and were found to have an initial shockable rhythm, different from prior TTM studies. These differences may have contributed to increased survival overall, altering the power of the study as its sample size was calculated based on prior research. The authors note a sample of closer to 3,000 would be required to detect a difference based on the results of their study, which would be extremely difficult to accomplish. Therefore, whilst the authors state that there was no statistically significant evidence to support cooling for 48-hours, more research is required to validate the trial results and possibly to evaluate the rate of cooling as another variable affecting mortality.


As a follow-up to the study comparing 24-hour to 48-hour duration of TTM, coined the TTM48 trial, the authors reanalyzed the data to evaluate different methods of cooling. Their outcomes in this post-hoc analysis were cooling precision, survival, neurologic outcome (specifically poor neurologic outcome), and adverse events among survivors, of which only cooling precision was not a primary or secondary outcome in the original study. The two groups analyzed were those using intravascular catheters (IC) and those using surface cooling devices (SFC) to achieve target temperature.

Three hundred and fifty-two of the original cohort of 355 were included in this analysis, of which 218 were cooled by IC and 134 by SFC. Both groups were allowed to use infusion of cold intravenous fluids and there was no difference in overall percentage of patients who received cold IV fluids between groups. There was no significant difference in cooling method between original cohorts. Time to TTM was statistically significantly shorter in the IC group (2.2 vs. 4.2 hours; p<0.001) but they also started at a lower temperature (35.0 vs 35.5°C, p=0.02). There was less temperature variability in the IC group, however more time spent outside of goal temperature range and post-re-warming fever were also noted in this group.

There was no significant difference in mortality, neurologic outcome, or adverse event rates between groups. Consistent with this study, other studies on this subject have also noted that IC has less variability and better control of temperature than SFC, but without changes in clinical outcomes.13-15 One major flaw of this post-hoc analysis is that the authors of both studies state in the TTM48 manuscript that the power of the original study was not sufficient and a larger study is needed. Therefore, a secondary analysis of the data is unlikely to demonstrate any significant difference. Additionally, as the patients were not randomized based on their cooling method, there were many statistically significant differences in baseline characteristics as well as their performance findings during the study between groups that could affect the authors’ conclusions, hence a larger, properly randomized study is required to detect any significant differences that might exist.


The HYPERION trial was an open-label randomized control trial that compared moderate therapeutic hypothermia (33°C for 24 hours) with targeted normothermia (37°C for 24 hours) for patients admitted to the ICU after ROSC from a cardiac arrest secondary to a non-shockable rhythm. The primary outcome was the 90-day Cerebral Performance Category score (CPC) ranging from 1 to 5, with a higher number indicating greater disability. Participants aged 18 years or older who had achieved ROSC after an in-hospital (IHCA) or out-of-hospital cardiac arrest (OHCA) secondary to a non-shockable rhythm, and a Glasgow Coma Scale (GCS) of ≤8 at ICU admission (or if the patient was sedated, a GCS ≤ 8 prior to sedation) were included. Exclusion criteria included time from collapse to initiation of CPR of >10 minutes, CPR time of >60 minutes, hemodynamic instability requiring vasopressors...
(epinephrine or norepinephrine >1μg/kg body weight per minute), time from arrest to screening of >300 minutes, Childs-Pugh class C hepatic cirrhosis, moribund condition, pregnant or lactating mothers, status of being incarcerated or under guardianship, inclusion in another trial assessing neurological function post-cardiac arrest at 90 days, lack of health insurance, and next-of-kin decision not to participate. The trial was conducted in 25 ICUs in France between 2014 and 2018. Patients were randomized in a 1:1 ratio to either the hypothermia or normothermia groups.

For patients who were assigned to the hypothermia group, a core body temperature of 33°C (± 0.5°C) was induced and then maintained for 24 hours per each center’s protocol (internal or external cooling with or without a specific device), and then patients were rewarmed at a rate of 0.25-0.5°C to a goal of 36.5 or 37.5°C over 24 hours. Sedation was tapered after core temperature rose above 36°C. For patients assigned to the normothermia group, core body temperature was maintained at 37°C (± 0.5°C) for 48 hours according to each center’s standard protocol; patients were sedated only during their first 12 hours. The primary outcome of all surviving patients was assessed at 90 days and a CPC score of 1 (good cerebral performance or minor disability) or 2 (moderate disability) was defined as a favorable neurologic outcome. Secondary outcomes included mortality, duration of mechanical ventilation, ICU and hospital length of stay (LOS), infections, and hematologic adverse events. Due to French Law, informed consent was not required as both groups were considered to be receiving components of standard of care, though patients (or their representatives) had the opportunity to decline the usage of their data.

Five hundred and eighty one patients were included in the final analysis: 284 in the hypothermia group and 297 in the normothermia group. The baseline characteristics of the two groups were similar. Overall, 27% suffered from OHCA and 73% from IHCA.

At the 90-day mark, 29 of the hypothermia patients demonstrated a CPC score of 1 or 2 compared to 17 for the normothermia group (10.2 vs. 5.7%). Secondary outcomes were similar between the two groups, including 90-day and ICU mortality, ICU LOS, and duration of mechanical ventilation among those who survived to ICU discharge or died in the ICU.

This trial carried several limitations. Survivor neurologic outcome was assessed using a telephone rather than in-person assessment. There were a significant number of patients who were hyperthermic (temperature > 38°C) after the TTM period, and to avoid rebound hyperthermia, TTM was performed for 56 to 64 hours in the hypothermia group versus 48 hours in the normothermia group. Patients with missing data (one in the hypothermia group and two in the normothermia group) were assumed to have died. While this yields a total of only three patients with missing data, it carries significant ramifications as the trial had a fragility index of one. As such, while the HYPERION trial suggests a neurological benefit to TTM for non-shockable rhythms, further study is required for more concrete support.

Conclusion
There has been a significant amount of research over the past twenty years regarding TTM after cardiac arrest. The most recently updated American Heart Association guidelines from 2015 are supportive of TTM between 32°C and 36°C;16 based on some of the studies stated above it is unclear whether the method or a longer duration of cooling confers statistically significant differences at this time; further clinical trials are needed to assess for optimal duration of TTM, modality of cooling, and which patient groups would have the best neurological outcomes using TTM. ●

References
