Clinical Review

Targeted temperature management after out-of-hospital cardiac arrest

Who, when, why, and how?

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Abstract

Objective To provide a succinct review of the evidence, framed for the emergency department clinician, for the application of targeted temperature management (TTM) for patients after out-of-hospital cardiac arrest (OHCA).

Sources of information MEDLINE, EMBASE, and the Cochrane database were searched for prospective and retrospective studies relevant to the indications of TTM, optimal timing of TTM initiation, method of cooling, and target temperature.

Main message Two prospective interventional trials reported improved neurologically intact survival with the use of TTM (goal temperatures of 32°C to 34°C) compared with no temperature management in comatose OHCA patients with shockable initial cardiac arrest rhythms. A more recent, high-quality randomized controlled trial including OHCA patients with shockable and nonshockable initial rhythms compared TTM at 33°C versus TTM at 36°C. Despite the study being well powered, superiority of one target temperature over the other was not demonstrated. The benefit of TTM in patients with initial nonshockable rhythms is not clear; however, some observational studies have suggested benefit. There is no evidence that any particular method of temperature regulation is superior. The relationship between time and TTM initiation has not been well established.

Conclusion Targeted temperature management, with a target temperature between 32°C and 36°C, as a component of comprehensive critical care is a beneficial intervention for comatose patients with return of spontaneous circulation after OHCA.

EDITOR’S KEY POINTS

- Although targeted temperature management (TTM) is a widely recommended therapy for patients after out-of-hospital cardiac arrest (OHCA), many questions remain regarding the patient populations who would benefit from this therapy, as well as the optimal time to initiate therapy, method of cooling, and goal temperature.

- Current evidence indicates that TTM within a comprehensive protocol for resuscitated patients after OHCA, compared with usual care, is a beneficial intervention for patients who are not responsive to verbal commands after OHCA.

- An organized protocol for resuscitated patients after OHCA including the use of TTM with a goal temperature of 32°C to 36°C should be implemented in all OHCA patients upon arrival to the ED, followed by timely transfer to a critical care environment.

POINTS DE REPÈRE DU RÉDACTEUR

- Bien que la gestion ciblée de la température (GCT) soit un traitement communément recommandé pour les patients ayant subi un arrêt cardiaque hors de l’hôpital (ACHH), de nombreuses questions demeurent quant aux populations de patients qui en bénéficieraient, au moment optimal pour amorcer le traitement, aux méthodes de refroidissement et aux valeurs de température ciblées.

- Les données probantes actuelles indiquent que, comparativement aux soins habituels, la GCT suivant un protocole complet pour les patients réanimés ayant subi un arrêt cardiaque hors de l’hôpital est une intervention bénéfique lorsque ces derniers ne réagissent pas aux commandes verbales après un ACHH.

- Un protocole structuré pour les patients réanimés après un ACHH, incluant l’utilisation de la GCT visant des valeurs de de 32 °C à 36 °C, devrait être mis en œuvre pour tous les patients dès leur arrivée à l’urgence, suivi d’un transfert aux soins intensifs en temps opportun.

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**Gestion ciblée de la température après un arrêt cardiaque hors de l'hôpital**

**Qui, quand, pourquoi et comment?**

**Résumé**

**Objectif** Présenter une synthèse des données probantes, élaborée à l'intention des cliniciens des services d'urgence, en ce qui concerne les mesures de gestion ciblée de la température (GCT) chez les patients ayant subi un arrêt cardiaque hors de l'hôpital (ACHH).

**Sources des données** On a effectué une recherche dans MEDLINE, EMBASE et la base de données Cochrane pour trouver des études prospectives et rétrospectives concernant les indications de la GCT, le moment optimal pour amorcer la GCT, les méthodes de refroidissement et les valeurs de température ciblées.

**Message principal** Dans deux études interventionnelles prospectives, on a signalé une amélioration du taux de survie sans lésion neurologique avec l'utilisation de la GCT (températures ciblées de 32 °C à 34 °C) comparativement à celui des patients comateux victimes d’un ACHH et présentant des rythmes initiaux à l’arrêt cardiaque justifiant une défibrillation dont la température n’avait pas été prise en charge. Plus récemment, une étude randomisée contrôlée de grande qualité portant sur des patients victimes d’un ACHH et présentant des rythmes initiaux justifiant ou non une défibrillation comparait la GCT à 33 °C à la GCT à 36 °C. Bien que l’étude ait été bien menée, elle n’a pas démontré la supériorité de l’une ou l’autre des températures ciblées. Les avantages de la GCT chez les patients présentant des rythmes initiaux ne justifiant pas une défibrillation ne sont pas clairs même si, dans certaines études observationnelles, on a fait valoir certains bienfaits. Il n’y a pas de données probantes établissant qu’une méthode particulière de régulation de la température soit supérieure à une autre. Le moment opportun d’amorcer la GCT n’a pas été bien établi.

**Conclusion** La gestion ciblée de la température, visant des valeurs entre 32 °C et 36 °C, en tant que composante des soins intensifs complets est une intervention bénéfique pour les patients comateux qui ont eu un rétablissement de la circulation spontanée après un ACHH.

**Sources of information**

We performed a MEDLINE search from January 1, 1900, to December 31, 2013, to identify all studies examining neurologic outcomes or mortality in patients with OHCA of presumed cardiac causes relevant to the following questions.

- Does TTM improve outcomes and, if so, in which populations have studies shown benefits? (Trials comparing TTM to usual care and those comparing TTM of different temperature targets were included.)
- Does earlier initiation of TTM improve outcomes compared with later initiation?
- Are certain techniques of patient cooling, for the purpose of TTM, associated with improved outcomes?

Studies were included regardless of language of publication. The search strategy used and combined the following MeSH terms: heart arrest, induced hypothermia, humans, and adult. A similar search was performed in EMBASE. The Cochrane database of systematic reviews was searched using the term hypothermia. We included all prospective and retrospective human adult studies of randomized, pseudo-randomized, and observational
designs. References of studies examined were also reviewed to widen the search.

Main message
Our search yielded 445 citations. After review for relevance by title and abstract, we reviewed 145 articles in full. We included 57 of these in the final review.

Indications for TTM
Initial shockable rhythms (ventricular fibrillation [VF] and pulseless ventricular tachycardia): Two prospective interventional trials, both published in 2002, examined the use of TTM after OHCA with a presumed cardiac cause, with goal temperatures of 32°C to 34°C. Bernard et al enrolled 77 patients (men older than 17 and women older than 49 years of age) with an initial rhythm of VF in “persistent coma” after OHCA and compared TTM with those receiving usual care.4

Targeted temperature management was initiated by EMS in the intervention group and continued for 12 hours. Forty-nine percent of patients in the TTM group had a “good outcome” (discharged to a rehabilitation facility or home) compared with 26% in the control group (P = .046). The Hypothermia after Cardiac Arrest Study Group randomized 273 patients aged 18 to 75 years after witnessed OHCA with an initial rhythm of VF or nonperfusing ventricular tachycardia who had no “response to verbal commands” and an interval time of collapse to EMS arrival of 5 to 15 minutes.5 The intervention group received TTM for 24 hours, commencing in hospital; 55% of patients had favourable outcomes (cerebral performance category score of 1 or 2) compared with 39% among those who received usual care (P = .009). Further, there was a reduction in mortality. In addition, several observational studies have reported benefits in mortality and neurologic outcomes when comparing the use of TTM with historical controls in patients with initial shockable rhythms.6-10

The protocols of the initial 2 studies examining TTM4,5 used target temperatures of 32°C to 34°C. Subsequent widespread implementation of TTM and guidelines endorsed this strategy11,12; however, evidence supporting these specific temperature goals was lacking. It was theorized by some that the true benefit of TTM was in its ability to prevent hyperthermia after cardiac arrest, as opposed to a benefit of subnormal temperatures.13

Nielsen et al performed a multicentre randomized controlled trial, enrolling 950 unconscious patients after OHCA, comparing targeted temperature groups of 33°C and 36°C.14 Patients of all initial rhythms, with the exception of unwitnessed asystole, were considered for inclusion; however, 79% of participants had shockable initial cardiac rhythms. The study was powered to detect an absolute reduction in mortality of 11%. Targeted temperature management was initiated within 240 minutes of ROSC and was continued, with mandatory sedation, for 28 hours followed by slow rewarming. Measures to avoid hyperthermia continued for a total of 72 hours. An assessor-blinded standardized evaluation for neuroprognostication took place 72 hours after the rewarming phase to make recommendations for further life-sustaining treatment. Despite being well powered, superiority of one target temperature over the other was not demonstrated in terms of neurologic outcomes or mortality.

There have been no studies comparing patients with a TTM goal of 36°C with usual care.

Initial nonshockable rhythms (pulseless electrical activity and asystole): No large prospective randomized studies have examined the use of TTM in patients with nonshockable initial rhythms in comparison with usual care; however, several retrospective studies, all with target temperatures of 32°C to 34°C, have indicated benefit.15,16 Testori et al reviewed 374 cases with nonshockable initial rhythms and reported better neurologic outcomes and a lower mortality rate in those treated with TTM.16 Conversely, in other similarly designed studies, including one study examining 1145 consecutive cardiac arrests,17 benefit was limited to only those with initial shockable rhythms.18-22 Nielsen and colleagues compared temperature targets of 33°C and 36°C in patients with initial nonshockable rhythms in a subgroup analysis and reported no benefit seen with the more aggressive TTM goal.14

Given the low survival rate of OHCA patients with nonshockable initial rhythms, extremely large sample sizes would be required to detect benefit.23 Several observational studies have examined the implementation of TTM in all resuscitated patients after OHCA, regardless of initial rhythm, and have reported benefit in neurologic outcomes or mortality.24-32 To isolate the effect of TTM on nonshockable rhythms, Kim et al performed a meta-analysis incorporating data pertaining only to these rhythms from 10 non-randomized studies involving 1292 patients. They concluded that TTM was associated with reduced in-hospital mortality (relative risk 0.84; 95% CI 0.78 to 0.92); however, there was no statistical benefit seen in neurologic outcomes at hospital discharge.23 The authors concluded that the quality of evidence was low and that high-quality randomized trials were required.

It is unclear why patients with initial nonshockable rhythms have a worse prognosis considering that the pathophysiology of anoxic brain injury is likely similar in all instances of cerebral hypoperfusion.33 Resuscitated patients after OHCA with initial non-shockable rhythms are much more likely to have longer collapse-to-ROSC durations,34 which might play a role in the worse outcomes observed.4
Oddo et al performed a multivariable analysis on prospective data from 74 resuscitated patients after OHCA treated with TTM to assess for predictors of outcomes. They reported that initial arrest rhythm, in contrast to time from collapse to ROSC, was not independently associated with neurologic outcomes or mortality. Soga et al reported similar outcomes for patients with shockable and nonshockable rhythms whose collapse-to-ROSC interval was 16 minutes or less. The sole data point of shockable versus nonshockable initial rhythms for the decision on whether to initiate TTM in a patient is likely overly simplistic and negates other variables that might play a large role in the success of this treatment and patient outcomes.

**Issues of timing**

Time to initiation of cooling and time to target temperature in studies investigating TTM, with goal temperatures of 32°C to 34°C, vary widely. Multiple animal models have shown benefits of earlier and faster cooling strategies; however, the importance of this variable on outcomes in humans remains unknown. Four retrospective studies have reported benefits of earlier cooling, including improved neurologic outcomes and mortality rates. Conversely, some studies have indicated a lack of benefit for shorter time to target temperature, and 4 studies reported worse outcomes.

Five RCTs examined the effects of prehospital TTM induction using cold saline. No study found significant differences in patient neurologic outcomes or mortality; however, differences in mean patient temperatures between intervention and control groups at hospital arrival were modest (0.8°C to 1.3°C).

**Methods of TTM**

Multiple methods of cooling for TTM have been described, including use of ice bags, cold saline infusions, cooling blankets, and intravascular or intranasal cooling devices. There is no evidence to suggest that any one method is superior.

Cold saline has been proposed as a favoured option for induction of TTM owing to its relatively low cost, convenience, universal availability, and ease of use in patient transport. The American Heart Association currently recommends a cold intravenous fluid bolus to induce TTM. Several studies, including 4 randomized controlled trials, have reported cold saline infusions to be safe and effective while not inducing pulmonary edema. However, a recent large study that randomized patients to prehospital administration of a rapid 2-L bolus of 4°C normal saline, compared with usual care, reported increased prehospital recurrence of cardiac arrest and pulmonary edema within the first 12 hours of hospitalization; there was no difference in overall mortality. Cold saline infusions are effective induction agents but appear less effective in the maintenance of a particular body temperature.

**Case resolution**

The patient was moved to a resuscitation bay in the ED with a cardiac monitor, 2 large-bore intravenous catheters were placed, and oxygen was administered to achieve an oxygen saturation of 94%. An endotracheal tube was inserted and sedation was commenced. A 500-mL bolus of 4°C normal saline was initiated, with a goal temperature of 36°C, and a bladder temperature catheter was inserted for monitoring. A total of 1 g of acetaminophen was given rectally. The regional cardiac referral centre was contacted and arrangements were made for urgent transport.

**Conclusion**

Unanswered questions remain with regard to the optimal TTM strategy and the magnitude of its effectiveness. However, there is compelling evidence that TTM protocols, compared with the usual care before the TTM era, lead to improved outcomes for patients with initial shockable rhythms and nonshockable rhythms. Recent data presented by Nielsen and colleagues support the conclusion that when employing the protocol of 108 or more hours described in the study—including strict temperature control, mandatory sedation, and delayed standardized prognostication—TTM with a goal temperature of 33°C is not superior to a goal of 36°C.

Current evidence indicates that TTM within a comprehensive protocol for resuscitated patients after OHCA, compared with usual care, is a beneficial intervention for patients after OHCA who are not responsive to verbal commands. Normal saline at 4°C is effective for initial temperature regulation; however, until there is further evidence supporting the safety of this technique, it might be advisable to avoid large rapid boluses. An organized protocol for resuscitated patients after OHCA including the use of TTM with a goal temperature of 32°C to 36°C should be implemented in all OHCA patients upon arrival to the ED, followed by timely transfer to a critical care environment.

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*Further information on targeted temperature management protocols can be found at www.emergencymedicine.utoronto.ca/research/ptmr/CS/SPARC.htm.
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1. Heart and Stroke Foundation [website].


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