Prehospital initiation of mild therapeutic hypothermia for out-of-hospital cardiac arrest (OHCA): where are we now?

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Over the past decade, much research has been devoted to the field of mild therapeutic hypothermia (MTH) and targeted temperature management (TTM) for patients resuscitated from out-of-hospital cardiac arrest (OHCA). Two studies indicating benefit for MTH were simultaneously published in 2002, sparking a wave of global excitement and research in this field and subsequent widespread clinical implementation of this therapy. Despite questions of the true effect of subnormal temperatures on outcomes and whether the available evidence justified the endorsement by international resuscitation organizations,[1] the advent of MTH undoubtedly impacted survival and neurological outcomes, even if indirectly. Many observational studies, most often using historical controls, demonstrated benefits in mortality and neurological outcomes after incorporating MTH for OHCA management.[2-22]

Based on the success of animal models,[23,24] the two landmark prospective controlled clinical studies were based on the theory that post-arrest hypothermia mitigated the effects of cerebral reperfusion injury.[25,26] These trials enrolled unresponsive adult patients resuscitated from OHCA of presumed cardiac etiology with initial shockable rhythms, and compared the use of MTH at goal temperatures of 32°C – 34°C (89.6°F – 93.2°F) to usual care (unregulated temperature).[25,26] Bernard et al. included 77 patients, with MTH initiated by emergency medical services in the intervention group and continued for 12 hours.[25] At 2 hours, the group mean temperature was at 33.5°C (92.3°F). The hypothermia-after-cardiac-arrest group randomized 275 patients after witnessed OHCA.[26] MTH was commenced in the hospital, had a median time to target temperature of 8 hours, and continued for 24 hours. Benefits in neurological outcomes were seen in both studies.

With evidence supporting the use of MTH, it is not surprising that the assumption was made that earlier MTH initiation and faster induction could provide even greater benefit, as was demonstrated in controlled animal studies.[27-30] Several observational studies were performed to investigate this hypothesis; however, results ranged from demonstrating benefit,[31-34] no benefit,[35,36] or even worse outcomes.[37-40] Observational studies have significant biases, however, because 1) patients with lower initial temperatures prior to MTH initiation appear to have worse outcomes than their comparators[39,41,42]; and 2) those with worse anoxic brain injuries may be "easier to cool"[43]; both of which may be due to impaired thermoregulation, a possible marker of more profound brain injury and therefore a reduced likelihood of survival.

Several randomized controlled trials (RCTs) were performed, enrolling consecutive patients in the prehospital setting to examine the effects of earlier MTH initiation.[44-49] While these studies demonstrated that modestly lower temperatures at hospital arrival can be achieved, there were no differences in patient outcomes. In the largest of these studies, Kim et al. randomized 1,359 patients in the prehospital environment to either MTH induction with large boluses of iced saline as soon as possible after initial return of spontaneous circulation (ROSC), or usual care.[48] The intervention group demonstrated a lower mean temperature upon hospital arrival and reduced times to therapeutic range; however, there was a higher incidence of prehospital re-arrests

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and pulmonary edema, possibly owing to the large fluid boluses used for induction. There was no difference in overall survival to hospital discharge.

In this *CJEM* issue, Schenfeld et al. report a pragmatic observational study examining the effectiveness of prehospital MTH in decreasing the time-to-target temperature among those who survived to intensive care unit (ICU) admission and were treated with a MTH protocol, in comparison to historical controls who had MTH initiated upon emergency department arrival.[50] Due to the study's restrictive and subjective inclusion criteria and observational design, conclusions of the intervention's effectiveness on survival and neurological outcomes cannot be drawn. However, this study provides insight into the real-world application of prehospital MTH. Similar to the controlled trial setting of Kim et al.,[48] the prehospital MTH group demonstrated longer times to hospital arrival. In contrast to several previous RCTs,[47-49] time to therapeutic range was not decreased. This study adds to the body of evidence, indicating the lack of benefit of prehospital MTH, when compared to MTH initiated upon hospital arrival.

An alternative theory emerged, that perhaps the apparent benefit of MTH was not in its subnormal temperatures but in its ability to mitigate the detrimental effects of hyperthermia,[51] a common occurrence in post-OHCA patients.[52] If this hypothesis were true, earlier MTH induction would be largely irrelevant because hyperthermia is rare in the early course of the post-arrest patient.[26,53] MTH was rebranded to the more general term, *targeted temperature management*, and a large multicentre randomized control trial was undertaken, randomizing 950 unresponsive patients after OHCA to the temperature goals of 33°C (91.4°F) and 36°C (96.8°F).[53] The only initial rhythm that was excluded was asystole in unwitnessed arrests. TTM was initiated within 240 minutes of ROSC, and measures to avoid hyperthermia continued for a total of 72 hours, with assessor-blinded, standardized neuroprognostication taking place at a minimum of 108 hours after TTM initiation. The results of this study were neutral, without demonstration of superiority in neurological outcomes or mortality of one target temperature over the other. This was the largest and most rigorously performed MTH/TTM study to date, and has led to practice changes in goal temperatures within critical care post-OHCA protocols, while ensuring continued attention to temperature regulation.[54]

Although the strategy of preventing hyperthermia in the days subsequent to an OHCA appears beneficial, there may still be benefit with immediate post-arrest or intra-arrest hypothermia to reduce or prevent reperfusion injury, as has been demonstrated in multiple animal models.[29,55] With the exception of the original study by Bernard et al.,[25] the comparator groups in studies examining prehospital MTH induction have been in-hospital MTH, resulting in small differences in cooling time metrics, possibly the reason for neutral outcome results. Although likely a systematically different patient population, remarkable neurological outcomes with prolonged CPR have been reported in patients with pre-arrest hypothermia.[56] The ongoing RINSE[57] and PRINCESS[58] trials may provide insight into this question and into the safety of iced saline induction, randomizing patients to intra-arrest prehospital MTH using iced saline and a novel intranasal device, respectively. If harm is shown with the intervention groups, then this will likely be the last nail in the coffin for prehospital MTH. However, in the absence of this, because the comparator group in these studies is hospital-based MTH, a comparison to normothermic TTM may be required to detect a possible benefit of MTH in limiting early reperfusion injury.

Schenfeld et al. should be commended on their contribution to the field of resuscitation research. Acknowledging this and other data, at the current time, we are still lacking compelling evidence for a role of MTH/TTM in the prehospital environment. We will eagerly await the results of further studies to help determine the ideal initiation method and time, and patient populations for whom MTH and/or TTM therapies would be most beneficial.

Keywords: cardiac arrest, hypothermia, emergency medical services

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