Therapeutic Hypothermia on Its 10th Anniversary
Is it Time to Turn the Thermostat Down?

Tomas Drabek, MD; Patrick M. Kochanek, MD

It has been 10 years since 2 seminal articles reported a dramatic improvement in survival and neurological outcome of comatose survivors from out-of-hospital ventricular fibrillation cardiac arrest (CA) with postresuscitative therapeutic hypothermia (TH). These exciting findings came after many years of resuscitation research that failed to yield a breakthrough therapy substantially advancing the outcome of CA victims. The results sparked a new enthusiasm in resuscitation research and launched multiple initiatives to bring this method to practice. Surprisingly, the protocol used in these studies was very simple: induce TH to between 32°C and 34°C and maintain it for 12 to 24 hours. The obvious simplicity and the apparent lack of need for sophisticated equipment made the technique very appealing. It was readily adopted in the both 2005 and 2010 resuscitation guidelines and soon started to be implemented worldwide.

These findings were not surprising to those who closely followed resuscitation literature. In fact, hypothermia has been used for CA survivors and other critically ill patients for decades. To our knowledge, the initial series of TH applied to victims of CA of various origins (anaphylactic shock, respiratory failure, and trauma) was published in 1958. Surprisingly, the target temperatures and duration of cooling (30–34°C for 24–72 hours) closely resembled current recommendations (32–34°C for 12–24 hours). In 1959, Benson et al reported the first case series of in-hospital CA patients. Their data revealed favorable neurological recovery in 50% of patients treated with hypothermia versus 14% in those treated with normothermia. In 1964, TH was already endorsed by Safar in his first “ABCs of resuscitation.” However, variable use of hypothermia, being implemented at levels ≤30°C or for prolonged durations, was associated with adverse effects that stalled the future developments. On the other hand, experimental studies continued to provide data supporting the unequivocal benefits of hypothermia on outcome from brain ischemia, already anticipating upcoming clinical trials. The benefits observed in these studies, combined with a large body of evidence stemming from the use of hypothermia in cardiac surgery, provided cornerstones for the paramount success of TH in ventricular fibrillation CA survivors. The evidence was further strengthened by the fact that similar results were achieved simultaneously on 2 continents in 2 independent clinical trials. The patient population was limited to ventricular fibrillation CA, to target the victims who were not deemed beyond the limits of resuscitability, although the full scope of the efficacy of TH remains to be determined.

Ten years ago, we were left with multiple questions that could be turned into hypotheses: (1) Is early initiation of TH better? (2) How long should TH maintained for? (3) Should we target the duration of TH to the severity of the insult? (4) Are temperatures between 32°C and 34°C optimal regardless of the insult? (5) Is TH beneficial in other CA scenarios, for example, in nonshockable rhythms or in-hospital CA? (6) Could TH be beneficial in other closely related settings, for example, stroke, intracranial hemorrhage, or traumatic brain injury? and (7) What about asphyxial CA in children? Last, but not least, the question of utmost importance is how exactly does hypothermia work?

The next decade focused mostly on 2 aspects of TH, evaluation of early initiation and varying duration. These efforts were sparked by the evidence that the deleterious postreperfusion cascades result in delayed neuronal death that starts to occur at ≈48 to 72 hours, often beyond the time that TH is discontinued in clinical practice. This was of a concern, because there are fears that brief applications of TH may delay rather than prevent neurological damage.

In this issue of Circulation, Lopez-de-Sa et al took the next logical step and compared the 2 margins of the depth of TH using the protocol that is currently endorsed, that is, 32°C versus 34°C. Unlike the original studies, they not only evaluated comatose survivors of shockable rhythm, but they also enrolled patients with asystole. The primary outcome was survival free from severe dependence at 6 months. This is in accordance with a recent consensus statement of the American Heart Association, which stated that longer-term end points, such as 90 days, coupled with neurocognitive and quality-of-life assessments, should be considered in large trials of resuscitation science, because neurological assessments can fluctuate for ≈90 days after CA. Lopez-de-Sa et al demonstrated that, in patients surviving CA from shockable rhythm, a lower level of TH, that is, 32°C, resulted in better outcome than TH at 34°C. All of the patients who were resuscitated from asystole died. Importantly, the patients subjected to deeper hypothermia also showed a lower incidence of clinical seizures.

These results are certainly intriguing and merit further investigation in larger studies. The efforts by Lopez-de-Sa et
al\textsuperscript{11} were facilitated by enormous technological advances in the cooling devices. In contrast, the breakthrough success in the original studies was achieved by using simple techniques such as applying cold packs\textsuperscript{9} or forced air-cooling, respectively.\textsuperscript{1} Despite the slow induction of TH and rather imprecise control of the target range, the method still proved effective. Multiple novel devices have been developed ranging from surface-applied gel pads to servo-controlled smart catheters, which can facilitate targeted temperature management in essence allowing the temperature to be clamped at the desired range.

This clinical trial by Lopez-de-Sa et al\textsuperscript{11} was preceded by many experimental studies exploring different levels of TH in both small and large animal models. The work by other researchers has systematically explored the effects of different levels of hypothermia in small animal models, whereas Safar\textsuperscript{6} and others pioneered the field in large animals. They independently showed that the protection offered by TH depends on the level and duration. If we could briefly summarize the results of multiple studies, it became apparent that even the smallest differences in temperature could have an enormous impact on the outcome. However, it also became clear that mild hypothermia seemed more efficacious than moderate (28°C) or deep (15°C) hypothermia after CA in dogs.\textsuperscript{13,14} Surprisingly, there is a lack of clinical data comparing different levels of TH. There is a currently ongoing clinical trial comparing the effects of 36°C versus 33°C in comatose survivors after CA.\textsuperscript{15} Nevertheless, the optimal level of hypothermia thus remains unresolved. The study by Lopez-de-Sa et al\textsuperscript{11} thus, adds an important piece to the unresolved puzzle and suggests the need for careful exploration of the depth of TH. However, caution is advised given the well-known association between overcooling (<32°C) and cardiovascular complications.\textsuperscript{16}

Recent advances also introduced continuous EEG monitoring into the critical care for comatose survivors largely to aid in prognostication.\textsuperscript{17} However, continuous EEG also helped to reveal a frequently overlooked phenomenon, the occurrence of subclinical nonconvulsive seizures that could be masked by a concurrent neuromuscular blockade to facilitate TH.\textsuperscript{18} These electrographic seizures and epileptiform activity are common continuous EEG findings in comatose patients treated with TH. In a recent report by Mani et al\textsuperscript{19} most seizures were status epilepticus, had onset before rewarming, evolved from previous interictal epileptiform activity, and were associated with short-term mortality and poor neurological outcome. These findings are important because they may represent a valid therapeutic target. The current study by Lopez-de-Sa et al\textsuperscript{11} reports lower incidence of seizures with deeper hypothermia. We may speculate that this could be one of the key underpinning mechanisms responsible for the improved outcome in the patients maintained at 32°C.

The lack of effect of either level of TH on outcome in patients from nonshockable rhythm in the current study is certainly disappointing. Recent meta-analyses showed a positive effect of TH in patients presenting with nonshockable rhythms on in-hospital mortality but not on neurological outcome\textsuperscript{20} or no effect at all.\textsuperscript{21} In contrast, other studies reported benefits of TH even in this setting.\textsuperscript{22,23} Not all studies were able to reproduce the success of the 2002 trials.\textsuperscript{24} However, the overwhelming majority of studies support the benefits of TH.\textsuperscript{25} There remains some skepticism regarding whether the effects of hypothermia are not rather caused by the avoidance of hyperthermia that is now known to aggravate neurological injury. Of note, hyperthermia was not systematically treated in the control groups of the 2 seminal articles.

It is becoming apparent that not “all hypothermias are created equal,” but rather “some levels are more equal than others,” to paraphrase George Orwell. The effects of TH are still understudied. It is clear that the effects of TH after CA could be highly dependent on depth and duration of cooling, vary greatly with regard to the type and severity of the insult, vary within versus outside of the central nervous system, and even differ in individual brain regions. Determining how to optimally titrate TH will be essential to maximize its therapeutic potential. We have come to realize that TH is a very complex therapy.\textsuperscript{26} However, given its unique value in neuroprotection, future experimental and clinical trials must address some of the aforementioned conundrums and define its optimal applications to improve neurological outcome of patients after CA.

For now, something as simple as turning the down the thermostat slightly to 32°C may help to save more “hearts and brains too good to die.”\textsuperscript{27}

**Disclosures**

Dr Drabek is funded by grants 09BIA2310196 from the American Heart Association, W81XWH-07-1-0682 from the US Army, and from the Laerdal Foundation for Acute Medicine. Dr Kochanek is funded by grants NS070324, NS070003, and HD040686 from the National Institutes of Health, and W81XWH-09-2-0187 and W81XWH-10-1-0623 from the US Army. Dr Kochanek is a coprovisional patent holder on the following: (1) a hypothermia strategy “Emergency Preservation and Resuscitation”; (2) a Carnegie Mellon University Invention Disclosure 2012-081 “Validation of a Multiplex Biomarker Panel for Detection of Abusive Head Trauma in Well-Appearing Children”; and (3) US Provisional Patent “Small Molecule Inhibitors of RNA Binding MOTIF (RBM) Proteins for the Treatment of Acute Cellular Injury.”

**References**


**Key Words:** Editorials ■ cardiac arrest ■ mortality ■ outcomes research ■ resuscitation ■ hypothermia
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*Circulation*. 2012;126:2803-2805
doi: 10.1161/CIRCULATIONAHA.112.153619

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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