How Low Should We Go?

Hypothermia or Strict Normothermia After Cardiac Arrest?

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Current guidelines from the American Heart Association recommend use of therapeutic hypothermia (TH) after witnessed cardiac arrest (CA) to mitigate posthypoxic injuries. This is based on results of 3 randomized, controlled trials (RCTs) enrolling 385 patients, 43 before–after studies enrolling 10442 patients, and supporting evidence from the field of neonatal asphyxia where 7 RCTs enrolling 1329 patients also demonstrated neuroprotective effects of hypothermia. However, this has been called into question by a recently published RCT enrolling 939 patients, which found no benefit of cooling to 33°C compared with maintaining 36°C. In this article we review the literature, with extra attention for strengths and weaknesses of the recently published RCT. In view of potential weaknesses in the new study (including a possibility of selection bias, long delays before initiation of cooling, a time to target temperature of 10 hours, and a rapid rewarming rate), we conclude that there are sufficient grounds to continue using hypothermia in most patients with witnessed ventricular fibrillation (VF)/ventricular tachycardia (VT) arrest, pending results of further studies which should examine multiple temperature levels (32–36°C) and multiple treatment durations (24–72 hours). The bases for these conclusions are discussed in detail below.

Why We Came to Use Hypothermia After Cardiac Arrest, and Why a New Trial Was Done

The use of TH to mitigate various types of injury, in particular posthypoxic injury to the brain, has been studied since the late 1930s. Interest was initially kindled by reports of survival after prolonged exposure to cold, or submersion in ice-cold water, indicating a possible protective effect of low temperature on hypoxic injuries. Use of hypothermia after CA was first described in the late 1950s, but conclusive proof that hypothermia could improve outcome in these patients remained elusive. At the time it was thought that protective effects of TH were purely a result of hypothermia-induced lowering of metabolism; therefore, it was presumed that very low temperatures (25–28°C) were needed to provide significant neuroprotection. This perception changed in the late 1980s, when animal studies demonstrated that significant protective effects also occurred with mild hypothermia (30–34°C), with far fewer side effects, and that a variety of destructive mechanisms were moderated by hypothermia rather than just reductions in brain metabolism.

In the late 1990s a number of small nonrandomized, clinical trials provided better evidence for the efficacy of TH. This led to the initiation of 2 landmark multicenter RCTs to test the treatment, the results of which were published in 2002. Both reported clear and significant improvements in outcome in CA patients treated with therapeutic cooling (Table).

The largest study, performed in 11 centers in Europe, enrolled 275 patients with witnessed CA and an initial rhythm of VF or pulseless VT. The authors observed a 15.8% absolute (35.1% relative) improvement in outcome in the hypothermia group (P<0.01). The other RCT enrolled 77 patients across 4 centers in Australia, reporting an absolute improvement of 22.3% (relative improvement 43.7%) in patients with witnessed VT/VF treated with hypothermia compared with controls (P<0.05). A meta-analysis calculated that 1 additional case of good neurological outcome would be gained for every 6 patients treated with TH. Guidelines from various medical societies such as the American Heart Association (AHA), European Resuscitation Council (ERC), and Neurocritical Care Society (NCS) began recommending cooling after CA; the 2010 AHA guidelines strongly recommend use of hypothermia (32–34°C) after out of hospital cardiac arrest (OHCA) with an initial rhythm of VF or pulseless VT (class I, level of evidence B), and state that TH should also be considered for in-hospital arrest or initial pulseless electrical activity or asystole (class IIb, level of evidence B). A Cochrane review published in 2012 supported these recommendations.

The initial publications were followed by 43 before–after studies in centers that began using the new therapy, most of which were performed in Europe. Altogether these studies reported outcome data from 10442 patients with witnessed VT/VF arrest. All noted significant improvements with TH implementation compared with historical controls; the average rate of good neurological outcome in patients treated with TH was 53.1%. Further supporting evidence came from the field of neonatal asphyxia, where 7 multi-centered RCTs demonstrated that TH could mitigate global posthypoxic injury occurring during birth. These studies, using core temperatures of 32 to 34°C for periods of 48 to 72 hours with cooling initiated within 6 hours after birth in newborns showing signs of severe
Although, this last strength (vast experience in use of TH) may also be a significant weakness, as this introduces the risk of selection bias. The reason for this is that, in contrast to previous studies, with predefined subgroup analyses to correct for various risk factors. The results of this study were negative (Table).23 Rates of survival with good neurological outcome were 46.5% in the 33°C group versus 47.8% in the 36°C group (P=0.78). The rate of survival with excellent outcome (no neurological residual) was 41.6% versus 39.4%, whereas survival with mild neurological impairment was 4.9 versus 8.4%.23 The authors conclude that maintaining core temperature at 36°C has equally good outcomes as cooling to 33°C.

This observation seems to contradict the findings of all previous studies. How can this be explained, and how should we move forward? Many centers are considering a change in their treatment protocols based on the results of this trial, specifically changing from therapeutic hypothermia to just fever control. There is discussion within the AHA and ERC on whether current resuscitation guidelines recommending use of TH should be changed. Thus, it is important to take a close look at all the available evidence (particularly the TTM study), and examine the pros and cons of maintaining current guidelines versus shifting to a fever management–only approach.

### Strengths and Weaknesses of the TTM Trial
The TTM trial has a number of significant strengths. In terms of number of patients enrolled it is 1 of the largest studies performed in the field of resuscitation medicine. The study had a rigorous, predefined protocol for withdrawal of care to help avoid risk of treatment bias, and follow-up of enrolled patients was meticulous; only 6 patients were lost to follow-up. In addition, the participating centers all had experience in use of TH; indeed, many had previously published scientific articles describing their experience with TH implementation.24–27

However, this last strength (vast experience in use of TH) may also be a significant weakness, as this introduces the risk of selection bias. The reason for this is that, in contrast...
to all previously performed trials, hypothermia was already standard of care in all hospitals participating in the TTM trial. Therefore, in contrast to all previously published randomized and nonrandomized TH studies, the default option for all patients not enrolled in the trial was therapeutic cooling to 32 to 34°C.

It is worth elaborating on how crucial this difference could be. In (almost) every randomized study to test the efficacy of a therapeutic intervention, the only way to receive the treatment under investigation is to participate in the trial, and to be randomized to either receive the new treatment or placebo/standard care. This certainly applied to the previous RCTs of therapeutic hypothermia, where only study patients could receive TH (if they were randomized to the treatment arm).\textsuperscript{10,11} Patients admitted to participating hospitals while these trials were ongoing were not, and could not be, treated with TH. Subsequent nonrandomized trials simply began using TH in all or most or all of their witnessed CA patients, comparing outcomes with historical controls or with patients who for various reasons were ineligible for TH.\textsuperscript{24–27}

In marked contrast, in centers participating in the TTM trial the default option for patients not enrolled in the study was to be treated with 32 to 34°C TH, while patients who were enrolled in the TTM trial could either receive standard TH (33°C), or NOT receive standard TH but only strict fever control.

If given the choice, would this not lead to ethical dilemmas in those making the decision whether to screen patients for trial eligibility? Many hospitals participating in the TTM trial had previously published excellent outcome results in their own centers associated with introduction of TH, and had strongly endorsed the use of TH after CA.\textsuperscript{24–27} In fact, these previously reported outcomes were much better than those achieved in either group of the TTM trial: 56% (registry, n=686),\textsuperscript{24} 63% (2 centers, n=38),\textsuperscript{25} 57% (4 centers, n=360),\textsuperscript{26} and 63% (2 centers, n=94).\textsuperscript{27}

Many other hospitals participating in TTM that had not previously published their outcome data in cardiac arrest had participated in the Northern Hypothermia Network (NHN), a registry for CA patients treated with hypothermia. The outcome data of 986 registry patients treated with TH were published in 2009; survival in patients with initial rhythm of VT/VF was 61%, with favorable neurological outcome in 56%.\textsuperscript{24} For all of the centers participating in the NHN registry this represented a huge improvement compared with historical controls, and also compared with patients admitted in the same time period but who for miscellaneous reasons had not received TH. Based on these results it is beyond doubt that many local physicians and nurses would have become strong advocates of TH. In fact, 1 of the stated goals of the NHN registry project was “to promote the use of Therapeutic Hypothermia.”

In the unusual situation in which the treatment to be investigated is already standard of care for nonparticipating (and nonconsenting) patients, and where there is likely to be a widespread acceptance of the efficacy of the treatment among the members of the medical and nursing staff, the only way to avoid selection bias is to rigorously screen all cardiac arrest patients for eligibility according to strict, predefined criteria, and then to make every effort to enroll those meeting the criteria. On close examination of the TTM study results and the number of patients screened and enrolled, it seems unlikely that a generalized screening of all CA patients occurred. Indeed, the enrollment numbers very strongly suggest that there was some type of preselection. The average number of patients screened per center per year is 18, of whom 12 per center per year were enrolled.* \textsuperscript{*Calculated as follows: Trial period 2 years and 2 months, 36 participating intensive care units; 1431 patients screened, 939 enrolled. 1431+26 months = 55 patients/mo; +36 centers = 1.5 patient/mo. 939/26=36/mo; 36/36=1 patient/mo/center enrolled. Four coauthors of the TTM study subsequently published a statement indicating that it took 9 months before >50% of sites had started recruitment, and that the median enrollment rate was 21 patients.\textsuperscript{28} This information was not contained in the original manuscript but if correct does not change the essence of the argument; the number of enrolled patients then rises from 12 to 17 per year (26−9=15 months, median 21 patients + 15 months = 16.8 patients per center per year). This number remains low and thus preselection remains likely.] This enrollment percentage is almost two-thirds of screened patients: this is unusually high compared with previous studies for cardiac arrest, and indeed is unusually high by any standard. But even leaving the percentage of successful enrollment after screening aside, the absolute number (1 patient per center per month enrolled) is very low for these high-volume centers. In fact those centers that had previously published outcome studies in CA patients always reported significantly higher monthly enrollment numbers, by a factor of 2 to 5.\textsuperscript{24–27} Thus, based on these numbers it seems almost certain that some type of preselection must have occurred.

The question then becomes whether this selection was systematic or random, whether it is likely that both treatment groups would have been equally affected, and whether this selection could have had a major impact on the results of the trial. Unfortunately, we believe that the answer to the last question is yes: the potential impact on the study results could be substantial. The reason is that specific patients with greater potential to benefit from TH might have been (subconsciously) directed to receive routine TH rather than being screened for trial eligibility, whereas those less likely to benefit would be more likely to be screened and enrolled in the trial.\textsuperscript{29}

It could be argued that the overall rates of good outcome in the TTM trial (46.5% versus 47.8%) are relatively good, and that this proves that not only nonsalvageable patients were enrolled in the trial. This is true but misses the point. Any potential bias by those doing the prescreening would be subconscious, and certainly not designed to spoil the study. Rather, those with perceived benefits from TH would be less likely to be screened and enrolled—leaving a higher proportion of not just nonsalvageable patients but also a higher proportion of those with less severe injuries—those who would have done well regardless of the type of temperature management. Indeed, it transpired during discussions of the logistics of the TTM trial at meetings and symposia that study coordinators would be called by emergency department physicians when these physicians thought that they had a suitable patient for the study—exactly the situation that could have led to the type of subconscious bias described above.
In our mind the potential for selection bias is the most important issue, though not the only one that needs to be addressed when interpreting the results of the TTM trial, and when deciding what if any changes in clinical practice these results should lead to. Some other issues include the following:

- Patients requiring chest compressions for >20 minutes were excluded, and an unusually high percentage (73%) received bystander cardiopulmonary resuscitation within 1 minute (median) after arrest. These criteria may (partly) explain the relatively high rates of good outcome in both groups, and may have selected for patients less likely to benefit from lower temperature targets. It should be noted that compared with Europe fewer patients in the United States would meet these criteria, as rates of bystander cardiopulmonary resuscitation are generally lower and many patients require >20 minutes of resuscitation.20

- There was a long delay (up to 4 hours after arrest) before cooling was initiated. The published article does not provide the average time to initiation of cooling (except for stating that it could be up to 4 hours),23 but during subsequent presentations and interviews the authors have indicated that on average 130 minutes elapsed before any cooling was initiated. This seems long, as cooling usually begins immediately on hospital arrival (and sometimes at the site of the arrest or in the ambulance). For comparison, the study by Bernard et al11 initiated cooling in the ambulance, and had achieved target temperature after 150 minutes. However, cooling was started after an average of 105 minutes in the HACA trial,20 which is more comparable with TTM.

- Time to target temperature in the TTM trial was 8 hours, meaning that patients reached the target of 33°C on average 10 hours after return of spontaneous circulation. This is an extremely long time by most standards. The time to temperature <34°C (5 hours) is more acceptable, though still slow by modern standards. Of note, a small pilot study published recently in Circulation randomized post-CA patients to target temperatures of either 32°C or 34°C, and reported significantly better outcomes at 32°C (61.5% versus 15.4%, P=0.029).23 This implies that getting temperatures well below 34°C may be crucial in at least some CA patients; if true this means the late start of cooling and slow cooling rates could have significantly affected treatment results in the 33°C group of the TTM trial.

- In addition, outcomes in the TTM trial could have been affected by temperature fluctuations in the maintenance phase, and especially by a subsequent rapid rate of active rewarming (from hypothermia to normothermia in 6 hours).23 Rapid rewarming can have severe detrimental effects in posthypoxic brain injury when patients are rewarmed after treatment with TH, and can completely negate the protective effects of TH.4,5,32

- The temperature graphs in the original TTM publication,23 as well as in subsequent articles,28 are cut off at 36 hours; at this time the 33°C group was still rapidly warming but temperatures between the 2 groups had not yet equalized, with a remaining temperature difference of ±0.7°C. It would be interesting to see if any rebound hyperthermia occurred in the 33°C group after rewarming, or if there were other differences between the groups. This is important because fever developing after TH treatment has been linked to increased mortality after CA,33 in other words, fever is more harmful after hypothermia treatment. For comparison, the HACA paper provides temperatures for 48 hours — the point where temperatures of the HACA treatment groups converge.10 To date, despite publishing numerous comments and spin-off papers from the original trial, to our knowledge the authors of the TTM trial have not yet published a more complete set of temperature data.

- Finally, there are subtle imbalances between the 2 groups that may indicate somewhat greater severity of initial injury in the 33°C group.20 The following factors known to be associated with unfavorable prognosis after OHCA were more prevalent in the 33°C group (absolute percentage of difference calculated from raw numbers in Table 1 of the TTM article and its online supplement, all absolute differences >0.3% listed): absence of pupillary reflexes (4.5%) and corneal reflexes (1.0%); persistent circulatory shock (0.4%); lower incidence of witnessed arrest (0.9%), initial rhythm of ventricular fibrillation (2.6%), or other shockable rhythm (1.6%) as first recorded rhythm; higher incidence of pulseless electrical activity (1.8%); history of chronic heart failure (0.5%), previous acute myocardial infarction (4.2%), ischemic heart disease (6.0%), CABG (0.9%), cardiac arrhythmia (1.4%), percutaneous coronary intervention (1.5%), or arterial hypertension (1.9%); male sex (4.1%); and a 1-minute longer median time until start of advanced life support (10 versus 9 minutes). Far fewer factors favored the 33°C group; these were lower incidence of previous TIA or stroke (0.7%), diabetes mellitus (4.3%), or asthma/COPD (0.4%); and perfusing rhythm after bystander cardiopulmonary resuscitation (1.0%). None of these individual differences are statistically significant, but cumulatively they could have had an impact on the overall results of the trial.

Other observations from the TTM study also suggest greater severity of initial injury in the 33°C group. These include a greater prevalence of spontaneous hypothermia (before start of active cooling), potentially indicating greater severity of brain injury with diminished shivering response4,5,32; a higher incidence of myoclonic seizures (absolute difference 5.4%), in spite of the fact that hypothermia suppresses epileptic activity which should have lowered the risk of seizures4; and the fact that more patients in the 33°C group met criteria for early withdrawal of care (absolute difference 3.2%).23 again suggesting greater severity of initial injury.

Where to Go From Here?

As outlined above, current AHA guidelines are based on 2 RCTs (admittedly smaller than the TTM trial), on dozens of observational studies, and on strong supporting clinical and pathophysiological evidence (including well-designed multicenter clinical trials in patients with neonatal asphyxia). Taking all this into account we feel that the TTM results should not lead to a fundamental change in AHA guidelines at this time, although we believe that some smaller changes may be warranted. The TTM results do demonstrate that
strict fever control may be a sufficient form of temperature management in some patients, and can lead us to consider this in patients who are at higher risk of side effects from TH (e.g., those with high risk of active bleeding). But in our view, based on all currently available evidence, the TTM results should not lead to an upward change in recommended target temperature in the majority of patients with witnessed cardiac arrest at this time, and certainly should not be taken as a reason to completely abandon temperature management after CA. The results of this latest study should be weighed against previous evidence, and possible selection bias and other issues affecting the TTM trial should be taken into account.

It is noteworthy that in recent years published outcomes in patients with OHCA in the United States have, with 2 notable exceptions discussed in more detail below,35,36 been significantly worse than in Europe and Australia. A large multicenter study published in 2008 reported 3.0% to 16.3% (median 7.9%) survival after OHCA37; for patients with initial rhythm of VT/VF good outcomes ranged from 7.7% to 39.9% (median 21%). A multicenter cohort study using a database of intensive care units from 120 U.S. hospitals reported favorable outcomes in 34% of OHCA patients admitted to the intensive care unit.38 Aside from the astounding differences between centers (5 times better outcomes in the best performing compared with the worst performing center),37 it is noteworthy that even the best number is well below the average of 53.1% reported in centers using TH.3 Of course there are other important factors potentially contributing to worse outcomes in the United States, such as higher rates of obesity, greater distances to the closest hospital, staffing of ambulances by physicians in some European countries, and others.30 However, it is noteworthy that TH, which is standard of care in most European hospitals, is underused in the United States despite published guidelines. Recent publications suggest that only 2% to 6% of CA patients in the United States receive TH38,39; these studies were performed in a period when published guidelines already strongly recommended use of TH after CA.35,36 and long before the results of the TTM trial were published. In contrast, 2 recently published U.S. studies that did report outcomes comparable with the best centers in Europe both used TH in all patients.35,36 The largest study (1364 patients enrolled, of whom 583 had a shockable rhythm), comparing prehospital cooling with cooling initiated at hospital admission, found no benefits of prehospital cooling but had an overall rate of survival to hospital discharge of 63.5% (!) among cooled patients with VT/VF;59.7% had long-term survival with good neurological outcome. Rates of good outcome were 58% in a study by Mooney et al59 reporting on the roll-out of their hypothermia protocol. In contrast, rates of favorable outcome were only 34% in the study by Kilgannon et al,38 where <6% of patients had been treated with TH.

In summary, in witnessed VT/VF arrest average rates of good outcome are generally >50% when TH is used, whereas no study that did not use TH ever reached this number. Whatever the strengths and weaknesses of the TTM trial, on any interpretation the results do not justify altogether abandoning temperature management, or ignoring temperature as a crucial parameter in post-CA patients. The TTM trial applied intensive temperature control in both groups, and not even the TTM authors’ advocate cessation of active temperature management after CA.40

Unfortunately, some may use the TTM trial results to argue that temperature is not important, or that it can be controlled sufficiently through administration of acetaminophen or non-steroidal anti-inflammatory drugs without use of mechanical cooling devices. However, the average drop in temperature that can be achieved with high doses of anti-inflammatory drugs is only 0.3 to 0.7°C,4,41,42 which is insufficient to achieve even adequate fever control, let alone the mild degree of hypothermia (36.0°C) that was maintained in the control group of the TTM trial. Even if one were to uncritically accept the results of the TTM study, it still would not justify ignoring temperature or even tolerating normothermia of 37 or 37.5°C in patients after CA.

Of note, it can be more difficult to maintain normothermia than to maintain hypothermia, as the shivering response is usually much stronger and harder to suppress at temperatures around 36.0°C than at temperatures of 32 to 33°C.4,32

This phenomenon may have occurred in the TTM trial itself, because on average more drugs were required to control shivering in the 36.0°C than in the 33.0°C group.4,32 It is a misconception that strict fever control would be somehow easier than inducing and maintaining hypothermia.4,32

As discussed above, the results of the TTM trial clearly suggest that in some CA patients strict fever control is sufficient to mitigate hypoxic injury. However, we currently have no reliable way to identify these patients, and to distinguish them from those who might benefit from deeper and perhaps more prolonged hypothermia. In theory, one could argue that deeper hypothermia should be used only in patients with longer downtime, or perhaps those with initial rhythms of pulseless electrical activity or asystole, whereas 36.0°C could be used in patients with a likely less severe injury. However, in truth there is no reliable way to decide which temperature target is appropriate for individual patients; in fact it could be argued with equal validity that less severely injured patients might benefit more from hypothermia, because they have a better chance of full neurological recovery.

**Conclusion**

Because there is persuasive evidence that at least some patients benefit from lower (32°C) temperature goals,31 because the best published outcomes have been achieved with protocols using hypothermia rather than just fever control,35,36 and because numerous studies have demonstrated that TH treatment can be applied safely and with minimal side effects in this patient category, we feel that we should continue to cool most CA patients to 32 to 33°C at this time, pending the results of further studies which should compare different temperature levels (32°C, 34°C, and 36°C) and determine optimal duration (24, 48, or 72 hours) of TH, always with a slow (0.1 to 0.25°C/hr) rewarming rate. Perhaps in years ahead improved monitoring tools such as continuous EEG, biomarkers, regional monitoring of brain perfusion and oxygenation, brain temperature mapping, and other tools will allow us to better tailor temperature management to the needs of individual patients.43
Finally, recent studies clearly demonstrate that rates of good outcome in witnessed VT/VF arrest can, and should, be ≥50% or better, and that even patients with nonshockable rhythms should have a 1 in 5 chance of full recovery. Our primary challenge should be to meet these targets in all centers treating patients with cardiac arrest.

Disclosures

None.

References


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