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CURRENT PERSPECTIVES

Through the Looking Glass: The Paradoxical Evolution of Targeted Temperature Management for Comatose Survivors of Cardiac Arrest

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Abstract
For the past two decades, targeted temperature management (TTM) has been a staple in the care of comatose survivors following cardiac arrest. However, recent clinical trials have failed to replicate the benefit seen in earlier studies, bringing into question the very existence of such clinical practice. In this review, we explore clinical scenarios within critical care that appeared to share a similar fate, but in actuality changed the landscape of practice in a modern world. Accordingly, clinicians may apply these lessons to the utilization of TTM among comatose survivors following cardiac arrest, potentially paving way for a re-framing of clinical care amidst an environment where current data appears upside down in comparison to past successes.

Keywords Targeted temperature management · Cardiac arrest · Hypothermia · Neuroprotection

Introduction

It has been 20 years since the publication of two landmark clinical trials that demonstrated favorable neurological outcome and reduced mortality among comatose survivors of cardiac arrest treated with mild induced hypothermia (32–34 °C) [1, 2]. The global impact of these trials was substantial, leading to the widespread adoption of induced hypothermia, now known as targeted temperature management (TTM), for cardiac arrest as well as other forms of acute brain injury. A flurry of single-center before-and-after reports replicated and supported the findings of these trials, consistently finding improved outcomes among cardiac arrest victims after a therapeutic hypothermia protocol had been implemented [3]. TTM became an entirely new therapeutic modality that was unique to neurocritical care, helping it emerge as a legitimate medical subspecialty.

In recent years, however, two important clinical studies—the TTM-1 and TTM-2 trials—have failed to replicate the positive results from 2002. At first glance, it may appear clinicians are faced with clinical equipoise with regard to the care of this patient population amidst these conflicting results. However, a glimpse into the past with respect to similar clinical questions within critical care may offer an explanation to the discordant results of the various trials involving TTM following cardiac arrest. Understanding how breakthrough treatments in critical care often seem at first to work, before then losing their singular impact as the overall treatment milieu evolves, may enable clinicians to re-frame their approach in clinical practice not only with respect to TTM but also other challenging areas of critical care as well. Herein, we review the history of the pre-clinical and clinical studies leading to our current understanding of TTM following cardiac arrest. We then look into clinical schemas based on other critical care interventions in an attempt to reconcile the current state of evidence for and against TTM.

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The Evolution of Targeted Temperature Management

Leading to the clinical trials that have impacted our clinical practice of TTM, there were numerous investigations throughout the twentieth century into the basic science of hypothermia and how it may benefit the brain following a period of anoxia. Proposed mechanisms that emerged included a reduction in overall oxygen consumption [4, 5], early restoration of cerebral adenosine triphosphate levels [6, 7], reduction of intracellular acidosis [7], and a decrease in the release of excitatory neurotransmitters that could facilitate neuronal death following ischemia [8]. Collectively, these alterations potentially reduce delayed cerebral energy failure by preserving mitochondrial function [9]. Furthermore, induced hypothermia has been demonstrated to decrease cytotoxic edema and lessen overall seizure intensity and burden that may lead to secondary injury after a hypoxic-ischemic insult [9].

In 1960, Kenneth Wolfe built off the ideas of Rosomoff et al. [10], among others, who reported reduced mortality in canines under hypothermic conditions following surgery. Wolfe's [11] experiment involved controlled hypothermia to 31 °C for a period of 24 h following induced ventricular fibrillation (VF) with return of spontaneous circulation (ROSC). All control subjects died, while all experimental subjects either had a prolonged lifespan (up to 192 h post-ROSC) or were without any reported cerebral damage. Closer to the turn of the century, Leonov et al. [12, 13] published two studies in 1990 that demonstrated a reduction in the total brain histologic damage score and an improvement in neurological outcome among canines when cooled to 34 °C following cardiac arrest with ROSC. These early animal investigations were further substantiated by numerous studies in the years that followed, many of which were conducted during the time period human trials were performed. For example, Arrich et al. [14] conducted a systematic review and meta-analysis that included 45 animal studies with nearly 1000 subjects. The studies investigated TTM in a range of animals (dogs, pigs, rabbits, and rats), had a targeted temperature range of 32–36.2 °C in experimental subjects versus 36.5–39.3 °C in control subjects and had a hypothermia period ranging from 1 to 24 h. The overall results were notable for a significant difference of favorable neurological outcome in favor of the hypothermia groups, with an increase in effect size observed with lower target temperatures, shorter duration of induced hypothermia, and faster cooling rates. With the ever-increasing evidence of the benefit of TTM among animal subjects, human trials became the next logical step. In 1997, a small trial of 22 human subjects underwent induced hypothermia to 33 °C following out-of-hospital cardiac arrest (OHCA) and was compared to historical controls. There was a statistically significant reduction in mortality, with no significant difference in adverse effects [15]. The feasibility of such studies in human subjects continued to gain traction over the next several years, paving way for the breakthrough clinical trials that changed the TTM landscape.

In 2002, the two largest clinical trials at the time were simultaneously published. The Hypothermia after Cardiac Arrest (HACA) Study Group randomized 275 patients to undergo induced hypothermia to a goal of 32–34 °C versus normothermia (37 °C) among comatose survivors [1]. Nearly all of the arrests were witnessed, had shockable rhythms and achieved the goal temperature at a median of 8 h post-ROSC, followed by passive re-warming approximately 24 h later. There was a significant difference among the groups with regard to the primary outcome of favorable neurological outcome, defined as a cerebral performance category (CPC) of 1–2 at 6 months, in favor of the hypothermia group. In addition, there was a reduction in mortality among the hypothermia group as compared to the normothermia group at 6 months, with no statistically significant difference among adverse effects.

In comparison, the trial by Bernard et al. [2] randomized only 77 patients who remained comatose post-arrest. All patients had an initial rhythm of VF, a hypothermia goal of 33 °C, which was achieved within 2 h post-ROSC and maintained for 12 h, and utilized "good outcome," defined as discharge to home or a rehabilitation facility, as the primary outcome. At the completion of the study, the hypothermia group had a more favorable outcome with no significant difference in adverse events. In combination, these trial results led to the American Heart Association and the International Liaison Committee on Resuscitation to formally recommend TTM among comatose survivors following cardiac arrest, which remain in effect today [16, 17].

In 2013, the TTM trial investigators published a clinical trial comparing a hypothermia goal of 33 to 36 °C among comatose survivors of cardiac arrest in order to help answer the question as to whether the degree of hypothermia influenced functional outcome and survival. In comparison to the previous two trials, there were substantially more patients enrolled ($n = 939$), all of whom were OHCA, with the majority having an initial shockable rhythm [18]. There was no statistically significant difference between the groups for the primary outcome of all-cause mortality or any difference among any of the secondary outcomes of neurological function at follow-up (CPC score 3–5, modified Rankin scale [mRS] 4–6) or death at 180 days.

Until this point, there had not been large-scale trials investigating TTM focusing on patients with an initial non-shockable rhythm. As such, in 2019, the HYPERION trial

sought to investigate this question and compared a goal temperature of 33 °C vs. normothermia (37 °C). There were a total of 584 patients included in the analysis, of which 159 were in-hospital cardiac arrests, with the maintenance of goal temperature for 24 h followed by slow re-warming [19]. At the conclusion of the trial, there was a significant difference in favor of the hypothermia group in the primary outcome, defined as a favorable 90-day neurological outcome. There was no difference in overall mortality at 90 days or serious adverse events during the trial. Though this data seemed to support the trial results from 2002, there were a number of limitations. Among these included a number of patients in both groups having temperatures above 38 °C during and after the TTM period, maintenance of TTM up to 64 h in the hypothermia group as compared to 48 h in the normothermia group and a fragility index of 1, suggesting that a change in the outcome of just one patient would make the primary outcome non-significant.

In an attempt to clarify many questions of its predecessors, in 2021, the TTM-2 trial randomized 1850 comatose survivors of cardiac arrest to a target temperature of 33 °C or normothermia (≤ 37.5 °C) with early treatment of fever for a period of 28 h followed by slow re-warming and maintenance of normothermia for 72 h. All patients were OHCA, and the majority had shockable rhythms, though approximately 25% in each group had an initial non-shockable rhythm [20]. There was no significant difference in the primary outcome, which was defined as death from any cause at 6 months. This non-significant difference remained in all subgroup analyses, which consisted of gender, age (≥ 65), time to ROSC (≥ 25 min), initial cardiac rhythm, and whether a shock was administered on admission. As a secondary outcome, there was no significant difference in the proportion of patients with a mRS of 4–6 at 6 months. Of note, there were some potential limitations of the trial, such as standardized protocols for sedation, paralysis, and ventilation management that may not have been representative of routine clinical practice. Nonetheless, the robust sample size and sound trial design have resonated with many in the critical care world.

While the trials outlined above have strongly driven clinical guidelines regarding TTM following cardiac arrest, there have been additional key studies during this same time period that have investigated the issue. Among these include two trials by Lopez-de-Sa et al., the first being a small pilot study of 36 OHCA comatose survivors randomized to undergo TTM at a temperature of 32 °C or 34 °C [21]. There was no significant difference among the groups in the primary outcome of survival free from dependence at 6 months, but a subgroup analysis among those with an initial shockable rhythm favored patients within the 32 °C group. This pilot study was followed up by the same group in 2018 in the FROST-I trial, which was a multicenter randomized clinical trial of 150 OHCA comatose survivors with an initial shockable rhythm comparing TTM goals of 32 °C versus 33 °C versus 34 °C. There was no significant difference among the different temperature groups with regard to the primary outcome of mRS ≤ 3 at 90 days [22].

There have also been numerous studies investigating the timing of TTM initiation. For example, Bernard et al. investigated initiation of TTM in the pre-hospital setting after ROSC among OHCA comatose survivors with shockable [23] and non-shockable rhythms [24], as well as initiation of TTM during cardiac arrest [25], all compared to initiation of TTM within the hospital following arrival. In each of these trials, there was no significant difference in favorable neurological outcome among the groups. While these three trials utilized prehospital administration of cold intravenous saline for initiation of TTM, Scales et al. [26] used cold intravenous fluid and ice packs, which decreased the time to initiate TTM in the hospital, but did not result in more favorable neurological outcome. Nordberg et al. [27] utilized a prehospital trans-nasal evaporative cooling method to initiate TTM, which resulted in faster time to achieve target temperature, but no increase in favorable neurological outcome as defined as a CPC score of 1–2 at 90 days. A recent systematic review and meta-analysis by Granfeldt et al. [28] included many of the aforementioned studies, among others, to analyze the different temperature goals, timing of TTM initiation, and method of cooling, but found no significant difference in favorable neurological outcome or survival among the various comparisons.

Adding to the clinical confusion regarding TTM among human subjects, there have been numerous positive clinical trials utilizing TTM in neonatal encephalopathy. In 2012, a systematic review and meta-analysis of seven clinical trials noted therapeutic hypothermia resulted in a significant reduction in the risk of death and neurodevelopmental disability and increased survival with normal neurological function at age 18 months [29]. The included trials initiated induced hypothermia to 33–35 °C for a period of 72 h for newborns with moderate to severe encephalopathy within 6 h of birth. A subsequent meta-analysis in 2013 supported these conclusions [30], and a long-term follow-up of one trial confirmed functional outcome at 7 years was associated with neurodevelopmental assessment at 18 months following induced hypothermia for neonatal encephalopathy [31]. From an adult perspective, Kirkegaard et al. [32] compared a target temperature of 33 °C for 24 versus 48 h among OHCA comatose survivors but found no significant difference in favorable neurological outcome at 6 months, though the authors note the study may have been underpowered. Correlating with these clinical studies are the pathophysiological manifestations of hypoxic-ischemic injury at the cellular level discussed earlier, with secondary injury beginning after 6 h [33]. A key hallmark of secondary cellular

injury is delayed onset seizures, which are often refractory to anti-epileptic medications, emphasizing the narrow window for initiation of induced hypothermia, especially within the neonatal population [33]. Taken together, given the conflicting results of the extensive number of TTM investigations, there has been speculation among clinicians that the era of utilizing TTM among comatose survivors of cardiac arrest has come to a close.

Lessons Learned from Other Critical Care Disease States

Rather than shunning TTM to the medical archives as an example of an ineffective intervention within the medical world, reflections on the journey until this point may prove useful in an attempt to reconcile why the landmark trials in 2002 were strongly positive, whereas subsequent trials failed to replicate these findings. To begin, one must consider the methodology of any clinical trial and how this evolves with time as new knowledge is discovered. A key example in history relevant to this discussion is the utility of intensive insulin therapy (IIT) in critically-ill patients. A seminal paper published by Van den Berghe et al. [34] from Leuven in 2001 demonstrated reduced mortality among surgical critical care patients treated with IIT targeting a glucose level of 80–110 mg/dL. In later years, additional trials failed to replicate these results, including another study by Van den Berghe et al. [35] with an identical glucose target among patients hospitalized in a medical intensive care unit (ICU). This culminated with the publication of the NICE-SUGAR trial, which demonstrated increased mortality among patients randomized to IIT (goal glucose level 81–108 mg/dL) compared to conventional glucose control (goal glucose level < 180 mg/dL) [36], leading to sweeping recommendations that persist today.

The search for answers as to why the results of the Leuven surgical trial were not replicated by others yields some important lessons with regard to trial methodology. The Leuven study was a single-center experience, not entirely blinded, and consisted of only surgical intensive care patients, raising concerns about the generalizability of the results. By contrast, the NICE-SUGAR trial enrolled a total of 6104 patients from multiple centers around the world [37, 38]. In examining the HACA trial, there were similar methodologic concerns, as only 275 patients were enrolled, and a formal power calculation was absent [1]. With subsequent TTM trials, the total patient enrollment was substantially greater and trial methodologies included appropriate power calculations. In particular, the TTM-2 trial was especially robust, with a total enrollment nearly equivalent to the sum total of all previously discussed TTM trials (1850 vs. 1886 patients) and had a power of 90%. Furthermore, other potentially advantageous trial methodologies in the TTM-2 trial included high generalizability (large number of patients across multiple centers), and a more heterogeneous population with broader inclusion criteria (e.g., no age limit, shockable and non-shockable rhythms, witnessed vs. unwitnessed cardiac arrest) that may have led to less selection bias [39].

The pioneering work of Van den Berghe et al., despite the lack of replicability, raised another important question: had the surrounding environment changed since the publication of the Leuven surgical study, thereby negating the impact of IIT in later trials? Recall that in the late 1990s, the standard of care for managing hyperglycemia in ICUs was to tolerate extremely high glucose levels (hypoglycemia was thought to be the enemy), and to treat hyperglycemia with intermittent intravenous push regular insulin every 6 h, which led to dramatic swings in blood glucose without a sustained effect. By the time NICE-SUGAR was published in 2009, much more emphasis was being paid to glycemic control in general, the potential harms of sustained severe hyperglycemia were more generally recognized, and the trial itself effectively compared insulin drips directed at two different targets (81–108 mg/dl vs. < 180 mg/dl). In effect, the Leuven surgical trial had influenced and changed the entire treatment milieu with regard to stress hyperglycemia.

This "change the world" dynamic is also illustrated with a parallel clinical conundrum: the utility of early goal-directed therapy (EGDT) for sepsis prior to admission to an ICU. Rivers et al. [40] published their groundbreaking EGDT trial in 2001, which utilized monitoring of mean arterial pressure, central venous pressure and central venous oxygen saturation (ScvO2) to guide resuscitation and treatment decisions (antibiotics, ionotropic agents, vasopressors, transfusion, fluid administration) in the emergency department. At the conclusion of the trial, in-hospital mortality was significantly reduced in the interventional arm of the study (30.5% vs. 46.5%, $p = 0.009$), leading to widespread practice changes as the importance of early hemodynamic resuscitation was increasingly recognized. In the years that followed, there were three additional trials (ProCESS, ARISE, ProMISe) [41–43], in addition to a meta-analysis of these same trials (PRISM) [44], that failed to demonstrate any mortality benefit of EGDT among patients with sepsis. Thus, similar to the Leuven study, subsequent EGDT investigations seemed to negate what appeared to be a significant and highly influential advancement in patient care.

However, analysis of the above studies suggests that the landscape of sepsis treatment changed since the publication of the Rivers study, resulting in a "less ill" population being treated in the trials that followed as a result of an evolving and improved standard of care. For example, patients in the Rivers trial had a higher average lactate level, more use of mechanical ventilation, less intravenous fluid and antibiotic administration prior to randomization and lower

ScvO2 values compared to patients enrolled in the ProCESS, ARISE, and ProMISe trials [45]. There were no standard protocols for sepsis identification prior to the Rivers trial, conducted at Henry Ford Hospital in Detroit, while subsequent trials had "enhanced" usual care in the setting of established sepsis screening and treatment protocols (largely influenced by the Surviving Sepsis Campaign, first published in 2004), and new government-mandated hospital-wide initiatives that promoted early diagnosis and treatment of sepsis [46]. The environment of sepsis recognition and treatment changed in the intervening years since the Rivers et al. trial, as the EGDT concept profoundly influenced the overall standard of care, despite the negative trials that formally re-evaluated the utility of EGDT in the years that followed.

While understandably there is often more focus on the interventional arm within clinical trials, re-evaluation of the characteristics of the control arm can occasionally lead to important insights. An example of this can be seen following the publication of the landmark trial by the acute respiratory distress (ARDS) Net research group [47], which demonstrated a decrease in mortality among patients when a low tidal volume ventilation strategy was employed for the treatment of ARDS. Though this effect has withstood the test of time, with three prior negative studies [48–51], additional factors to explain the mortality benefit were sought. In particular, it was noted the plateau pressure within the control arm of the ARDSNet trial was above a theorized threshold value of 32 cm H_2O that could lead to lung injury and increased mortality [52]. This catalyzed further trials investigating the effect of higher versus lower positive-end-expiration pressure (PEEP) levels, which were also negative [53, 54], until finally elevated driving pressure (plateau pressure minus PEEP) was determined to be an important factor that negatively influences survival among patients with ARDS [55].

The Increasing Sophistication of Care for Cardiac Arrest

The survival rate of OHCA has been increasing globally since the publication of the HACA trial, with survival to discharge rates reported to be 8.6% in 1976–1999 compared to 9.9% in 2010–2019, and a 1-month survival rate of 9.0% in 2000–2009 compared to 13.3% in 2010–2019 [56]. Has the setting of post-cardiac arrest care changed, independent of TTM, to account for these differences? Similar to the revolution that took place in the recognition and early management of sepsis in the early 2000s, care of the cardiac arrest survivor has evolved substantially during the same time period. Chief among these changes is the recognition that not all cases of hypoxic-ischemic coma are hopeless: neurological recovery is possible in some cases. In addition, the constellation of pathophysiological organ dysfunction that occurs with hypoxia and reperfusion (myocardial dysfunction, vasomotor paralysis, lactic acidosis, acute kidney, and hepatic injury) has collectively been conceptualized as post-cardiac arrest syndrome, which is now widely viewed as reversible and recoverable, as opposed to the beginning of the end [57]. Within these broad categories, advancements in therapeutics have likely contributed to the improved survival rates, with the establishment of standardized recognition and treatment protocols, similar to that seen in sepsis [58]. Compounding this effect has been a deeper understanding of coma and return of consciousness, as well as improved methods of prognostication after cardiac arrest, that has evolved since the original TTM trials, thereby postponing withdrawal of life-sustaining treatment, as the literature continues to suggest more delayed awakening in this population [59–61].

What can we learn from the control arm of the TTM trials that may re-frame our thinking? In the TTM-2 trial, 46% of the patients underwent active temperature management with a device [20]. Furthermore, the temperature spread in the control arm of the HACA trial illustrates that many patients were actually febrile, as there was no active temperature management in this arm of the study [1]. Fever has been associated with worse neurological outcomes among stroke and traumatic brain injury patients, with the proposed pathophysiological mechanisms involving increased levels of excitatory amino acids, breakdown of the blood–brain barrier, and decreased enzymatic function [59], as well as increased cerebral edema and seizures leading to secondary injury [9]. Additionally, fever in cardiac arrest survivors has likewise been associated with worse functional outcomes in retrospective studies [60, 62]. While the focus has been on mild hypothermic temperatures following cardiac arrest, perhaps maintenance of normothermia is the driving factor, which simply re-frames our thinking rather than abandoning the science behind it. This point may be of particular importance, as more advanced methods for temperature management have been developed, such as intravascular catheters and surface temperature devices, compared to the external cooling mattress and ice packs utilized in the TTM trials from 2002. As such, more meticulous control of potentially deleterious effects of pyrexia with devices employing real-time biofeedback in control groups may have contributed to the obliteration of any perceived benefit of induced hypothermia seen in the earlier trials.

While the emphasis on neurological recovery following cardiac arrest has been on temperature management, it is worth mentioning there are several other aspects of post-cardiac arrest care that are highly relevant to the discussion, with the precise role of each yet to be determined. Among the many physiological parameters being studied among post-cardiac arrest survivors include optimal oxygen and carbon dioxide levels, ideal mean arterial pressure, and administration of various medications for control of

intracranial pressure [63]. As an example, a recent randomized controlled trial investigated different blood pressure goals among comatose survivors of OHCA. Patients were randomized to a mean arterial pressure goal of 63 mmHg versus 77 mmHg, with the primary outcome being a composite of death from any cause or a CPC score of 3–4 within 90 days [64]. At the conclusion of the trial, there was no statistically significant difference in the primary outcome, and there was a similar number of adverse events among the groups. Important limitations of the trial included a lower-than-expected difference in mean arterial pressure between the groups, in addition to lower-than-expected follow-up among patients, highlighting the need for further investigations. Each of these physiological parameters has important implications for cerebral perfusion during the immediate post-cardiac arrest state, particularly when cerebral autoregulation may be impaired [65], and represent a subset of additional factors that could influence patient prognosis. While fever control has been a constant in neurocritical care, a recent meta-analysis investigating fever control among critically ill patients, suffering from a wide range of clinical conditions, did not seem to increase the risk of death or adverse events [66], leading many clinicians to question whether a TTM trial with the control arm having no active temperature management may be warranted. No matter the fate of TTM, clinicians must be mindful that other intensive, neurologically-focused critical care exists and may be equally important in leading to favorable neurological outcomes.

Clinical Implications and Conclusion

Although TTM has been ubiquitous following cardiac arrest among comatose survivors during the last two decades, a crossroads has been reached. Since the original groundbreaking clinical trials led to its inception, a multitude of studies have failed to support the therapeutic benefits of mild-to-moderate hypothermia within this patient population. On the surface, the negative TTM-1 and TTM-2 trials might appear to seal the fate of therapeutic hypothermia within the medical community, suggesting that intensivists can safely abandon TTM after cardiac arrest if taken at face value. Drawing from parallel clinical scenarios within critical care, we have highlighted several plausible explanations which support the concept that TTM was foundational for creating an entirely new therapeutic milieu for cardiac arrest, mostly by embodying the concept that global hypoxic-ischemic brain injury is treatable. For this reason alone, it is well justified to continue to routinely use TTM as the cornerstone of neuroprotection after cardiac arrest. We have shown this to be the case by demonstrating treatment effects seen in single-center studies are often large, with a substantially smaller effect in larger, multi-center trials. Second, the background care of cardiac arrest survivors has improved significantly throughout the years, leading to enhanced care of the control group within trials, thereby diminishing the treatment effect of induced hypothermia. Lastly, increased vigilance and treatment of the variable of interest—whether it be fever, glycemic control, early volume resuscitation and antibiotic administration, or plateau pressure—has led to a reduction in the differences between control and interventional groups, leading to a trend towards neutral results in the most recent clinical trials.

Given the heterogeneity among individuals suffering from cardiac arrest, there likely are specific sub-populations of patients that may or may not benefit from TTM, which warrant further investigation prior to erasing TTM from post-cardiac arrest care. For example, a cohort study of 1319 survivors of cardiac arrest investigated TTM of 33 °C versus 36 °C stratified based on illness severity, which was measured by the presence of severe cerebral edema, identification of malignant electroencephalogram (EEG) patterns, coma grade and organ failure scores. In the absence of severe cerebral edema or malignant EEG patterns, patients with more severe coma had higher survival to hospital discharge within the 33 °C group, while those with mild to moderate coma and no cardiovascular shock had higher survival to hospital discharge in the 36 °C group [67]. In similar fashion, a post hoc analysis of a cohort study investigated functional outcome among survivors undergoing TTM to either 33 °C or 36 °C stratified by severity of encephalopathy based on EEG patterns at 12 and 24-h post-cardiac arrest. There was a higher proportion of patients with moderate encephalopathy with good functional outcome in favor of the 33 °C group, while among patients with mild encephalopathy there was no significant difference [68]. These studies serve as just two examples of patient characteristics that could serve as a framework for future large-scale TTM clinical trials, which may couple such variables with varying temperature goals, delivery method, duration of induced hypothermia, and specialized systemic post-cardiac arrest care. While these clinical questions are considered, clinicians should proceed with caution in abandoning TTM. There was a trend of lower compliance with target temperature, increased incidence of fever and less favorable neurological outcomes when many centers around the world altered the TTM goal from 33 °C to 36 °C following the publication of the TTM trial, illustrating translation of clinical trial methodology to real-world practice may have unintended effects [69–71]. Being mindful of these many nuances will be vital in this age of precision medicine that strives to deliver individualized therapeutic plans. In doing so, we must continue to acknowledge the many interventions that have appeared to mature as inconsequential, but in actuality altered the landscape of treatment and improved the lives of the patients we encounter each day. Similar to its predecessors within critical care, TTM changed the world.

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References

1. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549–56.
2. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–63.
3. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet. 2008;371:1955–69.
4. Hegnauer AH, D'Amato HE. Oxygen consumption and cardiac output in the hypothermic dog. Am J Physiol. 1954;178:138–42.
5. Mezrow CK, Sadeghi AM, Gandsas A, Shiang HH, Levy D, Green R, et al. Cerebral blood flow and metabolism in hypothermic circulatory arrest. Ann Thorac Surg. 1992;54:609–15; discussion 15–6.
6. Kramer RS, Sanders AP, Lesage AM, Woodhall B, Sealy WC. The effect profound hypothermia on preservation of cerebral ATP content during circulatory arrest. J Thorac Cardiovasc Surg. 1968;56:699–709.
7. Chopp M, Knight R, Tidwell CD, Helpern JA, Brown E, Welch KM. The metabolic effects of mild hypothermia on global cerebral ischemia and recirculation in the cat: comparison to normothermia and hyperthermia. J Cereb Blood Flow Metab. 1989;9:141–8.
8. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke. 1989;20:904–10.
9. Drury PP, Gunn ER, Bennet L, Gunn AJ. Mechanisms of hypothermic neuroprotection. Clin Perinatol. 2014;41:161–75.
10. Rosomoff HL, Shulman K, Raynor R, Grainger W. Experimental brain injury and delayed hypothermia. Surg Gynecol Obstet. 1960;110:27–32.
11. Wolfe KB. Effect of hypothermia on cerebral damage resulting from cardiac arrest. Am J Cardiol. 1960;6:809–12.
12. Leonov Y, Sterz F, Safar P, Radovsky A. Moderate hypothermia after cardiac arrest of 17 minutes in dogs. Effect on cerebral and cardiac outcome. Stroke. 1990;21:1600–6.
13. Leonov Y, Sterz F, Safar P, Radovsky A, Oku K, Tisherman S, et al. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab. 1990;10:57–70.
14. Arrich J, Herkner H, Mullner D, Behringer W. Targeted temperature management after cardiac arrest. A systematic review and meta-analysis of animal studies. Resuscitation. 2021;162:47–55.
15. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med. 1997;30:146–53.
16. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: post-cardiac arrest care: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:S465–82.
17. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, et al. Temperature management after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation. 2016;98:97–104.
18. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369:2197–206.
19. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019;381:2327–37.
20. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullen S, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med. 2021;384:2283–94.
21. Lopez-de-Sa E, Rey JR, Armada E, Salinas P, Viana-Tejedor A, Espinosa-Garcia S, et al. Hypothermia in comatose survivors from out-of-hospital cardiac arrest: pilot trial comparing 2 levels of target temperature. Circulation. 2012;126:2826–33.
22. Lopez-de-Sa E, Juarez M, Armada E, Sanchez-Salado JC, Sanchez PL, Loma-Osorio P, et al. A multicentre randomized pilot trial on the effectiveness of different levels of cooling in comatose survivors of out-of-hospital cardiac arrest: the FROST-I trial. Intensive Care Med. 2018;44:1807–15.
23. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122:737–42.
24. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest*. Crit Care Med. 2012;40:747–53.
25. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (Rapid Infusion of Cold Normal Saline). Circulation. 2016;134:797–805.
26. Scales DC, Cheskes S, Verbeek PR, Pinto R, Austin D, Brooks SC, et al. Prehospital cooling to improve successful targeted temperature management after cardiac arrest: a randomized controlled trial. Resuscitation. 2017;121:187–94.
27. Nordberg P, Taccone FS, Truhlar A, Forsberg S, Hollenberg J, Jonsson M, et al. Effect of trans-nasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: The PRINCESS randomized clinical trial. JAMA. 2019;321:1677–85.
28. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW, International Liaison Committee on Resuscitation Advanced Life Support Task F. Targeted temperature management in adult cardiac arrest: systematic review and meta-analysis. Resuscitation. 2021;167:160–72.
29. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. Arch Pediatr Adolesc Med. 2012;166:558–66.
30. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013:CD003311.
31. Guillet R, Edwards AD, Thoresen M, Ferriero DM, Gluckman PD, Whitelaw A, et al. Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy. Pediatr Res. 2012;71:205–9.
32. Kirkegaard H, Soreide E, de Haas I, Pettila V, Taccone FS, Arus U, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA. 2017;318:341–50.

33. Davidson JO, Gonzalez F, Gressens P, Gunn AJ, Newborn Brain Society Guidelines and Publications Committee. Update on mechanisms of the pathophysiology of neonatal encephalopathy. Semin Fetal Neonatal Med. 2021;26:101267.
34. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
35. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–61.
36. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
37. Bellomo R, Egi M. What is a NICE-SUGAR for patients in the intensive care unit? Mayo Clin Proc. 2009;84:400–2.
38. Preiser JC. NICE-SUGAR: the end of a sweet dream? Crit Care. 2009;13:143.
39. Taccone FS, Lascarrou JB, Skrifvars MB. Targeted temperature management and cardiac arrest after the TTM-2 study. Crit Care. 2021;25:275.
40. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.
41. Pro CI, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
42. ARISE Investigators and the ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496–506.
43. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301–11.
44. Investigators P, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, et al. Early, goal-directed therapy for septic shock - a patient-level meta-analysis. N Engl J Med. 2017;376:2223–34.
45. De Backer D, Vincent JL. Early goal-directed therapy: do we have a definitive answer? Intensive Care Med. 2016;42:1048–50.
46. Nguyen HB, Jaehne AK, Jayaprakash N, Semler MW, Hegab S, Yataco AC, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care. 2016;20:160.
47. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
48. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, The Multicenter Trail Group on Tidal Volume reduction in ARDS, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. Am J Respir Crit Care Med. 1998;158:1831–8.
49. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338:347–54.
50. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Pressure- and Volume-Limited Ventilation Strategy Group, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med. 1998;338:355–61.
51. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999;27:1492–8.
52. Slutsky AS, Ranieri VM. Mechanical ventilation: lessons from the ARDSNet trial. Respir Res. 2000;1:73–7.
53. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351:327–36.
54. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303:865–73.
55. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372:747–55.
56. Yan S, Gan Y, Jiang N, Wang R, Chen Y, Luo Z, et al. The global survival rate among adult out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation: a systematic review and meta-analysis. Crit Care. 2020;24:61.
57. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Bottiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation. 2008;79:350–79.
58. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S768–86.
59. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008;39:3029–35.
60. Picetti E, Antonini MV, Bartolini Y, DeAngelis A, Delaj L, Florindo I, et al. Delayed fever and neurological outcome after cardiac arrest: a retrospective clinical study. Neurocrit Care. 2016;24:163–71.
61. Henson T, Rawanduzy C, Salazar M, Sebastian A, Weber H, Al-Mufti F, et al. Outcome and prognostication after cardiac arrest. Ann N Y Acad Sci. 2022;1508:23–34.
62. Zeiner A, Holzer M, Sterz F, Schorkhuber W, Eisenburger P, Havel C, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med. 2001;161:2007–12.
63. Andersen LW, Lind PC, Vammen L, Hoybye M, Holmberg MJ, Granfeldt A. Adult post-cardiac arrest interventions: an overview of randomized clinical trials. Resuscitation. 2020;147:1–11.
64. Kjaergaard J, Moller JE, Schmidt H, Grand J, Molstrom S, Borregaard B, et al. Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med. 2022.
65. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke. 2001;32:128–32.
66. Holgersson J, Ceric A, Sethi N, Nielsen N, Jakobsen JC. Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses. BMJ. 2022;378:e069620.
67. Callaway CW, Coppler PJ, Faro J, Puyana JS, Solanki P, Dezfulian C, et al. Association of initial illness severity and outcomes after cardiac arrest with targeted temperature management at 36 degrees C or 33 degrees C. JAMA Netw Open. 2020;3:e208215.
68. Nutma S, Tjepkema-Cloostermans MC, Ruijter BJ, Tromp SC, van den Bergh WM, Foudraine NA, et al. Effects of targeted temperature management at 33 degrees C vs. 36 degrees C on comatose patients after cardiac arrest stratified by the severity of encephalopathy. Resuscitation. 2022;173:147–53.
69. Bray JE, Stub D, Bloom JE, Segan L, Mitra B, Smith K, et al. Changing target temperature from 33 degrees C to 36 degrees C

in the ICU management of out-of-hospital cardiac arrest: a before and after study. Resuscitation. 2017;113:39–43.
70. Lascarrou JB, Dumas F, Bougouin W, Chocron R, Beganton F, Legriel S, et al. Temporal trends in the use of targeted temperature management after cardiac arrest and association with outcome: insights from the Paris Sudden Death Expertise Centre. Crit Care. 2019;23:391.
71. Minini A, Annoni F, Peluso L, Bogossian EG, Creteur J, Taccone FS. Which target temperature for post-anoxic brain injury? a systematic review from "real life" studies. Brain Sci. 2021;11.