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Targeted Temperature Management After Cardiac Arrest: From Therapeutic Hypothermia to Active Normothermia

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ABSTRACT

For a long time, targeted temperature management (TTM) has been considered a crucial neuroprotective intervention in post-cardiac arrest care. Once spontaneous circulation returns, a cerebral ischemia-reperfusion injury may occur. This significantly increases mortality while also contributing to deteriorating neurological outcomes in survivors. These factors have prompted research into therapeutic hypothermia as a means to reduce secondary brain injury. Mild hypothermia (32–34°C) improved both survival and neurological recovery in comatose survivors of out-of-hospital cardiac arrest, according to early randomized controlled trials published in 2002. Consequently, hypothermia protocols were widely adopted in international resuscitation guidelines. Nevertheless, the extent of this benefit has since been reassessed in later large-scale studies. No discernible difference in all-cause mortality or neurological outcomes between the groups in the 2013 trial, comparing temperature targets of 33°C and 36°C among patients, was observed. More recently, targeted hypothermia at 33°C did not lower six-month mortality when compared to targeted normothermia combined with active fever prevention, according to a 2021 study. The trials also indicated a potential increase in adverse events like arrhythmias, but didn't find any consistent benefits in terms of survival or neurological outcomes compared to controlled normothermia. Overall, the growing body of research has pivoted its focus to clinical practice, straying away from routine induction of therapeutic hypothermia and moving towards active prevention of fever. However, there still remains uncertainty regarding optimal temperature targets and possible advantages amongst particular patient subgroups, thus highlighting the need for further research to improve post-cardiac arrest temperature management techniques.

Keywords: targeted temperature management, post-cardiac arrest, therapeutic hypothermia, fever prevention, active normothermia

1. INTRODUCTION

Cardiac arrest has long been associated with an elevated mortality rate, as well as considerable neurological impairment in survivors, therefore making it a major worldwide public health concern. Rates of survival after out-of-hospital cardiac arrests are still comparatively low, despite advancements in cardiopulmonary

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resuscitation (CPR), emergency medical systems, and post-resuscitation care. Neurological injury is a major cause of death and long-term disability among patients who achieve return of spontaneous circulation (ROSC) (Fernando et al., 2021). As a consequence, one of the primary objectives of post-cardiac arrest care is now to improve neurological outcomes.

Brain tissue is particularly vulnerable to oxygen deprivation - even brief disruptions to cerebral blood flow can initiate intricate processes of neuronal damage. Once previously ischaemic brain tissue undergoes reperfusion after ROSC, it may cause oxidative stress, excitotoxicity, inflammatory reactions, as well as disruptions to the blood-brain barrier (Nielsen et al., 2013). Consequently, these processes cause post-cardiac arrest brain injury, which in turn influences both the survival of the patients and their neurological recovery. These pathophysiological mechanisms have incentivized the search for therapeutic interventions that could reduce secondary brain damage following resuscitation.

According to the evidence that lowering body temperature can reduce cerebral metabolic demand and mitigate ischaemic injury, therapeutic hypothermia has been identified as one such strategy (Hypothermia After Cardiac Arrest Study Group, 2002; Bernard et al., 2002). Two seminal clinical trials conducted in 2002 (Hypothermia After Cardiac Arrest Study Group, 2002; Bernard et al., 2002) showed better neurological outcomes among comatose survivors of out-of-hospital cardiac arrest who were treated with mild hypothermia (32–34 °C) compared to those with standard care following the incident. Beyond this, one of these trials also revealed lower mortality. Consequently, hypothermia protocols gained in popularity and soon were included in international resuscitation guidelines.

The TTM strategy, which entails actively keeping a patient's body temperature within a specified range for a predetermined amount of time after resuscitation, developed from temperature control techniques over time (Nielsen et al., 2013), but the requirement for aggressive hypothermia has been questioned by later large randomized trials. The findings of the 2013 TTM trial (Nielsen et al., 2013) showed no discernible difference in neurological or survival outcomes between patients treated at the temperature of 33 °C and those kept at 36 °C.

The more recent research has also called into question the benefits of therapeutic hypothermia over controlled normothermia and active fever prevention (Dankiewicz et al., 2021). The ideal temperature target for post-cardiac arrest care is still up for debate as a result of these findings. Therefore, an important question remains: to what extent does TTM improve survival and neurological outcomes after cardiac arrest, and which temperature strategy appears most beneficial according to current clinical evidence?

2. REVIEW METHODS

A literature search was carried out to find clinical studies assessing temperature management interventions after cardiac arrest. Publications that matched the criteria were sought with the help of electronic databases such as PubMed, The New England Journal of Medicine (NEJM), JAMA, and Resuscitation. Between 2000 and 2023, therapeutic hypothermia and TTM were both actively investigated in randomized clinical trials, the search focused on that time period. For the relevant articles, lists of references were also screened to identify additional eligible studies. Search terms, used both individually and in combination, included: cardiac arrest, therapeutic hypothermia, targeted temperature management, normothermia, and post–cardiac arrest care.

The process of selecting studies for the literature review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Figure 1 illustrates this process step by step. First, 340 papers were retrieved through database searches. Once the duplicates were removed, 298 records were left to be screened by titles and abstracts. After the initial screening, 229 were excluded, leaving 69 full texts for further assessment. Referring to predefined criteria, 51 papers had to be excluded. At last, 18 studies were chosen for the qualitative synthesis, with 10 randomized controlled trials included in that number forming the core evidence base of this review.

Studies that fulfilled a number of predetermined selection criteria were included in the analysis. Firstly, only randomized clinical trials were considered, which allowed for the most reliable scientific evidence. Next, only studies that involved adult patients experiencing cardiac arrest and being subject to post-resuscitation cooling therapy were chosen. Lastly, selected studies needed to report data related to survival or neurological outcome and to address temperature control strategies, including therapeutic hypothermia or TTM.

Several exclusion criteria were used to ensure the review's quality and relevance. Non-clinical research, such as laboratory, mechanistic, and animal investigations, was not included. Additionally, because pediatric populations differed from adult populations in terms of temperature management practices and results, research involving children was excluded. Furthermore, since they did not address temperature management, studies that only addressed prehospital interventions or CPR procedures were disregarded. The review was able to concentrate on important clinical trials that impacted current knowledge of temperature control after cardiac arrest by using this structured approach.

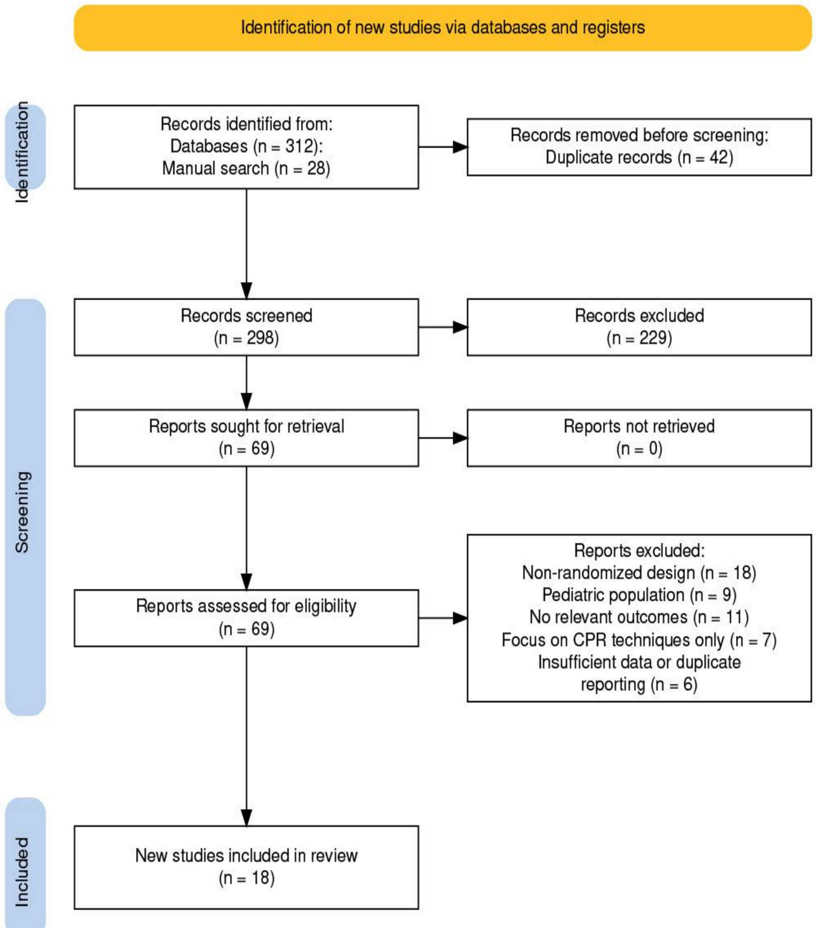

Figure 1. PRISMA flow diagram visualizing the screening process of the studies to be included in the analysis

3. RESULTS AND DISCUSSION

Early Evidence Supporting Therapeutic Hypothermia

In 2002, two seminal studies were conducted to assess the effects of controlled cooling in comatose patients who experienced out-of-hospital cardiac arrest. They provided the first clinical evidence in favour of therapeutic hypothermia. Aforementioned studies examined whether lowering body temperature in order to maintain a mild hypothermic range of 32–34 °C could potentially decrease neurological damage that was brought on by cerebral ischemia and reperfusion after spontaneous circulation returns (Hypothermia After Cardiac Arrest Study Group, 2002; Bernard et al., 2002). A group assembled specifically to obtain more data on this, back then novel approach - The Hypothermia After Cardiac Arrest (HACA) Study Group carried out one of the most significant trials, which was published in NEJM in 2002 (Hypothermia After Cardiac Arrest Study Group, 2002). This randomized controlled trial included 275 patients who experienced out-of-hospital cardiac arrest caused by ventricular fibrillation and remained unconscious. Participants were randomly assigned either to a group of standard care without controlled cooling or to therapeutic hypothermia. In the latter, patients' body temperature was kept between 32 and 34 degrees Celsius for a full day. In line with the study's results, neurological outcomes of the patients from the hypothermia group proved to be significantly better. Favorable neurological recovery was observed among 55% of cooled patients, while the figures reached only 39% in the control group. Furthermore, the hypothermia group had a lower six-month mortality rate (41% vs. 55%), therefore indicating that cooling had both neurological as well as survival benefits (Hypothermia After Cardiac Arrest Study Group, 2002).

A second study conducted by Stephen A. Bernard and colleagues, also published in NEJM, evaluated a comparable cooling technique in 77 patients who experienced out-of-hospital cardiac arrest related to ventricular fibrillation (Bernard et al., 2002). While once again, the control group received standard care, patients in the intervention group were cooled to about 33 °C, with this state of hypothermia being maintained for 12 hours until the target temperature had been reached. As the outcome, the hypothermia group presented with a significantly higher rate of promising neurological outcomes at time of hospital discharge (49% vs. 26%) (Bernard et al., 2002).

Both of these studies showed consistent improvements in neurological recovery, in spite of minor differences in both cooling duration and methodology. When viewed collectively, these studies offered the first solid clinical proof that therapeutic hypothermia could facilitate neurological recovery after cardiac arrest. Subsequently, international resuscitation guidelines adopted their findings, therefore significantly influencing clinical practice. Temperature control became a crucial part of post-cardiac arrest care after organizations such as the American Heart Association and the European Resuscitation Council recommended therapeutic hypothermia for comatose adult survivors of cardiac arrest (Nordberg et al., 2019).

Development of Targeted Temperature Management

Temperature control became of the essence in post-cardiac arrest care after early therapeutic hypothermia trials were published in 2002 (Hypothermia After Cardiac Arrest Study Group, 2002; Bernard et al., 2002). As cooling techniques began being more frequently used in clinical settings, the focus of studies shifted to creating more organized and reliable methods of temperature control. As a result, TTM, understood as active maintenance of a predefined body temperature after the return of spontaneous circulation, emerged (Nielsen et al., 2013).

At the beginning, what was considered "therapeutic hypothermia" and how it was implemented in clinical practice, especially when it came to cooling methods, treatment durations, and monitoring procedures, varied between different institutions. One example of this could be the fact that some facilities used more advanced technologies, like intravascular cooling devices, thereby allowing for more accurate temperature control. On the other hand, others relied on relatively straightforward external techniques such as cooling blankets or ice packs. Thus, this variability in early practices brought to light the need for more precise treatment protocols. They were to guarantee dependable temperature control while also reducing complications such as overcooling, electrolyte imbalances, and cardiac arrhythmias (Nielsen et al., 2013; Dankiewicz et al., 2021).

As previously mentioned, the TTM process requires its operators to determine a designated temperature target that must be maintained throughout the entire treatment schedule. The initial research protocols established temperature targets ranging from 32°C to 34°C, as this scope of temperatures represented the original hypothermia research trials. Later researchers started testing higher temperature settings, as they believed they would present similar protective benefits to those produced by extreme hypothermia. Modern temperature management methods operate within the rather wide range of 32°C to 36°C. One specific temperature target is chosen to maintain throughout the entire monitoring process. In order to control the TTM method with utmost precision, it's been incorporated into intensive care units. Dedicated temperature control equipment, ongoing observation, sedation, and cautious handling during the cooling and rewarming phases are all incorporated into modern ICU practices. These advancements allowed TTM to become a prominent component of post-cardiac arrest care. They also acted as a starting point for the studies that followed, allowing them to concentrate the focus on optimal temperature targets (Nielsen et al. 2013, Dankiewicz et al. 2021).

Evidence Comparing Different Temperature Targets

Researchers had begun to investigate whether different target temperatures produced comparable clinical outcomes as temperature management became a more established component of the post-cardiac arrest care. Early research on hypothermia treatment showed that cooling patients to body temperature between 32 and 34 degrees Celsius would protect their brain function. Still, scientists could not conclusively determine whether deeper cooling was necessary in order to obtain neurological protection. This question was addressed in several major randomized controlled studies comparing two different temperature control systems (Nielsen et al., 2013).

Arguably, one of the most influential studies in this area was the Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest trial, published in NEJM in 2013 (Nielsen et al., 2013). This multicenter randomized trial included 950 comatose patients who suffered out-of-hospital cardiac arrest, presumably due to cardiac causes. The researchers conducted random assignments of patients to receive temperature management treatment at either 33 °C or 36 °C, which included 28 hours of active temperature control before the start of gradual rewarming. The study results showed that both groups had nearly identical outcomes, which included a 50%

all-cause mortality rate for the 33 °C group and a 48% rate for the 36 °C group. Similarly, neurological outcomes, which were measured using standard neurological assessment scales, showed no significant difference between treatment groups (Nielsen et al., 2013).

The results of the aforementioned study proved particularly important since they challenged the previously believed assumption that deeper hypothermia was necessary to provide greater neuroprotective benefits. Instead, the findings suggested that perhaps maintaining strict temperature control and preventing fever could be more important than obtaining a specific low body temperature. The trial by comparing two actively managed temperature targets rather than hypothermia versus uncontrolled normothermia had demonstrated that careful temperature regulation itself may represent the critical therapeutic component (Nielsen et al., 2013).

These outcomes and their interpretation urged a shift in how we understand post-cardiac arrest TTM. The question of whether aggressive cooling to temperatures reaching as low as 33°C was necessary for all patients arose amid many clinicians. What further incentivized this concern was logistical complexity of obtaining and maintaining the temperature, as well as potential complications associated with deeper hypothermia. Consequently, the study played a major role in reevaluating the strategy of TTM, bringing into focus-controlled temperature regulation, instead of mandatory hypothermia. This shift laid the groundwork for subsequent research to examine whether strict normothermia with active fever prevention could potentially yield similar results.

Recent Evidence Supporting Normothermia Strategies

The literature on therapeutic hypothermia during post-cardiac arrest treatment still undergoes reevaluation today - more recent studies draw attention to maintaining normothermia and preventing fever. Despite earlier studies' emphasis on cooling patients to hypothermic levels, later investigations have brought into question whether deeper temperature reduction provides any additional clinical benefit when compared with controlled temperature regulation (Nielsen et al., 2013; Dankiewicz et al., 2021).

A valuable contribution to this debate is the Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest trial, more commonly referred to as the TTM2 trial, published in NEJM in 2021 (Dankiewicz et al., 2021). 1,850 unconscious adult patients who had experienced out-of-hospital cardiac arrest were enrolled in this multicenter randomized controlled trial. Participants were assigned either to targeted hypothermia at 33 °C or to a group in which a strategy of controlled normothermia with active fever prevention was implemented. In the latter, if needed, interventions were used to keep body temperature below 37.8 °C, hence coining the term active normothermia (Dankiewicz et al., 2021).

The trial found there was no significant difference in six-month mortality between the two groups, with mortality rates reaching 50% in the hypothermia group and 48% in the normothermia group. Similarly, there were no significant differences in the neurological outcomes, thus indicating that deeper cooling did not improve recovery when compared with maintaining normal body temperature. On the other hand, the hypothermia group did in fact experience higher rates of arrhythmias associated with hemodynamic instability, thereby highlighting potential risks associated with such aggressive methods of cooling. It's important to note once again that the control group underwent active fever prevention rather than uncontrolled normothermia (Dankiewicz et al., 2021).

Our understanding of temperature management following cardiac arrest has been majorly influenced by these discoveries. Rather than frequently inducing hypothermia, new research indicates that the most significant goal in post-cardiac arrest care may be to maintain stable temperature and prevent overheating. Therefore, instead of aiming to achieve severe hypothermia, clinicians mainly perceive TTM as a means to prevent fever. This is indicative of a larger trend toward regulated normothermia in post-cardiac arrest care (Dankiewicz et al., 2021; Nordberg et al., 2019).

Critical Evaluation of the Evidence

The body of research exploring TTM after cardiac arrest that is cited in this article presents a number of methodological strengths. Numerous randomized controlled trials make up the data, hence providing the most rigorous framework for assessing therapeutic approaches. Table 1 provides a summary of key studies referenced in this review, also highlighting their study design, which proved to be of importance. By reducing the possibility of selection bias, randomization enhances the internal validity of comparisons between treatment regimens that have been put into practice. Furthermore, by using multicenter study designs, the clinical research included in this review recruited patients from various healthcare networks and medical facilities. Thanks to lessening the influence of region-specific components, like patient characteristics or institutional practices, such methodology enhances the study's external validity and generalisability. Beyond that, more recent clinical trials have investigated extensive study groups which typically comprise hundreds to thousands of participants, therefore enhancing statistical power while also increasing the precision of estimated treatment effects (Nielsen et al., 2013; Dankiewicz et al., 2021).

In spite of these strengths, the interpretation of available research on the subject is complicated by its several limitations. Namely, perhaps the greatest challenge is the heterogeneity of temperature management protocols used across those studies. Trails differed in their approach to cooling techniques, target temperatures, duration of therapy, and rewarming strategies (Kim et al., 2014). This limits how directly one can compare those investigations with one another. Variability among patient populations is also disadvantageous - differences in patient age, their underlying cardiac pathology, initial arrest rhythm, and duration of ischemia prior to ROSC could have substantially influenced both neurological recovery and survival outcomes (Nielsen et al., 2013; Dankiewicz et al., 2021).

The timing of temperature management is another important variable - some studies initiated the cooling process shortly after hospital admission, while others attempted an even earlier induction during prehospital care. Such variability in the timing of the treatment may influence the extent to which temperature modulation can attenuate injury related to the ischemia-reperfusion process, thus also making it harder to make comparisons between trials (Kim et al., 2014).

Divergent findings observed across studies may also stem from additional factors, including different intensive care management, to name a few - sedation practices, hemodynamic support, and neuroprognostic protocols, all of which could influence participants' outcomes independently of temperature targets. Additionally, decisions made regarding withdrawal of life-sustaining therapy may vary across both institutions and study designs, thus influencing reported mortality rates. The relative impact of standardized treatment may also have been reduced by the improvements in comprehensive post-cardiac arrest care over the past two decades, including standardization of treatment pathways and advances in critical care (Nielsen et al., 2013; Dankiewicz et al., 2021).

It becomes more challenging to identify the exact therapeutic significance of hypothermia when all these systemic aspects are taken into account. Although earlier research suggested that induced hypothermia enhanced neurological recovery, subsequent studies have refuted this theory, suggesting that structured temperature control and efficient fever prevention, rather than deep hypothermia itself, may be the primary cause of the observed benefit (Nielsen et al., 2013; Dankiewicz et al., 2021; Schenone et al., 2016).

Clinical Implications

The evolving research on temperature control following cardiac arrest introduces crucial ramifications to medical practices. It particularly affects the management of ICU patients. Although initial research on the matter strongly advised inducing hypothermia in survivors of cardiac arrest (Hypothermia After Cardiac Arrest Study Group, 2002; Bernard et al., 2002), more recently conducted randomized trials suggest that maintaining structured temperature control and preventing fever may be the key to post-cardiac arrest care. Consequently, instead of inducing deep hypothermia, thereby risking its possible complications, ICU management currently increases its focus on maintaining a stable temperature target (Nielsen et al., 2013; Dankiewicz et al., 2021).

In practical terms, this shift in viewpoint highlighted how essential active temperature regulation and ongoing temperature monitoring are to post-resuscitation care. Clinicians can prevent hypothermia and maintain consistent temperature objectives in the early post-arrest phase by using specialised temperature management systems, both intravascular and surface-level. However, controlling body temperature is just one component of a broader strategy to minimize secondary brain damage. Careful control of metabolic status, haemodynamics, and sedation must also remain essential (Kirkegaard et al., 2017).

These findings have also proved seminal enough to influence the development of international resuscitation guidelines. Most recent guidelines, published by American Heart Association and European Resuscitation Council, emphasise how important it is to opt for a controlled temperature target between 32 °C and 36°C and maintain it. Simultaneously, one must actively prevent development of fever. Instead of requiring all patients to have the same hypothermic target, the guidelines are moving toward a more flexible approach that allows for temperature targets within a set range. This shows that there is still some uncertainty as to what the optimal temperature strategy is.

The research evidence shows that medical practitioners should manage patient temperatures through continuous temperature monitoring. The research evidence shows that medical temperature management needs to establish temperature limits according to institutional protocols and patient needs (Lascarrou et al., 2019).

In line with contemporary evidence, stable temperature control and active avoidance of hypothermia should be prioritized. Furthermore, clinical practice should allow for flexibility when it comes to specific temperature targets. The targets should be based on protocols specific to institutions implementing them, and patient characteristics (Nielsen et al., 2013; Dankiewicz et al., 2021).

Table 1. Summary of key clinical studies on TTM after cardiac arrest referenced in this review

Study (Year)	Study Design / Sample Size	Population	Temperature Strategy	Key Findings	Clinical Significance
Hypothermia After Cardiac Arrest (HACA) Study Group (2002)	Randomized controlled trial (n = 275)	Comatose adults after out-of-hospital cardiac arrest due to ventricular fibrillation	Hypothermia (32–34°C for 24 h) vs standard care	Favorable neurological outcome: **55% vs 39%**; Mortality: **41% vs 55%**	First major evidence supporting therapeutic hypothermia; established cooling as standard post-arrest care
Bernard et al., (2002)	Randomized controlled trial (n = 77)	Out-of-hospital cardiac arrest survivors with ventricular fibrillation	Cooling to ~33°C for 12 h vs standard care	Favorable neurological outcome at discharge: **49% vs 26%**	Reinforced benefit of mild hypothermia and supported guideline adoption
TTM Trial (Nielsen et al., 2013)	Multicenter randomized controlled trial (n = 950)	Unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause	33°C vs 36°C for 28 h with controlled rewarming	Mortality: **50% vs 48%**; no significant neurological difference	Challenged assumption that deeper cooling provides superior neuroprotection
TTM2 Trial (2021)	Multicenter randomized controlled trial (n = 1,850)	Unconscious adults after out-of-hospital cardiac arrest	Hypothermia (33°C) vs normothermia with active fever prevention (<37.8°C)	Mortality: **50% vs 48%**; no neurological benefit; increased arrhythmias with hypothermia	Shifted focus toward active normothermia and fever prevention rather than routine hypothermia
Recent Meta-Analyses / Systematic Reviews (2021–2023)	Systematic reviews of multiple RCTs	Adult post-cardiac arrest patients	Hypothermia vs controlled normothermia	No consistent survival or neurological advantage of hypothermia; possible increase in adverse effects	Supports modern guideline shift toward individualized temperature control and fever avoidance

Future Research Directions

In lieu of significant improvements in post-cardiac arrest treatment methods, there still remain several areas of uncertainty that warrant further investigation. Future studies should aim to identify patient subgroups that may derive greater benefit from specific temperature strategies based on their arrest rhythm, cause of cardiac arrest, and the length of their ischemia. In order to clarify the optimal timing of temperature management initiation, including whether earlier interventions during the prehospital phase may improve neurological outcomes, additional research is needed (Kim et al., 2014). Emerging research is still exploring novel cooling technologies and approaches to how they are delivered, which may allow for more rapid and precise control of patient temperature. For instance, one such study introduced trans-nasal evaporative intra-arrest cooling. This approach, fascinating as it may seem, still hasn't presented satisfactory results (Lascarrou et al., 2019).

Nevertheless, continued evaluation may help to improve the efficiency and safety of temperature modulation in patient care post-cardiac arrest. Lastly, future trials should allow clinicians to tailor treatment to the physiological characteristics and risk profiles of individual patients. Hence, they should focus on investigating the combination of neuroprotective strategies and the potential role of individualized temperature targets.

4. CONCLUSION

Over the past two decades, the field of research on temperature management after cardiac arrest has undergone quite a substantial refinement, serving as a great example of how fast medicine can advance. Although initial findings showed improved survival and neurological recovery achieved with mild hypothermia, making its adoption into post-cardiac arrest care widespread, this notion was soon put into question. Large-scale studies that followed, comparing lower temperature targets with controlled normothermia didn't find any consistent advantage of more aggressive cooling in reducing mortality or enhancing neurological results. This suggested that the main benefit of temperature management lies in maintaining meticulous regulation of temperature and actively preventing fever in the early post-ROSC period. Still, certain ambiguity persists regarding the optimal temperature strategy and whether particular populations of patients may benefit from more aggressive cooling. As far as current evidence suggests, improved neurological outcomes after cardiac arrest are likely associated not so much with hypothermia itself but rather with structured temperature management and avoidance of fever. Supplementary high-quality clinical research would be necessary in order to determine whether individualized temperature targets can further improve neurological outcomes within comprehensive post-cardiac arrest strategies.

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Authors' Contributions

Zuzanna Żurawska: responsible for conceptualization, literature review, and preparation of the original draft

Sandra Prolejko: data verification, comparative analysis of the reviewed studies, and manuscript writing

Weronika Kotnis: supervision, critical editing, and final manuscript review

All authors contributed substantially to the interpretation of the literature, participated in revising the manuscript, and approved the final submitted version.

Informed consent

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Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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