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Temperature Control after Resuscitation

Student: **Oleksandra Levchenko, VI year, 1st group**

Clinic: **Institute of Clinical Medicine, Clinic of Emergency Medicine**

Supervisor Prof. Pranas Šerpytis, PhD

The Head of Department/Clinic Prof. Pranas Šerpytis, PhD

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Email of the student oleksandra.levchenko@mf.stud.vu.lt

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ABBREVIATIONS

AHA	American Heart Association
ALS	Advanced Life Support
CPC	Cerebral Performance Category
CA	Cardiac arrest
ERC	European Resuscitation Council
ESICM	European Society of Intensive Care Medicine
ICU	Intensive care unit
IHCA	In-hospital cardiac arrest
ILCOR	International Liaison Committee on Resuscitation
OHCA	Out-of-hospital cardiac arrest
ROSC	Return of spontaneous circulation
RCT	Randomised clinical trial
TT	Target temperature
TTM	Targeted temperature management
mRS	Modified Rankin Scale
VF	Ventricular fibrillation
WLST	Withdrawal of life-sustaining treatment

SUMMARY

This thesis reviews the current evidence of the active temperature control used during the post-resuscitation care of comatose survivors of cardiac arrest. The review includes the current, up-to-date literature with relevant randomised controlled trials, meta-analyses, and systematic reviews. Findings include that currently, there are many studies on active temperature control, investigating the neurological outcome and survival of cardiac arrest patients, which have controversial results regarding the target temperature, type and time of the start of management, duration, methods for cooling, and post-management care. Such differences appear due to the limitations and involvement of many internal and external factors in the survivors' outcomes, making the studies' design and analysis challenging. Because of that, present-day recommendations for temperature control are based on low or moderate-level evidence. However, this review concludes that active temperature control, regardless of the target temperature chosen, results in a more favourable neurologic outcome. Currently, international guidelines recommend temperature control with either hypothermia (32.0–35.9 °C) or normothermia (36.0–37.5 °C), along with active fever prevention (fever defined as temperature > 37.7°C), to improve neurologic outcomes in comatose survivors of cardiac arrest. The population of cardiac arrest survivors is heterogeneous; it can be suggested that different temperature targets may have beneficial or adverse effects on specific groups. This study highlights the importance of clinicians having an individual approach to temperature management in post-resuscitation care for each patient rather than rejecting temperature control with hypothermia or normothermia. It also indicates the need for future researchers to analyse existing data and appropriately design future randomised control trials that exclude the problems of the previous trials, such as inconsistent patient selection criteria and inadequate active temperature control management.

SANTRAUKA

Šiame darbe apžvelgiami dabartiniai duomenys apie aktyvią temperatūros kontrolę, taikomą po gaivinimo prižiūrint komos būklės asmenis, išgyvenusius širdies sustojimą. Apžvelgiama dabartinė naujausia literatūra su atitinkamais atsitiktinių imčių kontroliuojamais tyrimais, metaanalizė ir sisteminės apžvalgos. Prie išvadų priskiriama tai, kad šiuo metu atlikta daug tyrimų apie aktyviosios temperatūros kontrolės poveikį pacientų neurologinei būsenai ir išgyvenamumui, kurių rezultatai dėl tikslinės temperatūros, valdymo pradžios tipo ir laiko, trukmės, šaldymo metodų ir valdymo po kontrolės yra prieštaringi. Tokie skirtumai atsiranda dėl daugelio vidinių ir išorinių veiksnių ribotumo ir jų įtakos išgyvenusiųjų rezultatams, todėl tyrimų planavimas ir analizė yra sudėtingi.

Dėl šios priežasties dabartinės temperatūros kontrolės rekomendacijos yra pagrįstos menkais arba vidutinio lygio įrodymais. Tačiau šioje apžvalgoje daroma išvada, kad aktyvi temperatūros kontrolė, nepriklausomai nuo pasirinktos tikslinės temperatūros, lemia palankesnius neurologinius rezultatus. Šiuo metu tarptautinėse rekomendacijose siūloma kontroliuoti temperatūrą taikant hipotermiją (32,0-35,9 °C) arba normotermiją (36,0-37,5 °C), taip pat aktyviai užkirsti kelią karščiavimui (karščiavimas apibrėžiamas kaip temperatūra > 37,7 °C), kad būtų geresnės neurologinės pasekmės. Širdies sustojimą išgyvenusių žmonių populiacija yra nevienalytė; galima daryti prielaidą, kad skirtingos tikslinės temperatūros gali turėti teigiamą arba neigiamą poveikį tam tikroms grupėms. Šiame tyrime pabrėžiama, kaip svarbu, kad gydytojai taikytų individualų požiūrį į kiekvieno paciento temperatūros valdymą po gaivinimo, o ne atsisakytų temperatūros kontrolės taikant hipotermiją ar normotermiją.Jis taip pat rodo, kad būsimiems tyrėjams reikia išanalizuoti turimus duomenis ir tinkamai suplanuoti būsimus atsitiktinių imčių kontrolės tyrimus, kuriuose būtų pašalintos ankstesnių tyrimų problemos, pavyzdžiui, nenuoseklūs pacientų atrankos kriterijai ir netinkamas aktyvios temperatūros kontrolės valdymas.

KEYWORDS: targeted temperature management, active temperature control, cardiac arrest, therapeutic hypothermia, neuroprotection, post-resuscitation care.

INTRODUCTION

Sudden cardiac arrest is an essential public health-care problem which is associated with high mortality and morbidity, especially in the poor outcome for the neurocognitive function of the survivors. Between 67 and 170 per 100,000 inhabitants in Europe experience out-of-hospital cardiac arrest (OHCA) every year, and in-hospital cardiac arrest (IHCA) is counted at between 1.5 and 2.8 per 1,000 hospital admissions. Survival rates at 30 days or hospital discharge differ for the OHCA from 0% to 18% and for IHCA from 15% to 34% (1). Health outcomes and survival of the patients experiencing cardiac arrest (CA) differ from country to country, as they depend on the rhythm, the place of arrest, the level of monitoring at the time of the accident and the level of medical assistance provided. The survival rate differs by 24% in the shockable and 3% in the non-shockable groups (2). Initial shockable rhythm and quicker return of spontaneous circulation (ROSC) were independently associated with increased survival to hospital discharge (3). Good neurological outcomes after cardiac arrest are seen in EU countries where withdrawal of life-sustaining treatment (WLST) is implemented into daily practice. Meanwhile, worse neurologic outcomes are more common in countries that do not have such practices. Nevertheless, patients with good neurologic outcomes can experience neurocognitive and emotional problems, which affect their quality of life

(1). Unfortunately, two-thirds of post-resuscitated after CA comatose patients after ROSC die before hospital discharge; among them, 2/3 die from the consequences of the neurological injury (4). The improvement of the outcomes of CA is still a challenge to clinicians' practice, which is why researchers are looking for methods that can provide better outcomes.

Active temperature control is a method that aims to minimise the negative neurological outcome after CA. It involves any strategy focusing on reaching the target temperature and maintaining it for therapeutic effect. First-time active temperature control with hypothermia as target temperature management was investigated for its effectiveness on survival and neuroprotection in postcardiac arrest patients in clinical trials in 2002 (5,6). As the results of the trials were promising, active target temperature control with mild hypothermia was incorporated into the ILCOR recommendations 2003 for comatose survivors of cardiac arrest (7). Since then, several randomised controlled trials (RCTs), systematic reviews, and meta-analyses on temperature control and the management of comatose postcardiac arrest patients have changed with the changes in ALS protocols and the quality of medical assistance. Despite this fact, temperature control remains a debatable topic among clinicians. Currently, there is no internationally recommended active temperature control protocol or algorithm for postcardiac arrest patients management, which includes the indications and contraindications for temperature control, the target temperature for the specific groups, time of initiation, duration of temperature control, as well as monitoring during and after management.

It is essential to review the current data on active temperature control of comatose cardiac arrest survivors after resuscitation to make a proper analysis and establish recommendations for clinicians on temperature control management. This study aims to collect and summarise current and evidence-based studies, find knowledge gaps, and suggest future perspectives on temperature control management.

LITERATURE SEARCH STRATEGY

A literature search was conducted using electronic databases, including PubMed, Clinical Key, Vilnius University Library, and Google Scholar, from January 2024 to April 2024. A time range filter of 10 years was selected to keep the study up-to-date. The search strategy included the following terms for search: target temperature management, temperature control, TTM, therapeutic hypothermia, induced hypothermia, normothermia, and post-cardiac arrest care. Selected articles included both clinical and preclinical studies on RCTs, meta-analyses, cohort studies and systematic reviews. In the selected publications, the references were analysed to determine if additional articles

could be included. Only articles published in English were included in the review. Full texts of the relevant articles were extracted after being screened for titles and abstracts.

1. TERMINOLOGY

In the past decades, the terms “cooling”, “therapeutic hypothermia”, and “target temperature management” were used to define temperature control with hypothermia. Currently, the term “TTM- target temperature management” is now associated with the RCT (TTM, TTM2) (8,9) - this is why the ALS Task Force of the ILCOR decided to use the new term “temperature control” to define the management of reaching and maintaining the specific temperature in post-resuscitation care. According to the International Consensus on CPR and Emergency Cardiovascular Care (2022), the types of temperature control are as follows:

- Temperature control with hypothermia: active temperature control with the target temperature below 36°C. The level of hypothermia can be mild (34.0-35.9°C), moderate (32.0-33.9°C) or deep (31.0-31.9°C).
- Temperature control with normothermia: active temperature control with the target temperature between 36.0 and 37.5°C.
- Temperature control with fever prevention: monitoring and actively preventing and treating temperatures above the >37.7°C.
- No temperature control: no protocolised active temperature control strategy. (10)

This review will use the term “active temperature control” as the target temperature management.

2. PATHOPHYSIOLOGY OF CARDIAC ARREST AND POST-ARREST BRAIN DAMAGE

Cardiac arrest occurs in the absence of proper contractility of the heart, with clinics indicating no blood circulation (11). If the patient with CA does not achieve ROSC, sudden cardiac death appears. To understand the timeline of the ideas of usage of temperature control with hypothermia for neuroprotection in survivors of CA, it is crucial to differentiate the abnormal cardiac rhythms which cause CA: shockable (VF, pulseless ventricular tachycardia) and non-shockable (asystole, pulseless electrical activity) (12). Most IHCA have initial non-shockable rhythms, which have a worse prognosis (13); accordingly, patients with IHCA who have initial shockable rhythm have one-to-two-fold higher chances of survival compared to those who have initial non-shockable rhythm (14).

For the OHCA, non-shockable initial rhythm gives a 27% increase in the chances for intrahospital death, regardless of the healthcare resources and facilities where the patient presented (15). That is why clinicians and researchers have been exploring potential methods for improving outcomes for CA survivors, especially for conditions with a worse prognosis.

During the CA, the whole body experiences ischemia, which leads to all-organ dysfunction; however, the brain is the most sensitive to blood flow restriction because of its dependence on aerobic glucose metabolism. Usually, the brain is well-supplied by blood, which gets 15-20% of cardiac output and consumes about 20% of the total body oxygen (16). In case of the total cessation of the blood flow, a person loses consciousness in 4-10 seconds, and on EEG, there is an isoelectric activity 10-30 seconds after (17). As a result of CA, hypoxic-ischemic brain injury occurs. Its pathophysiology consists of primary ischemic and secondary reperfusion injuries, which follow each other after CA, resuscitation, and post-resuscitation care (18)**.** While CA occurs, there is a decrease in cerebral oxygen delivery, which causes ischemia of neuronal cells and, as a result, death (19). Ischemia changes the cell metabolism to anaerobic, which causes a decrease in ATP. Therefore, the neuron's ATP-dependent Na+/K+ ion exchange pump cannot function anymore, which results in cytotoxic oedema by an increase of intracellular Na and H2O. The influx of Na to the cell generates depolarisation of the membrane, which leads to the opening of the Ca++-dependent channels and an increase of Ca++ inflow. Because of the rise in the intracellular Ca++, damaged neurons start to release glutamate, which causes even more income of the Ca++ into the cell and its accumulation. Also, Ca++-dependent enzymes are activated, which enhances the damage, and Ca++-dependent mitochondrial dysfunction causes energy failure; the following step is the release of proteins, which induce apoptosis and reactive oxygen species, which causes even more damage. Next, the innate immune system and tissue inflammation are activated, leading to increased blood-brain barrier permeability and oedema. After ROSC, cerebral blood flow is restored, but the endothelium function is still compromised in the ischemic region, which starts a cascade which leads to secondary brain injury (17)**.** As a result, the blood-brain barrier is compromised, which leads to the development of cerebral oedema, the creation of microthrombi, and a restricted cerebral blood flow that intensifies cellular ischemia (18). Such physiological changes can continue to worsen the brain injury during post-arrest days and are potential targets for the management of neuroprotection.

3. MECHANISMS OF NEUROPROTECTION OF HYPOTHERMIA

Therapeutic hypothermia is the most potent neuroprotective agent and most studied on animal models in laboratories. Although, the pathophysiologic mechanism behind the neuroprotection of

hypothermia is currently unclear. Such neuroprotective effects could potentially be due to the lowering of oxygen and glucose utilisation by 5% for each degree Celsius reduced, which in turn decreases the metabolic activity of the brain. This preservation of energy molecules prevents the shift to anaerobic metabolism and minimises mitochondrial injury. As a result, the cascade of ischemic neuronal tissue damage is halted, and cell death is prevented. However, cooling has a non-linear protective impact, meaning that the level of neuroprotection does not increase in direct proportion to the decrease in temperature (20)**.**

A systematic review of preclinical studies on small and large animal models designed to investigate cardiac arrest effects on the brain has shown that temperature control with hypothermia favours neurologic outcomes and survival. However, the study results must be interpreted cautiously due to their heterogeneity and high risk of bias (21).

Neuroprotective effects of hypothermia are commonly used nowadays during cardiac surgeries. During the intervention, the whole body temperature is cooled to the level of deep hypothermia <20 °C; as a result, after the operation, there is no neurologic deficit even after 30-40 min circulatory arrest (22). There is confirmed the efficiency of temperature control with hypothermia for neuroprotection in neonatal encephalopathy caused by hypoxic-ischaemic events (20).

4. HISTORICAL PERSPECTIVE OF CLINICAL TRIALS ON TEMPERATURE CONTROL PROTOCOL

The first randomised clinical trials on temperature control started in 2002 (Figure 1) when two studies showed that survival and neurologic outcome benefit from temperature control with hypothermia during the post-cardiac arrest management of comatose survivors of CA (5,6). The HACA trial included 275 patients with ROSC after witnessed OHCA and IHCA with shockable rhythms and compared the temperature control of 32°C - 34°C for 24 hours with the standard normothermic life support protocols. Results of the trial showed better neurologic outcomes after six months in the hypothermic group, 55% vs. 39% in the control group (RR 1.40, 95% CI 1,08 - 1,81) (5). Bernard's trial had a smaller population, which included only 77 patients with ROSC after witnessing OHCA with VF; it compared the temperature control of 33°C for 12 hours with no temperature control. The conclusions were similar to those in the HACA trial, with a better neurologic outcome in the hypothermia group of 49% and 29% in the control group (P=0.046) (6). The results of these trials have to be interpreted now cautiously, as there are limitations in the studies. In Bernard’s trial, the number of patients involved was small, which could have influenced the results, and the randomisation in the trial was not done properly, as it occurred according to the

day of the month (6). In the HACA trial (5), a quarter of the control group had an increase of temperature up to 38°C according to the temperature graph, which is not in the normal range of the temperature and considered fever by the recent recommendations of ILCOR (10). Even though there were limitations in the studies, the results of the trials were taken into consideration and in 2003, ILCOR introduced the recommendation of active temperature control on the level of 32-34 °C for 12-24 h if the initial rhythm was VF with level 1 evidence. It is important to mention that in 1998, at least one RCT was required to get level 1 of evidence, which showed the lower limit of CI for treatment exceeded the minimal clinically important benefit (7). In 2011, a systematic review by Nielsen et al. was published, depicting the risk of systematic errors in the trials done in 2002 (5,6). It stated that there is a need to repeat trials because of the high bias risk with systematic errors, which makes the quality of evidence found in the HACA (5) and Bernard trials (6) low (23). After that, in 2013, the results of the biggest RCT were published, which included 939 comatose OHCA survivors and was later named the TTM1 trial. Results of which found no difference in the neurological and survival outcome between patients who received temperature control with TT of 33 °C versus a target of 36 °C (temperature control with hypothermia 54% vs control group 52% had poor neurologic function measured with CPC<2 (RR, 1.02; 95% CI, 0.88 -1.16; P=0.78)) (8). Such conflicting results can be explained by the change in the ALS in the ICU and usage of prognostication protocol by the investigators in the TTM1 trial (8): 72 hours after CA blinded neurologic examination was done to decide of continuing or withdrawing life-supporting therapy (24). However, there were limitations which should be considered while interpreting the TTM1 results: the timing needed to reach TT of 33 °C was, on average, 7 hours, which makes the temperature control for the majority of patients inadequate, as they did not reach TT quickly enough to have beneficial effects of hypothermia (25). After the results of the TTM1 trial were published, there were changes in clinical practice; the TT was changed from 33°C to 36°C. As a result of one retrospective cohort study, which compared the outcomes of cardiac arrest patients before and after changes, showed a decrease in the positive neurologic outcome of the postcardiac arrest patients, which can be explained by the misinterpretation of practitioners of the need for active temperature control management during normothermia (26). In 2019, RCT HYPERION compared the temperature control of 33°C during the first 24 hours with normothermia of 37°C in OHCA only with non-shockable rhythms. It showed different results from the TTM1 on the 90-day neurologic outcome. In the group with hypothermic temperature control, 10.2% of patients were alive with favourable neurologic outcome CPC score of 1-2 compared to 5.7% in the normothermia group (difference 4.5%; 95% CI 0.1 - 8.9; P = 0.04). The authors mention that because of the fragility index 1, results have more clinical significance than statistical (27). In 2021, the second TTM2 trial included the biggest number of the participants comatose OHCA survivors with any initial rhythm -

1850. This study found no difference in the group of temperature control of 33°C for 24 hours, compared to the group with early treatment of fever (≥37.8°C) in the neurological outcome (hypothermia group 50% and control 48% had CPC score >3, RR with hypothermia, 1.04; 95% CI 0.94-1.14; P = 0.37) (9). The results of both TTM studies (8,9) can be questioned due to the level of bystander CPR in the studies, which was higher than average in Europe (28). Patients with a shorter time of absence of cerebral circulation due to bystander CPR have more favourable neurologic and survival outcomes than those with longer cerebral circulation absence. In 2022, the first study on IHCA comatose survivors was done. A comparison of temperature control at 32°- 34°C with no active temperature control but avoidance of fever (defined as ≥37.8°C) was recommended, but there was no significant difference in neurologic outcome (CPC 1-2 by 180 days in the hypothermic group 22.5% vs 23.7% in control (RR, 1.04 95% CI, 0.78–1.44; P=0.822)) and survival (mortality by 180 days was 72.5% in hypothermic group vs 71.2% control (RR, 1.03 95% CI, 0.79–1.40; P=0.822)). The authors mentioned that results may not detect the clinically sufficient difference due to the early stop for futility (29).

Overall, current data from RCTs on the benefit of temperature control is controversial. It does not show clear profits for temperature control with hypothermia for the general population of patients with OHCA and IHCA, raising more questions about temperature management and a perfect target group for such management. That is why investigators of future research must analyse currently available data, focus on the criticism of the current trials, make inclusion criteria for selecting the defined part of the patient population for the RCT, and perform high-quality temperature control during the trials.

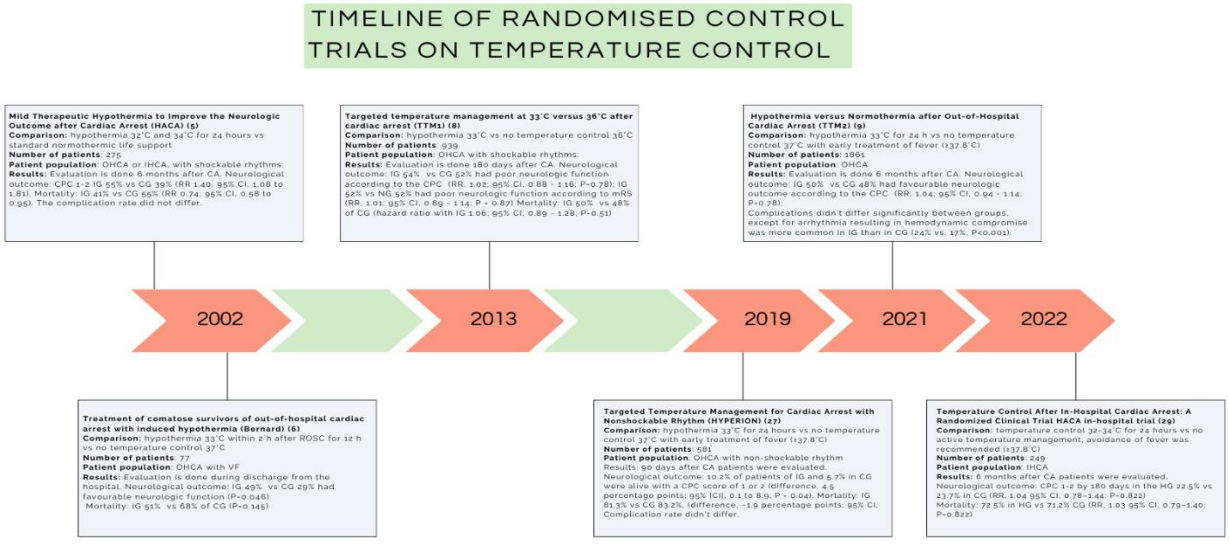

Figure 1. Timeline of randomised control trials on temperature control. The abbreviations used in the figure are CPC—Cerebral Performance Category, OHCA—Out-Hospital Cardiac Arrest,

IHCA—In-Hospital Cardiac Arrest, VF—Ventricular Fibrillation, CG—Control Group, IG—Intervention Group, and RCT—Randomised Control Trial.

5. ACTIVE TEMPERATURE CONTROL

Active temperature control consists of 3 phases.

- Initiation – phase started after ROSC. It includes selecting the temperature control method, choosing TT, and applying management as soon as possible.
- Maintenance – phase which lasts for 24 hours minimum, according to the current guidelines(30–32).
- Rewarming is the phase that includes the time of reaching the normothermic temperature range from hypothermic.

5. 1 Timing of initiation of temperature control

According to the study results on animal models, there is a time frame of 4 h from the start of CA, in which temperature control with hypothermia results in better neurological outcomes (33); this is supported by earlier animal studies, which concluded the same positive effect on neurologic outcomes with the early start of temperature control after CA (34,35). Because of these results, a hypothesis appeared that temperature control must be initiated as quickly as possible to have the most favourable neurologic outcome. Temperature control could be started before resuscitation, during resuscitation or after achieving ROSC in out-hospital settings for 15 minutes or inside a hospital during four 4-hour periods. The earliest RCT, Bernard (6) and HACA (5) initiated cooling with a median time of 2 hours after ROSC and had positive neurologic outcomes. Despite the results of the earlier studies, RCTs in adults on prehospital cooling, which compared cooling with IV infusion of cooled normal saline with no intervention, showed no difference in the survival and health outcomes for patients who had prehospital cooling compared to the patients with standard temperature control management with hypothermia. The intervention group with prehospital cooling was reported to experience more rearrest compared to the control group (26% (95% CI, 22%-29%) vs 21% (95% CI, 18%-24%), respectively; P = .008) (36). RCT, which used trans-nasal evaporative devices and IV cold saline during CPR, also showed no improvement in neurological and survival outcomes compared to the standard temperature control with hypothermia; studies showed that there might be even a decrease in the rate of ROSC(37,38). In 2016, a Cochrane systematic review concluded that there are neither beneficial nor harmful effects of the prehospital

cooling with IV infusions or intranasal cooling of the patients who had ROSC after CA. A higher incidence of the rearrest was also reported in the prehospital cooling group (RR 1.23; 95% CI 1.02 - 1.48; P = 0.03)(39). In 2021, a systematic review of Granfeldt, which included seven studies comparing the effectiveness of prehospital and intraarrest cooling with cooling pads and endovascular and intranasal devices, showed as well no improvement in survival (RR 1.01 95% CI: 0.92, 1.11) or neurologic (RR 1.00 95% CI: 0.90, 1.1) outcomes among survivors of CA at the hospital discharge (40). Post hoc analysis of the TTM2 trial (9) has shown no difference in the outcome in the hypothermic group, which was cooled faster during the first 4 hours after ROSC, compared to the normothermic group with early treatment of fever. Further analysis of the hypothermic group even concluded that more aggressive cooling was associated with higher mortality (41).

Current evidence suggests that there is no need for prehospital cooling with rapid IV infusion of cold saline or intranasal cooling during CPR of the patient after CA. According to the current recommendations(30–32), it is necessary to start active temperature control by monitoring the temperature as soon as possible after the patient has ROSC and choosing the type of management: hypothermic or normothermic with active fever prevention. However, there is still a knowledge gap regarding the therapeutic window of the start of cooling in which the patient may benefit from the management.

5. 2 Different methods of cooling their comparison

Three nonpharmacologic techniques are used in temperature control to achieve and maintain TT: surface, endovascular, and conventional cooling. Conventional cooling is the most affordable, easy-to-use, and widely available method, and it includes crushed ice, ice bags, or cold-saline infusions. The disadvantage of this technique is the absence of a feedback system, which reduces the effectiveness of maintaining and reaching TT. Another method - the surface cooling technique- uses blankets with circulated cold air or fluids covering the patient's body. These methods are more precise, as there is a computerised feedback system which changes the temperature of the blanket according to the skin or core temperature of the patient. Using such devices could cause skin irritation or burns; other disadvantages are difficulty maintaining the temperature and the higher probability of shivering as an adverse effect in the patient (42). Intravascular cooling techniques, on the other hand, include devices with catheters placed into the central vein that allow cold saline to circulate through the body. Such devices have adjustable cooling rate settings and are considered the most reliable among all cooling methods (43). A recent meta-analysis showed that specific invasive cooling methods had more favourable neurologic outcomes compared to the other methods

(5%, 95% CI 2% -8%) and no difference in the complications rate between the groups (44). Such results support the recommendations of ILCOR for using surface or endovascular temperature control devices with feedback systems (10). The Neurocritical Care Society advocates using intranasal, surface, or intravascular cooling devices, cold IV infusions over air cooling blankets, cooling fans, or cooling packs to maintain TT (45). Up to April 2024, the multicentre RCT - STEPCARE trial (NCT05564754) has been gathering data on the effectivity of feedback-controlled devices on active temperature control with fever management (46). One potential method for temperature control in the future is selective brain cooling, which currently has limitations due to the cooling reagent's insufficient cooling ability and expensiveness. However, this method can help avoid complications caused by the cooling of the whole body (47). Practitioners can also use pharmacologic temperature control methods, such as antipyretic drugs, to maintain TT. If it is impossible to maintain the temperature, other cooling methods can be used (31)– in the TTM2 trial (9), investigators used such management for a control group of normothermia with active fever prevention.

While performing active temperature control, either with hypothermia or normothermia, the practitioner must select a method for temperature cooling according to knowledge and experience of the methods, the patient's needs and the availability of the devices in the health care centre. Even if temperature control with normothermia and fever prevention is chosen, the patient still can require a cooling device.

5. 3 Target temperature during temperature control

Currently, two strategies for the temperature management of comatose post-cardiac arrest survivors that showed favourable neurologic outcomes could be described: active temperature control with hypothermia, active temperature control with normothermia, and fever prevention. TT is recommended to be in the values from 32° C to 37,5° C (30–32), such broad range includes normothermic temperature and mild, moderate and profound hypothermic temperatures.

Cochrane systematic review and meta-analysis published in 2023, which included the most recent RCT, compared conventional cooling methods versus any standard treatment and found that participants in the hypothermia group were more likely to reach a favourable neurological outcome (RR 1.41, 95% CI 1.12 -1.76; 11 studies, 3914 participants). They also compared the effects of temperature control with hypothermia to temperature management at 36 °C and concluded the absence of difference between groups for the neurologic outcome (RR 1.78, 95% CI 0.70- 4.53; 3 studies; 1044 participants). The certainty of the evidence stated in the review was low (48). The

same year, a meta-analysis done by the ILCOR ALS Task Force compared temperature control with a target of 31–34 °C with normothermia and fever prevention and showed that at 90- 180 days after CA with no improvement of survival (RR 1.06, 95%CI 0.91-1.23) or positive neurological outcome (RR 1.27, 95% CI 0.89 -1.81) (49). This study's results were supported by another systematic review, which included RCT on temperature control, which was done in 2016-2022 (50) and a meta-analysis, which included patients with initial non-shockable rhythm (51).

The different degrees of TT were compared during temperature control with hypothermia to evaluate the profit of deep hypothermia. The FROST-I trial compared TT 32 °C, 33 °C and 34 °C cooled by the endovascular cooling devices for 24 hours in comatose survivors of witnessed OHCA with initial shockable rhythm and concluded that there were no statistically significant differences in neurological outcomes for different hypothermic TT (52). Another trial, CAPITAL CHILL, compared temperature control 31 °C versus 34 °C for 24 hours and found no significant reduction of mortality or poor neurologic outcome at 180 days after CA (53). Recent meta-analysis comparing normothermia versus deep hypothermia 31°C-32°C (OR 1.30, 95% CI 0.73–2.30), normothermia versus moderate hypothermia 33°C-34°C (OR 1.34, 95% CI 0.92-1.94), or normothermia vs. mild hypothermia 35°C-36°C (OR 1.44, 95% CI 0.74–2.80) showed as well no significant difference in the survival or neurologic outcomes among survivors of OHCA (54).

The population of survivors of CA comatose after ROSC is heterogeneous, which is why there was a suggestion that there could be a specific group that can benefit more from hypothermic TT than from normothermic TT. Patients with ischemic stroke (55), severe brain injury with loss of motor response or brainstem reflexes, or malignant EEG patterns (56) might belong to such a group. There also is data that patients with moderate brain injury can benefit from temperature control at the level of hypothermic TT with better neurologic outcome (OR 1.70, 95% CI 1.03-2.83) and survival at 30 days (OR 1.90, 95% CI 1.15-3.16) (57). The duration of the resuscitation of postcardiac arrest patients can also influence the choice of TT: patients with ROSC in less than 30 minutes may benefit from hypothermic temperature control, as stated in RCT (58). The Cochrane systematic review concluded that patients with non-witnessed CA, with bystander CPR rates of less than 60% and no-flow times of more than 1 minute, might benefit from temperature control with hypothermia (48). However, in another post-hoc TTM (8) study, no association existed between the time to return to ROSC and better neurological outcomes (59).

Active temperature control is contraindicated when an advanced directive restricts the usage of invasive or intensive treatments or if such treatment is unsuitable for clinical situations, such as terminal illnesses. In clinical practice, active temperature control should not be used in responsive patients (GCS >8); temperature control with hypothermia should not be used for CA due to trauma,

sepsis or active bleeding, as there is no RCT which would examine the effects of temperature control in such conditions. Relative contraindications can be stated according to the known complications of temperature control with hypothermia (60): known coagulopathy, patients with severe underlying comorbid medical conditions of bleeding, arrhythmias, and electrolyte disturbances. Therefore, active temperature control with normothermia and active fever prevention can be recommended for patients with hypothermic management contraindications. Retrospective studies showed that this protocol results in a lower incidence of fever and reduced use of neuromuscular blockers, used in shivering treatment during temperature control with hypothermia (61). Implementing the temperature control protocol with normothermic TT is not easier than hypothermic—studies suggest a decrease in active temperature control in emergency departments after the normothermic protocol was implemented, followed by an increase in unpleasant outcomes (26). It is crucial to have high-quality temperature control with TT as hypothermic or normothermic, as poor-quality management can result in patient harm (62).

Overall, there is uncertainty about the best TT for different sub-groups of comatose patients-survivors of CA due to the low-quality evidence from the studies' results. The results of the RCT, as well as the systematic and meta-analysis of the TT, are controversial. Nevertheless, there is consensus: temperature control with active fever prevention, regardless of the TT in the normothermic or hypothermic range, is profitable for all comatose survivors of CA. Clinicians should adopt an individualised approach to postcardiac arrest patient management, evaluating the profits and harms of certain treatments for the patient.

5. 4 Duration of temperature control

International guidelines recommend maintaining active temperature control regardless of the chosen TT for at least 24 hours (30–32). An RCT on the temperature control duration has shown no difference in the outcomes for 24 hours versus 48 hours. However, the study had limited power to detect clinically significant characteristics. The group that had a longer duration of temperature control had a higher rate of adverse effects (difference, 5.6%; 95% CI 0.6%-10.6%; RR 1.06, 95% CI, 1.01-1.12; P = .04) (63).

According to the current guidelines, temperature control with active fever prevention is recommended for survivors of CA for 72 hours after the event (30–32). This statement is currently debatable, according to a recent RCT investigating active device-based fever prevention for 36 hours and 72 hours, in which patients were divided into two groups with temperature control of 36°C for 24 hours followed by a target of 37°C for either 12 or 48 hours, found no statistically

significant difference for survival or neurologic outcome at 90 days (64). The reduction of the duration of fever prevention can reduce the pharmacotherapeutic usage of sedatives and accelerate recovery for patients (65). Up to April 2024, a multicentre RCT is ongoing regarding the effect of the duration of the cooling on the outcome of post-cardiac arrest patients - ICECAP study (NCT04217551). This study hypothesises that extended cooling can improve neurological outcomes (66).

Until more data on the temperature control duration is obtained, clinicians must maintain TT for 24 hours regardless of the TT, after which there has to be active fever prevention for 72 hours.

5. 5 **Temperature control monitoring**

Temperature variations, without active control, can result in harmful outcomes (67); therefore, after ROSC, it is recommended that monitoring of the core temperature is immediately initiated (30–32). Oesophageal temperature measurement is the most precise technique for assessing core temperature during temperature control. Bladder temperature measurement may be inaccurate in cases of low urine output (less than 0.5 mL/kg per hour). Rectal, axillary, and tympanic measurements are insufficient and misleading when measuring core temperature (68). That is why it is recommended to use the oesophageal temperature probe during temperature control, and as an alternative, a bladder temperature probe can be used (45).

Temperature control with hypothermia results in physiologic changes in the body of the patient, which can cause adverse reactions such as shivering, metabolic and electrolyte disturbances, arrhythmias, pneumonia, sepsis and bleeding (69). However, the incidence of such complications showed no significant difference in the RCTs between normothermic and hypothermic management (5,28) except for the incidence of arrhythmias, which were higher in the group with hypothermic temperature control (hypothermia 33°C 24% versus control 17%, $P<0.001$) (9).

Shivering is one of the most common complications during temperature control with hypothermia, which can limit the effectiveness of temperature management due to increased oxygen consumption and heat production (60). It appears mostly during induction and rewarming phases as a physiological reaction to lowering the core temperature. The Bedside Shiver Assessment Scale (BSAS) is a well-known, standardised and reliable clinical practice tool to detect and evaluate the severity of shivering (Table 1). It consists of a scale with four grades, which depend on the groups of the muscle’s movement (70). The treatment of shivering during temperature control must include ladder management where prioritisation is done for non-sedating pharmacologic management such as acetaminophen and magnesium infusions or non-pharmacologic management with rewarming

over narcotic analgesics, sedatives or neuromuscular blockade (45). It is crucial to differentiate shivering from seizures, as their treatment is different, for this continuous EEG monitoring can help (30).

Table 1 Bedside Shiver Assessment Scale (BSAS) (70)

BSAS 0	No shivering was detected during palpation of the masseter, neck, or chest muscles.
BSAS 1	Shivering is localised to the neck and thorax only.
BSAS 2	Shivering involves gross movement of the upper extremities and the neck and thorax.
BSAS 3	Shivering involves gross movements of the trunk and upper and lower extremities.

Hypothermia induces coagulopathy, and as a result, the patient is likely to have bleeding and thrombosis complications during hypothermic temperature control. When the core temperature reaches 35°C, an increased bleeding time can be observed due to the reversible dysfunction of platelets and endothelium. Although coagulation values are different from usual during hypothermia, RCT data show that such changes do not result in clinically significant bleeding (71). An increased frequency of bleeding has been reported to occur after invasive procedures. However, it was not associated with increased mortality (OR 1.0, 95% CI 0.46-2.2, p = .91) (69). That is why it is recommended not to change the patient's routine care, especially when taking the necessary medications, which alter coagulation parameters such as aspirin, antiplatelet compounds, and thrombolytic agents (60). Thromboelastometry is recommended for monitoring bleeding and preventing thrombosis in patients undergoing hypothermic temperature control (45).

In temperature control with hypothermia, patients can experience the inhibition of immune system response due to the reduced chemotactic and phagocytic activity and production of the proinflammatory cytokines, which occurs in patients with a temperature of 33 °C (72). However, it is recommended not to change the standard care for monitoring infections among patients receiving temperature control with hypothermia not be changed (45).

During the cooling phase, electrolyte imbalances, including potassium, magnesium, phosphorus, and calcium levels, can arise; thus, they must be monitored, as potentially such disbalances can lead to heart rhythm problems, muscle weakness in the diaphragm, and coagulopathy. When the body temperature is lowered, electrolytes are moved into cells, and due to the cold, urine production increases, which can cause the kidneys to excrete potassium, magnesium, and phosphate (73). Electrolyte shifts are reversed during rewarming. Close monitoring of potassium levels is crucial to avoid heart arrhythmias, and it's recommended that the serum level be maintained between 3.0 and 3.5 mEq/L during the initial and maintenance phases (45). The pancreatic secretion of insulin as

well can malfunction during hypothermic management, leading to hyperglycaemia. As the body's metabolic functions return to normal during the rewarming phase, there is a risk of hypoglycaemia. If this drop in blood sugar is significant, it could lead to severe consequences such as seizures or coma (74).

Appropriate sedation has to be provided to the patients undergoing temperature control; for this, propofol and fentanyl continuous infusions can be used. In hypotensive patients, infusion with midazolam can be used as an alternative (75). However, it is crucial that hypothermia can change drugs' pharmacokinetics and pharmacodynamics, as it lowers medicines' absorption, distribution, and extraction (76).

Active temperature control management requires controlling the absence of temperature fluctuations to maintain TT and checking the parameters of whole body systems, especially during temperature control with hypothermia. It is vital to manage shivering, as it can limit temperature control efficiency and electrolyte changes, which can lead to arrhythmia.

5. 6 Rewarming duration

During the rewarming phase of temperature control, it is not recommended to actively rewarm patients (30,31). Also, if the patient has mild hypothermia after ROSC, it is recommended that the patient should not be rewarmed actively to achieve normothermia (45,62), or not faster than 0,5 °C /h (32). Studies show controversial results regarding the speed of rewarming: Japanese study concluded that longer rewarming duration after temperature control with TT of 34°C was an independent predictor of favourable neurological outcomes in OHCA patients who underwent temperature control with hypothermia (OR, 0.89; 95% CI 0.79-0.99; p = 0.032) and survival (OR per 5 h, 0.85; 95% CI, 0.74-0.96; p = 0.012); (77); meanwhile, another multicentre prospective cohort study also concluded in Japan as well, found that rapid rewarming after temperature control at 34°C was associated with a more favourable neurological outcome than slow rewarming (OR 1.57 95% CI 1.04-2.37; p = 0.031)(78). RCT comparing the rewarming rate after temperature control with hypothermia at 33 °C at a rate of 0.25 °C/h versus 0.50 °C showed no difference in serum IL6 levels – a marker associated with poorer functional outcomes among patients. The study concluded that there is no difference in the rate of rewarming and functional outcome in patients who remained comatose after shockable CA (79). After rewarming, it is crucial to prevent fever actively (fever defined as ≥37.8°C), as it is associated with increased mortality (80), although the duration of such management is also debatable.

Generally, cautious rewarming of patients who underwent temperature control is advised. The current literature presents conflicting results on the speed of rewarming, but preventing fever post-rewarming is critical due to its link to higher mortality.

5. 7 Neuroprognostication in active temperature control

All postcardiac arrest patients who are not awakened after clearance of sedatives must be assessed by qualified medical personnel for the prognostication of neurological outcomes. This task can be complicated and requires several methods for evaluation, such as neurological examination, neuroimaging, and chemical biomarkers, which have to be evaluated together to avoid false-positive predictions of poor outcomes. No single predictor can have 100% accuracy. A predicted poor outcome typically leads to the withdrawal of life-sustaining therapy (WLST) and death. (81). Patients with OHCA who get ROSC have WLST as the most common cause of mortality due to irreversible hypoxic-ischemic brain injury (4). Due to the reduction in the drug metabolism during temperature control with hypothermia, which means that sedatives and neuromuscular blockers may linger in the system, potentially affecting the clarity of neurological assessments, neuro prognostication is recommended to be postponed for at least 72 hours following ROSC, and potentially longer if temperature control has been used (82).

CONCLUSION

Temperature control is a complex topic in the management of comatose postcardiac arrest patients. The lack of definitive answers regarding temperature control management means that current recommendations are primarily based on low or moderate levels of evidence, leaving several knowledge gaps in this field. In order to fill them, researchers must accurately analyse existing data and appropriately design future randomised control trials that are more focused on critics and limitations of the previous trials. To avoid distorting results, these trials must prioritise high-quality temperature control management with early initiation and proper maintenance. It is essential to identify the potential subgroups in the population of comatose survivors of cardiac arrest which can benefit from the temperature control of certain temperatures. This identification will enable focused research on creating protocols for high-quality temperature control, including determining optimal start times, duration, procedural management, and post-temperature control supervision. It is crucial to understand that there is no simple answer to use or not to use temperature control, and that is why clinicians should adopt an individual approach to temperature management for each patient rather than reject temperature control with hypothermia or normothermia. It is essential to create protocols

with both hypothermic and normothermic management that will be adapted according to the local situation and implemented into the routine practice of the hospitals receiving patients with cardiac arrest. Active temperature control with avoidance hyperthermia (fever defined as >37.7°C) is considered optimal management for all patients- survivors of cardiac arrest. However, it is known that such a population is very heterogenic and, despite controversial results of recent randomised control trials and meta-analysis, temperature control with hypothermia can still have a beneficial neurological effect for a particular part of the population. Clinicians must stay updated regarding evolving recommendations on temperature control and adjust management according to the current evidence in the field.

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