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REVIEW

Temperature management and its role in cardiac arrest patients—a review

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Abstract

Thermoregulation constitutes one of the most important homeostatic systems of the human body. The human thermoregulatory system is highly complex and intertwined with other regulatory homeostatic systems. Different evolutionary adaptations have evolved to ensure a well-regulated body temperature, encompassing simple behavioural (e.g., seeking shelter, going underground) as well as physiological changes (e.g., vasodilatation, sweating). However, when the heat, cold or other stimuli cause a disruption in the thermoregulatory state and our adaptations can no longer cope with the additional stress, the body enters a pathological state. In such instances other measures must be undertaken. In medicine there are several pathological states associated with disruptions in temperature homeostasis. Consequently, these patients have to be, in broad terms, thermoregulated. Speaking specifically, the most common application of thermoregulation is therapeutic temperature management. A prominent example is the utilisation of this technique in post-cardiac arrest patients, who remain comatose after resuscitation. This technique has been in use for almost 20 years since the first major reports on its benefits in improving out-of-hospital cardiac arrest and in-hospital cardiac arrest survival as well as improving neurological outcome. Recently, the findings from one of the biggest targeted temperature international and multicentre trials to date have been published (TTM2 trial; https://ttm2trial.org/). The study surprisingly showed no difference in mortality between patients after out of hospital cardiac arrest, who underwent normo- or hypothermia. Consequently, we might need to re-evaluate certain guidelines, recommendations, and perspectives. The aim of the current review is to present an overview of targeted temperature management in the field of intensive care medicine and cardiac arrest.

Keywords

Thermoregulation; ICU referral; Cardiac arrest; Targeted temperature management; Physiology; Resuscitation

1. Introduction

Normal human physiology presents an intricate balance of many regulatory systems. One of those is thermoregulation [1]. Its complexity, manifoldness and indigenous evolutionary adaptations can be easily appreciated in a variety of animal species [2, 3]. Some examples include dynamically adapting insulation types (e.g., feathers, hair), neural and neurovascular controlling mechanism, different types of temperature regulating organisms (e.g., cryopreservation) and behavioural adaptations [3–5]. Speaking from an evolutionary standpoint, humans are part of the endothermic homeothermic group, produce their own heat through metabolism and can also utilise behavioural adaptations [3, 6]. In certain scenarios our intrinsic thermal regulatory mechanisms are disrupted. The underlying disease and its consequences can, when left untreated, lead to extensive irreparable organ damage (e.g., brain). In such cases targeted temperature management (TTM) can be utilised. The prime example of its usage, for almost 20 years, has been the application in comatose survivors after cardiac arrest. However, this method can be utilized for the management of various surgical cases as well [7, 8] (e.g., burn victims [9], neurocritical patients [10–12]). There are different techniques on how to perform and maintain TTM. It is important to understand the underlying physiology, its range of applicability as well as its limitations and possible drawbacks. Although guidelines strongly recommend TTM between 32 °C and 36 °C in comatose patients after an out of hospital cardiac arrest (OHCA), they also state the overall evidence is of low certainty. It has been stated that the available trials had high risks of bias and random errors [13]. The aim of this article is to present a review on the usage of TTM in cardiac arrest patients, with an added explanation of the most common pathologies as well as basic (patho)physiological concepts of

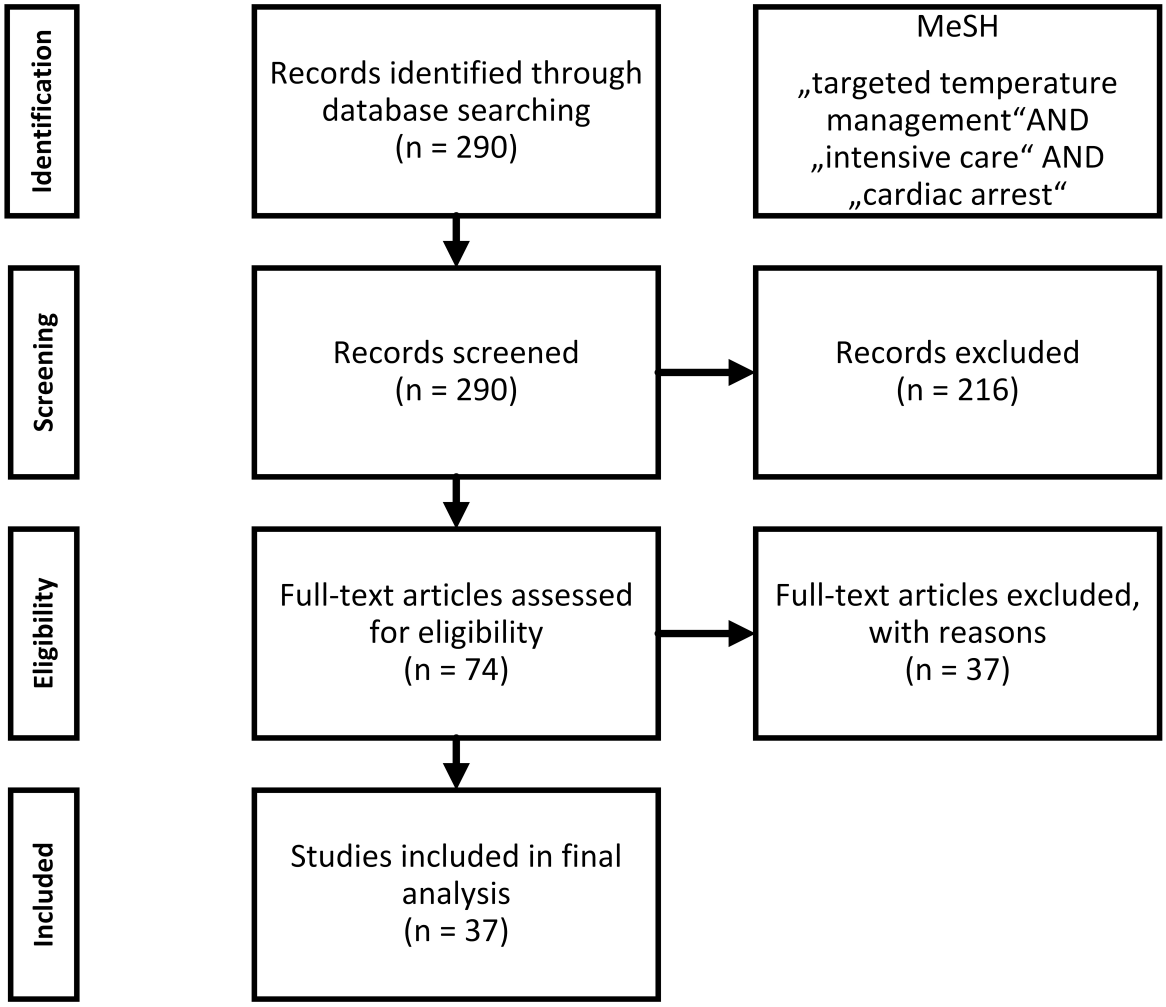

FIGURE 1. Literature search algorithm.

human thermoregulation.

2. Search method

A literature review was conducted via the biggest medical literature databases (Medline, PubMed, ScienceDirect) to obtain studies related to thermoregulation, the intensive care unit and cardiac arrest. The employed combined search term in the form of MeSH indexed keywords was: “targeted temperature management” and “cardiac arrest” and “intensive care”. With the help of this search algorithm and specific filters (5-years, human, clinical trial and review), we were able to find relevant new impactful studies on TTM in cardiac arrest patients. Included in the final manuscript were also founding studies that paved the way generations to come. The search inquiries and presentation of the final number of included studies after exclusion and filtering are presented in Fig. 1, which has been prepared in accordance with the PRISMA guidelines for review articles.

3. Physiological basics of the human thermoregulation

When looking at the physiological basis of human thermoregulation we must understand that the body needs a certain level of basal metabolism, which depends on multiple variables (e.g., age, race, sex, etc.) and is especially high in internal organs. The basal metabolism represents the minimal energy that is required for our functioning and survival (up to 70% of our daily energy consumption). This value is part of the daily metabolism alongside the digestive metabolism and work metabolism. To briefly mention, the preservation and thermal balance also depends on heat exchange with the environment due to: (1) radiation, (2) conduction; (3) convection; (4) evaporation. When heat storage is zero, the body is thermally balanced. It is evident that for a sustained and regulated core temperature, thermoregulation has to be kept in a dynamic balance between heat production/gain and heat loss [14]. The human bodies’ internal temperature, or also called core body temperature (CBT), remains stable at around 36–37.5 °C [1]. The temperature is regulated via a reflex which constitutes a feedback and a feedforward signal that meet in the thalamic region (preoptic area in the rostral hypothalamus) [1, 15], as schematically presented in Fig. 2. The acral parts of the body can have different temperature measurements. These temperature values can be referred to as peripheral shell temperatures and are normally 4 °C lower than the CBT. Causes for shifts in the CBT can be in their nature abrupt or gradual. They can also be part of an adaptive response to external or internal stimuli in the setting of an infection (e.g., fever). In such

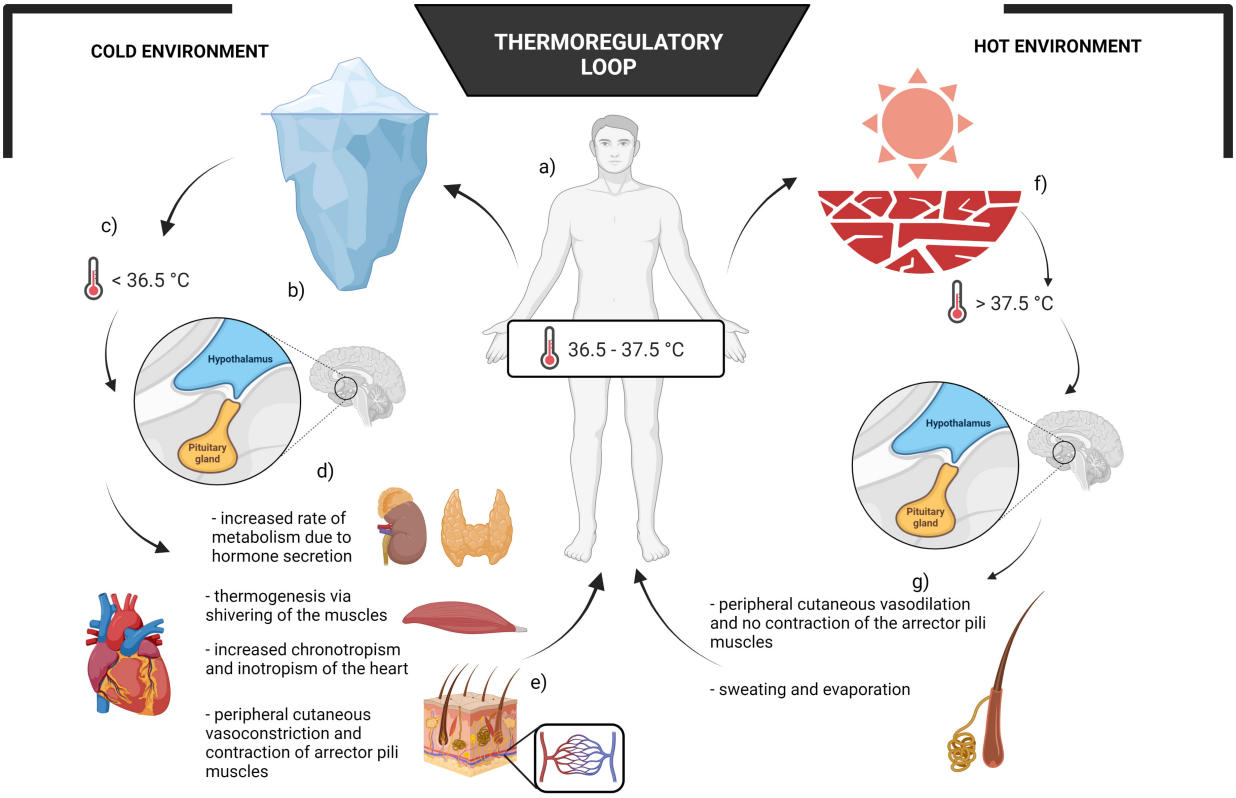

FIGURE 2. Simplified scheme of the thermoregulatory loop. Legend: (a) The body in a normothermic balanced state. (b) When exposed to a cold climate. (c) A drop in core body temperature. (d) The hypothalamic center integrates thermal information and directs changes in efferent activity to modify heat transfer and adequately adjust hormonal stimulation. (e) Sweat formation is stopped, hairs stand on end due to muscle contraction and form an isolation layer of air; vasoconstriction with centralisation of the blood flow as well as countercurrent heat exchange, shivering with thermogenesis, endocrine stimulation (e.g., thyroid gland, adrenal gland). (f) When exposed to a hot climate with an increase in body temperature. (g) Vasodilatation, sweating. Created with BioRender.com.

situations fever is the result of the body releasing pyrogens (e.g., cytokines, prostaglandins, and thromboxane). These lead to the conversion of arachidonic acid to prostaglandin E2 via the induction of cyclooxygenase 2. Consequently, via the binding of prostaglandin E2 to the receptors in the hypothalamus, the "set point" of the internal temperature control mechanism is increased [16]. In cardiac arrest patients, who remain comatose after successful resuscitation, the body's own thermoregulatory mechanisms are not functioning properly. This dysregulation can be partly caused due to the disease itself and partly due to potential sedation as well as analgesia. The latter are well known to impair thermoregulation [8, 16] and their effects can be summarised as follows: (1) increase in the threshold for sweating and vasodilatation by up to 1 °C [17]; (2) in a synchronous and dose dependant matter decrease vasoconstriction threshold by 2 °C. This subsequently leads to an increase of the normal interthreshold interval of a few tenths of °C by at least 10- to 20-fold [8, 18].

4. The intensive care and disbalances in thermal regulation

In certain settings the management of patients with refractory or complicated dysregulated thermal states requires more than conventional means. These patients need to be admitted to the intensive care unit (ICU). Temperature measurement can be done at peripheral sites or core sites [19]. The CBT is the only reliable way to continuously monitor the thermal state of critical care patients. Regarded as the gold standard for continuous core temperature monitoring are still readings from the pulmonary artery. However, bladder temperature readings via a urinary catheter are similar to blood temperature and present a less invasive option. Additionally, there is a 30% risk of adverse events with insertion and maintenance of the pulmonary catheter [20].

It has been stated that approximately one third of hospitalised patients develop fever [21]. In the ICU this percentage is even higher (up to 70%) and is associated with higher mortality [22, 23]. A fever that surpasses 41.5 °C can be categorised as hyperpyrexia. This is common in septic patients. The term hyperthermia is not interchangeable and is reserved for the state where the hypothalamic set temperature, in contrast to hyperpyrexia, is unchanged, while the body's temperature rises. The opposite spectrum is hypothermia. Temperatures below 28 °C are indicative of severe hypothermia. Values in between 28–32 °C or 32–35 °C correspond to moderate or mild hypothermia [24, 25]. Pathophysiological changes that occur in these states affect the cells, organs, and the body as a whole [25]. These include cellular (e.g., excitotoxic mechanisms, protein denaturation), local (e.g., inflammation,

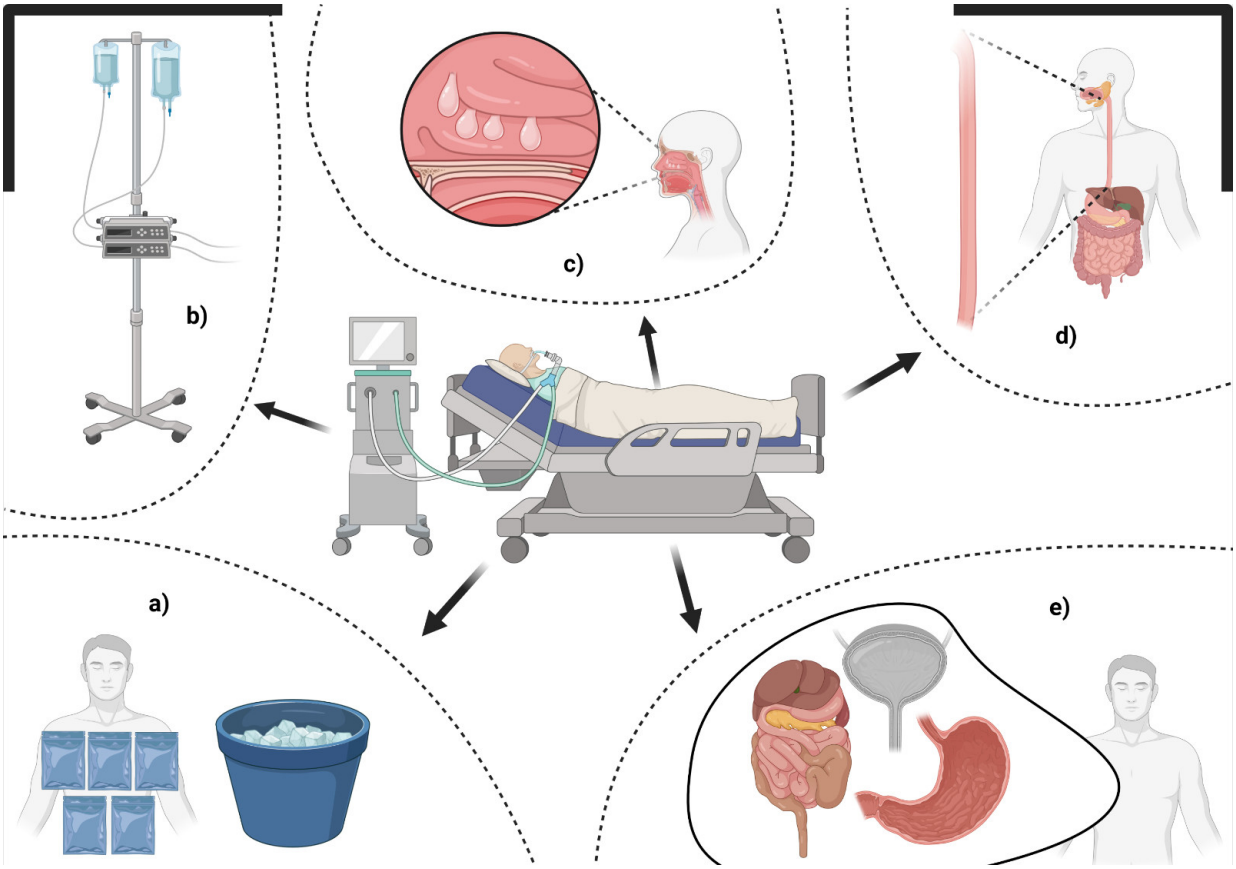

FIGURE 3. Different TTM methods. Legend: (a) surface cooling. (b) Intravenous cooling. (c) Transnasal cooling. (d) Transoesophageal cooling. (e) Intracavitary cooling. Created with BioRender.com.

oedema), systemic in form of sepsis and bacterial translocation [24]. It must be noted that patients with hypo- or hyperthermia may have underlying medical conditions that require treatment before the temperature can be corrected. The most common causes for fever in the ICU are infectious in nature (pneumonia, catheter associated urinary tract infections, etc.) [26–28]. Nevertheless, many non-infectious disorders result in tissue injury with inflammation and a febrile reaction. Studies on fever and mortality in ICU patients have predominantly reported a higher associated mortality [29–31]. Nevertheless, there have been reports that showed no change or even a decrease in mortality [26, 32]. The treatment modalities differ due to the various underlying pathologies. In addition, the clinician may need to decide whether antimicrobials, catheter or device removal, and/or treatment of the fever are indicated.

5. Targeted temperature management basics and methods

TTM has been previously known as "therapeutic hypothermia". The change in nomenclature has been decided 10 years ago in an attempt to stress the clinical relevance of the whole process (induction, hypothermia, rewarming, normothermia) and not limit it to only one aspect (hypothermia) [33].

There are several characteristics that all carry importance and can separate "low-quality TTM" from "high-quality TTM". The important points, as summarised after Taccone *et al.* [34], are as follows:

(1) Initiation time — As soon as possible, with the explanation to minimize reperfusion injury following return of spontaneous circulation [35]. However, some cooling techniques (e.g., rapid infusion of iced saline) used in a pre-hospital setting have potential negative side effects and complications and are not recommended (e.g., re-arrests and more pulmonary oedema) [36, 37].

(2) Duration of the cooling phase — At least 24 hours. No studies have shown significant differences in outcomes in prolonged cooling of adults [38]. Shorter cooling durations are not recommended.

(3) Duration of the rewarming phase — Slow and gradual (0.15–0.25 °C/h).

(4) Measurement of temperature — Immediate, continuous and CBT. The decision which localisation is to be used partly depends on the local environments, case, physician etc. (e.g., oesophagus, vessel, bladder).

(5) Targeted temperature — Values should lie within the range of 32–36 °C. Whether a highly specific temperature is better than another and whether interpatient variability in regard to comorbidities are of significance, remains to be seen [39, 40].

(6) Normothermia — Due to potential harmful effects (e.g., uncontrollable post-TTM fever) temperature should be monitored for an additional 48 hours after protocol termination.

There are multiple TTM methods, as illustrated in Fig. 3. The approaches vary in ease of use and invasiveness [2, 41–44]. Part (a) depicts surface cooling devices. These can

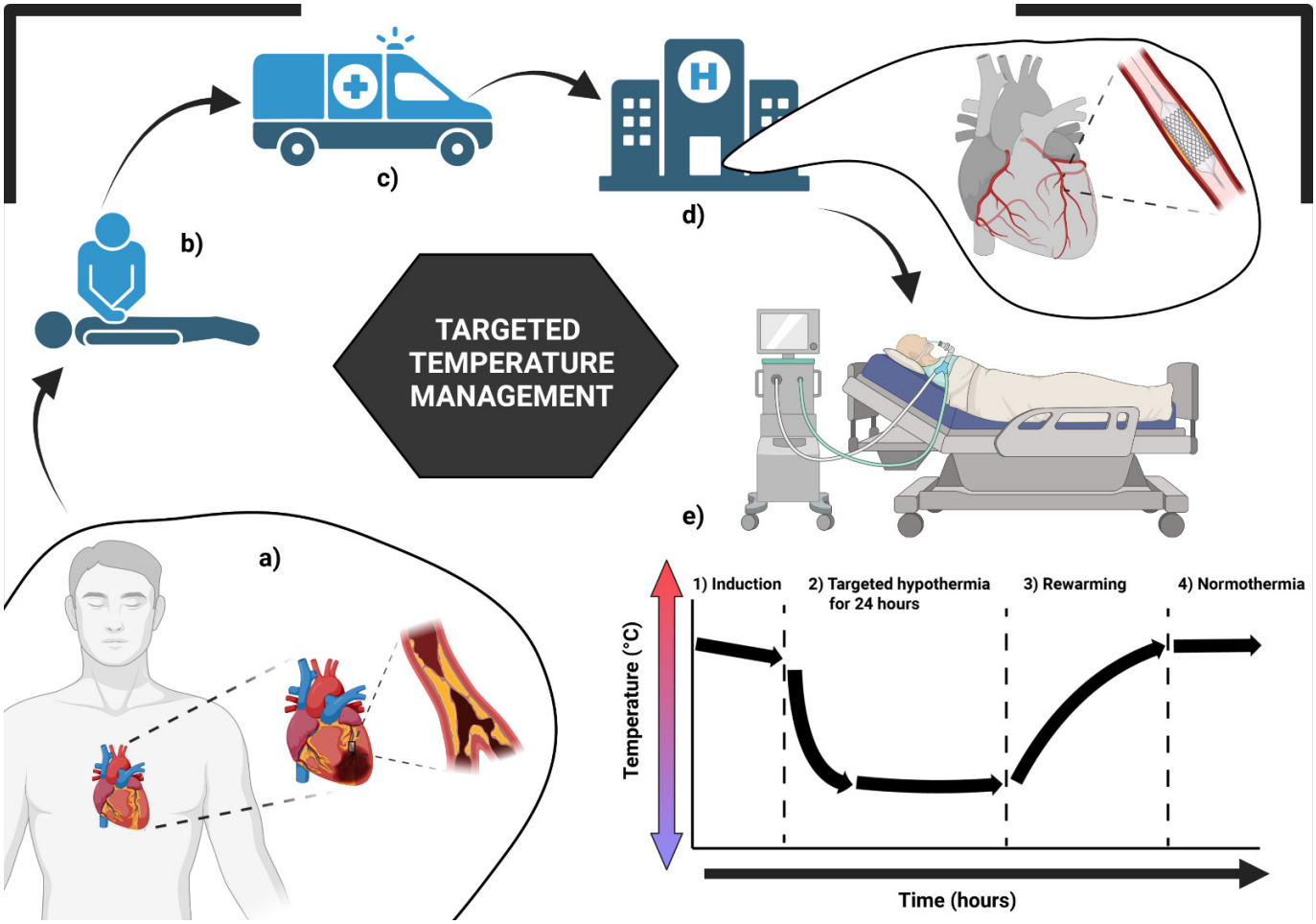

FIGURE 4. Simplified presentation of the treatment protocol of comatose patients after OHCA. Legend: (a) Person with a heart attack and subsequent cardiac arrest. (b) Resuscitation with return of spontaneous circulation (c) transfer to the hospital (d) percutaneous coronary angiography and stenting. (e) Protocol for hypothermia. Created with BioRender.com.

be in form of ice packs, cooling blankets or vests. The rate of temperature reduction is estimated to be 0.5–1 °C per hour [41]. Part (b) shows the administration of intravenous fluid. As mentioned previously, one has to be aware of the potential complications associated with such a method (e.g., fluid overload) [37, 45]. The estimated rate of temperature reduction is at >2 °C per hour when using 30 mL/kg of cold (4 °C) isotonic saline. When administering with the help of a pressure bag this can be even faster (1 °C in 15 minutes). Part (c) present an alternative approach that has been described in the setting during cardiopulmonary resuscitation in form of evaporative transnasal cooling [46], which, however, was reported to not show a statistically significant improvement in survival compared to patients following normal TTM protocol [47]. Part (d) shows the transoesophageal cooling technique that has been proven feasible and safe as a TTM method [48]. Finally, part (e) shows the possibility of intracavitary cooling that is the most invasive and comparatively least used technique [42].

6. Body temperature management after cardiac arrest

Out of hospital cardiac arrest (OHCA) is defined as the loss of mechanical cardiac function and the absence of systemic circulation [49]. It is one of the leading causes of mortality worldwide. It has been estimated that 275.000 people in Europe have all-rhythm cardiac arrest treated by emergency medical services per year. Only 29.000 of those survive to hospital discharge [50]. This is in line with reports stating that on average, less than 10% of all patients with OHCA will survive [49, 51, 52]. Despite all efforts, the survival rate of such patients is still relatively low. One therapeutic modality, which has been regularly employed since the year 2002 is TTM, visualized in Fig. 4.

A patient after cardiac arrest experiences several pathophysiological changes that manifest themselves on cellular, local tissue and systemic levels. These changes can be referred to as postcardiac arrest syndrome, which is comprised of 4 parts. These are: (1) the primary pathology that has led to the cardiac arrest (e.g., myocardial infarction, embolism, etc.); (2) cerebral hypoperfusion and ischemia-reperfusion injury; (3) myocardial dysfunction and 4) systemic ischemia/reperfusion response. All these changes combined lead to an inflammatory

response and an increase in CBT. In terms of physiology the effects of TTM are believed to result from a reduction of brain metabolism (e.g., reduced cerebral oxygen demand); reduction in the release of excitatory amino acids, free radicals and the intracellular consequences of excitotoxic exposure, which lessens the effect of the ischemia–reperfusion cascade, alongside possible cardioprotective effects [35].

The effects of TTM have been studied in animal research for a long time. Some of the earliest reports showed the influence and positive impact of lower temperatures on neuronal outcome [53–56]. Sterz *et al*. [56] have in one of their earliest studies reported that mild cerebral hypothermia started during or immediately after external cardiopulmonary resuscitation improves the neurologic recovery. Hicks *et al*. [57] have examined whether prolonged hypothermia induced 1 hour after resuscitation from asphyxia induced cardiac arrest would improve neurologic outcome. Their results suggested that prolonged hypothermia during later reperfusion is beneficial. Observed were also changes in the levels of stress proteins. A recent meta-analysis has tried to evaluate the evidence for TTM in animal models of cardiac arrest [58]. Their results suggested that TTM as a treatment of cardiac arrest was favoured under almost all conditions and in almost all cases. Nevertheless, most of the study populations were healthy animals and many studies were of low study quality increasing the risk of bias. Therefore, the authors conclude that the animal studies are not ideal simulations of the clinical environments. Consequently, the translatability of these results is questionable [58].

Since the original study by Barnard *et al*. [59], who concluded that treatment with moderate hypothermia improves survival outcomes in cardiac arrest patients, several additional studies have emerged, reporting a variety of new methods and techniques. Moreover, this method has also been associated with an increased rate of a favourable neurologic outcome and reduced mortality [60]. A recent study included a total of 584 patients during a time span of 4 years. The primary goal was the assessment of the neurologic outcome, which was predicted to be better in patients that undergo moderate therapeutic hypothermia in comparison with targeted normothermia [61]. The results showed that, among patients with coma who had been resuscitated from cardiac arrest with a nonshockable rhythm, moderate hypothermia (33 °C for 24 hours), in comparison with normothermia, led to a better neurologic outcome at day 90 [61]. The mortality between groups, did, however, not differ significantly [61]. This aspect has been further proven by the biggest (and newest) trial in this field to-date (TTM2 trial) [62]. The aim of the study was to compare the primary outcome (death from any cause at 6 months) in patients that underwent hypothermia or normothermia after OHCA. The results showed that there was no difference in incidence of death between the groups [62]. This in turn means that the hypothermia, which has been utilised for almost 20 years in this setting and has become a standard, may not have any meaningful impact on mortality. The findings are also in concordance with the results from the earlier TTM study [63]. Since the publication of the first trial there has been a number of comments regarding the high patient heterogeneity, the very short time to resuscitation, the slow induction phase of TTM, and the rapid rewarming period, which might have influenced the main results of the primary study [34]. Furthermore, the control group experienced fever. This might have also been partly responsible for a misinterpretation and overestimation of the beneficial effects of TTM [34]. Also, as commented on in other articles [34], the earliest studies in this field had methodological biases, which included no power calculation, relatively small cohorts, early stopping because of lack of funding, etc. [59, 60]. However, most likely the main reason for difficult translation of beneficial effects of hypothermia from laboratory to clinical setting are the circumstances of cardiac arrest, which make it impossible to provide cooling rapidly and without adverse effects in real-life scenarios. Furthermore, a number of additional treatment strategies that might have a beneficial effect on survival have been implemented in the past two decades (e.g., coronary angiography and interventions, better general ICU care, higher quality mechanical ventilation). It must be noted that, as has been nicely stated in the recently published editorial from Morrison and Thoma, the findings of the TTM trials do not oppose the use of TMM [64]. In the TTM2 trial 10–15% of patients from both groups had temperature spikes above 37.7 °C, despite close monitoring. The findings only further prove that close temperature monitoring and temperature management, with the use of multiple modalities, are crucial treatment strategies to improve outcomes in patients, who had a cardiac arrest. It remains to be seen how the recent findings will impact the current understanding and resuscitation guidelines. Whatever the conclusion might be, the topic is complex and to make matters more complicated, animal models repeatedly show beneficial effects of hypothermia [58].

7. Conclusions

Body temperature is a highly regulated parameter in humans. Changes in body temperature have been recognised as signs of illness for at least 2000 years. However, in spite of numerous laboratory and clinical studies, the optimal therapeutic window for temperature management has not been discovered, even in a very relevant and highly researched population, such as survivors after cardiac arrest. Even more interesting is the fact that the results from a large body of laboratory and animal studies indicating that hypothermia is beneficial after cardiac arrest could not be replicated in the setting of recent large clinical trials, where improved survival was not recorded in the group of patients who were exposed to hypothermia. The role of TTM as a potential treatment strategy to improve survival in comatose survivors after cardiac arrest has therefore been questioned. Given the highly regulated nature of temperature management in animals and humans, and well researched physiological effects of hypothermia, we should expect further research in this field, namely identification of patients that could benefit from hypothermia or other forms of TTM, the prognostic meaning of spontaneous temperature fluctuations in comatose survivors after cardiac arrest, and identification of patient-specific target temperatures in comatose survivors after cardiac arrest.

AUTHOR CONTRIBUTIONS

Conceptualization—AM and KS. Investigation: AM, MG, MD and KS. Methodology—AM, MG, KS. Supervision: AM. Writing–original draft—AM, KS. Writing–review and editing—AM, MG, MD and KS. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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