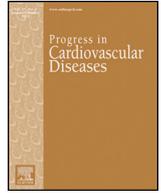




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## Targeted temperature management for cardiac arrest<sup>☆</sup>

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### ABSTRACT

Therapeutic hypothermia, or targeted temperature management (TTM), is a strategy of reducing the core body temperature of survivors of sudden cardiac arrest (SCA) to minimize neurological damage caused by severe hypoxia. Initial clinical trials examining this technique demonstrated significant improvement in neurological function among survivors of out-of-hospital SCA with an initial shockable rhythm. Since then, TTM has become an integral part of the care provided to comatose survivors of SCA. However, multiple questions persist regarding the target cooling temperature, duration of cooling, and utility of TTM in patient populations such as survivors of out-of-hospital SCA with non-shockable rhythms or in-hospital SCA. This review article summarizes the current evidence regarding optimal application of TTM and compares the recommendations for TTM in current guidelines.

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There are over 500,000 episodes of in- and out-of-hospital sudden cardiac arrest (SCA) each year within the United States. However, overall survival from cardiac arrest, especially with intact neurological

function, is unfortunately low – ranging from 9% for patients experiencing out-of-hospital cardiac arrest (OHCA) to 22% for patients with in-hospital cardiac arrest (IHCA). Interventions such as high-quality chest compressions as well as rapid defibrillation during active SCA have been shown to improve the likelihood of return of spontaneous circulation (ROSC) and subsequent survival with good neurological function.<sup>1–3</sup> In contrast, there are a limited number of interventions applied in the post-ROSC phase that have been shown to improve outcomes. One such strategy of actively inducing mild hypothermia or “targeted temperature management” (TTM) in patients successfully resuscitated from SCA to limit the degree of hypoxic injury, has shown promise in improving outcomes in this patient cohort.

*Abbreviations and acronyms:* SCA, Sudden cardiac arrest; OHCA, Out-of-hospital cardiac arrest; IHCA, In-hospital cardiac arrest; ROSC, Return of spontaneous circulation; TTM, Targeted temperature management; CPC, Cerebral Performance Category; VT, Ventricular tachycardia; VF, Ventricular fibrillation.

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In the current paper, we will review the rationale for TTM, methods of cooling, related outcomes, and current Guideline recommendations regarding the use of TTM among patients successfully resuscitated from SCA.

**Rationale**

SCA leads to the most extreme form of shock, with complete circulatory arrest and profound systemic ischemia. Among all organs, the brain is uniquely sensitive to ischemic injury. In the acute phase of the ischemic insult, there is increased cerebral lactate production, generation of excitatory neurotransmitters, and disruption of ion gradients. These processes cumulatively lead to cellular necrosis. Tissue death is further exacerbated by re-establishment of tissue perfusion, as this initiates multiple signaling cascades leading to cellular apoptosis (including generation of reactive oxygen species and inflammatory cytokines).<sup>4</sup> The observation that survivors of cold-water drowning were noted to have preserved neurological function despite being submerged for long periods under water<sup>5</sup> provided the necessary biological framework of using TTM as a potential therapeutic modality in limiting neurological damage in survivors of SCA. In subsequent animal and then human studies, hypothermia has been shown to mediate its neuroprotective effect by mitigating these pathways of cellular injury, resulting in decreased necrosis and apoptosis.<sup>4</sup>

Currently, application of TTM consists of three phases. First, there is rapid cooling to achieve a target core body temperature, followed by maintenance of this hypothermic temperature, then a slow rewarming phase (Fig. 1).

**Outcomes**

The data on outcomes from use of TTM in patients with SCA has largely been derived from patients with initial shockable rhythms [i.e., ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT)] that occurred out of the hospital. The major outcomes that have been studied in clinical trials examining the use of TTM as a treatment modality in survivors of SCA have been survival to hospital discharge and survival to hospital discharge with favorable neurological function, which is defined as a cerebral performance category (CPC) of 1 or 2. A CPC score of 1 indicates good neurological function with no or mild cerebral deficits, while a score of 2 indicates moderate cerebral disability.<sup>6</sup> A summary of important clinical trials in the field of TTM is shown in Table 1.

**OHCA with initial shockable rhythm**

The initial, large clinical trials examining the use of TTM in survivors of OHCA were published in 2002.<sup>7,8</sup> Bernard et al. recruited 77 comatose

patients who were successfully resuscitated from SCA after presenting with an initial shockable rhythm (i.e., pulseless VT/VF) in Melbourne, Australia.<sup>8</sup> The trial had a quasi-randomization design, with patients being admitted on odd-numbered days of the month undergoing TTM defined as a target temperature of 33 °C for 12 h with use of ice packs. Patients admitted on even-numbered days were assigned to standard therapy of no active temperature management. A significantly higher proportion of patients receiving TTM were discharged from the hospital with favorable neurological function (i.e., CPC score of 1 or 2) compared with patients not receiving any active temperature management (49% vs. 26%,  $P = 0.05$ ). The odds ratio for survival with favorable neurological function was 5.25 (95% C.I. 1.47–18.7,  $P = 0.01$ ) after adjustment for baseline characteristics and duration of arrest. Patients receiving TTM had higher overall survival compared with patients not receiving temperature management, but this did not achieve statistical significance (49% vs. 32%,  $P = 0.14$ ). The Hypothermia After Cardiac Arrest (HACA) trial was a European, multi-center clinical trial that recruited 275 survivors of SCA with an initial shockable rhythm.<sup>7</sup> Patients randomized to active temperature management were cooled to 32 °C to 34 °C for 24 h using cold air. Patients randomized to the control arm received no active temperature management. Compared to the control arm, patients who received active temperature management experienced significantly higher rates of survival with favorable neurological function (55% vs. 39%,  $P = 0.002$ ) as well as overall survival to hospital discharge (59% vs. 45%,  $P = 0.02$ ). There was no significant difference in adverse effects such as bleeding, sepsis, pneumonia, or lethal arrhythmias between the two groups in this study. Based on the combined results of these two studies<sup>7,8</sup> the number needed to treat (NNT) to improve survival with favorable neurological function is between 4 and 5, and NNT for overall survival is approximately 6.

A Cochrane review summarizing the results from five studies (incorporating the two trials mentioned above) including 1370 patients comparing active temperature management versus no cooling was published in 2016.<sup>9</sup> The authors concluded that there is moderate quality of evidence that use of TTM among survivors of OHCA is associated with increased survival with favorable neurological function (risk ratio: 1.94, 95% CI 1.18–3.2) as well as overall survival at hospital discharge (risk ratio: 1.35, 95% 1.10–1.65).

In light of this evidence, the current AHA guidelines give a Class I (Level of Evidence B) recommendation to the routine application of TTM to comatose survivors of OHCA with an initial shockable rhythm.<sup>10</sup>

**OHCA with initial non-shockable rhythm**

The data regarding routine use of TTM exclusively among patients with OHCA with initial *non*-shockable rhythms are generally of poor quality and largely derived from observational studies.<sup>11</sup> Additionally, these studies have demonstrated mixed results with regard to the

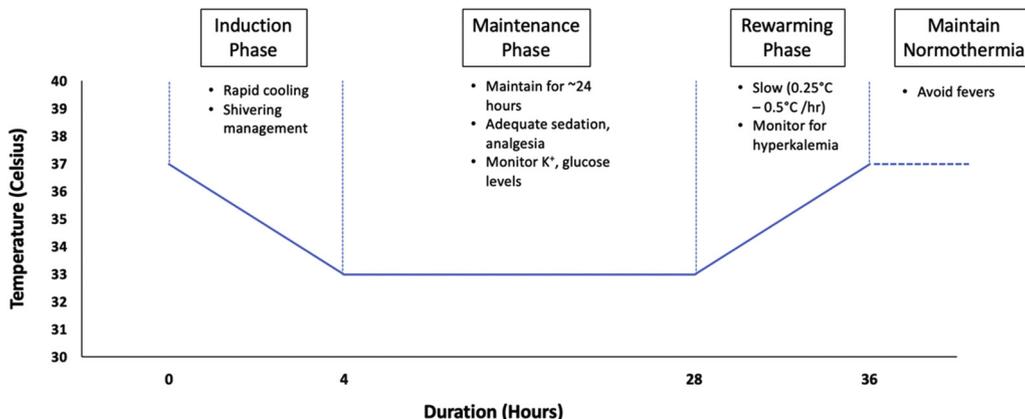


Fig. 1. Phases of Targeted Temperature Management.

**Table 1**  
Summary of major clinical targeted temperature management trials.

Trial	Design	Number of Participants	Outcome	Comment
Trials comparing TTM with no cooling				
Bernard et al., 2002 <sup>8</sup>	Randomized, single center study comparing application of TTM with no active cooling among survivors of OHCA	• TTM arm: 43 • Control arm: 34  <i>N</i> = 77	1. Survival 49% (TTM) Vs. 26% (Control) OR: 1.4 (1.0–2.0), <i>P</i> = 0.14 2. Favorable neurological function 49% (TTM) Vs. 26% (Control) OR: 5.2 (1.4–18.7), <i>P</i> = 0.01	• Initial trials that demonstrated benefit of TTM in comatose survivors of OHCA • Both trials only included patients with initial shockable rhythm
HACA trial, 2002 <sup>7</sup>	Randomized, multicenter study comparing application of TTM with no active cooling among survivors of OHCA	• TTM arm: 138 • Control arm: 137  <i>N</i> = 275	1. Survival 59% (TTM) Vs. 45% (Control) OR: 1.4 (1.1–1.7), <i>P</i> = 0.02 2. Favorable neurological function 53% (TTM) Vs. 36% (Control) OR: 1.5 (1.1–1.9), <i>P</i> = 0.002	• Of note, the patients in these trials were restricted to initial shockable rhythm of cardiac arrest
Trial comparing different cooling temperatures during TTM				
Nielsen et al., 2013 <sup>30</sup>	Randomized, multicenter study comparing outcomes among OHCA survivors who were actively cooled to 33 °C compared with 36 °C	• 33 °C arm: 473 • 36 °C arm: 466  <i>N</i> = 939	1. Survival 48% (33 °C) Vs. 50% (36 °C), <i>P</i> = 0.5 2. Favorable neurological function 52% (33 °C) Vs. 50% (36 °C), <i>P</i> = 0.2	• 80% of study population had initial shockable rhythm • Of note, this trial did not study a strategy of “cooling vs. no cooling”. Maintaining 36 °C required active temperature management and did not constitute normothermia
Trial examining pre-hospital cooling with infusion of cold saline vs standard in-hospital initiation of cooling				
Kim et al., 2014 <sup>27</sup>	Randomized study comparing outcomes among patients being actively cooled in the field by paramedics compared with standard in-hospital initiation of cooling	• Early cooling arm: 473 • Hospital cooling arm: 466  <i>N</i> = 1364	1. Survival: Shockable cohort 62.7% (paramedic cooled) vs. 64.3% (hospital cooled), <i>P</i> = 0.69 2. Survival: Non-shockable cohort 19.2% (paramedic cooled) vs. 16.3% (hospital cooled), <i>P</i> = 0.30	• Patients receiving early cooling with infusion of cold saline had higher rates of complication including higher rates of re-arrests in the field, increased diuretic use and pulmonary edema on presentation
Trial comparing duration of cooling				
Kirkegaard et al., 2017 <sup>39</sup>	Randomized study comparing outcomes among patients being actively cooled for 24 h compared with longer 48 h duration	• 24 h arm: 176 • 48 h: 175  <i>N</i> = 355	1. Survival 34% (24 h) vs. 27% (48 h), RR: 0.81 (0.59–1.11), <i>P</i> = 0.19 2. Favorable neurological function 64% (24 h) vs. 69% (48 h), RR: 1.08 (0.93–1.25), <i>P</i> = 0.33	• Longer duration of cooling beyond 24 h did not seem to confer any additional benefit • Patients cooled for longer duration had significantly proportion of adverse events such hypotension

OR: Odds ratio.  
RR: Risk ratio.

potentially beneficial effect of TTM on survival to discharge or survival with favorable neurological function.<sup>11–13</sup>

### In-hospital cardiac arrest

Randomized data demonstrating a clear benefit of TTM to improve outcomes after IHCA are lacking.<sup>14</sup> A large, observational study published in 2016 by Chan et al. using data from the national Get With the Guidelines–Resuscitation Registry, involving >26,000 episodes of IHCA, demonstrated no benefit to TTM. In fact, patients undergoing TTM had a significantly lower likelihood of survival (27.4% vs 29.2%;

relative risk: 0.88, 95% CI, 0.80 to 0.97) as well as survival with favorable neurological function (17.0% vs 20.5%; relative risk: 0.79, 95% CI, 0.69 to 0.80).<sup>15</sup> A limitation of the study was the lack of information on coma status, which could have biased study results.

Nevertheless, even though there are no data supporting TTM use in non-shockable rhythms, the current AHA guidelines writing committee gives a Class I recommendation (Level of evidence C) for the application of TTM among survivors of OHCA with non-shockable rhythms and in-hospital cardiac arrest.<sup>10</sup> This strong recommendation was made despite lack of randomized data because of the rarity of adverse effects in major clinical trials of TTM, the high neurologic morbidity and

mortality from SCA without any specific interventions, and the preponderance of data suggesting that temperature is an important variable for neurologic recovery.

### Target temperature for cooling

The initial TTM trials had set a target temperature of 32 °C–34 °C for hypothermia compared with no cooling. However, significant debate about optimal target temperature persisted. In 2012, Lopez-de-sa et al. conducted a single-center clinical trial recruiting 36 patients (26 with shockable rhythm and 10 with non-shockable rhythm) and randomized them to a target temperature of 32 °C versus 34 °C using infusion of cold saline for 24 h.<sup>16</sup> The primary outcome was survival free from severe dependence (defined as Barthel Index score  $\geq$  60 points) at 6 months. Overall, patients who were cooled to 32 °C compared with 34 °C had higher overall survival that did not achieve statistical significance (44.4% vs. 11.4%,  $P = 0.12$ ). When stratified based on initial presenting rhythm, by 6 months post-arrest, all patients with initial non-shockable rhythms had died. In contrast, among patients with a shockable rhythm, cooling to a lower temperature of 32 °C compared with 34 °C was associated with significantly higher survival at 6 months free from severe dependence (61.5% vs. 15.4%,  $P = 0.029$ ). Of note, the results were considered to be hypothesis generating at best given the small number of patients, mixed shockable and non-shockable rhythms, and overall negative trial results.

In 2013, Nielsen et al. published results of the largest clinical trial in this field, the Targeted Temperature Management Trial at 33 °C versus 36 °C After Cardiac Arrest (TTM Trial) in which the authors compared outcomes among patients actively cooled to 33 °C versus patients who were cooled to 36 °C. The trial recruited 939 patients with OHCA, with 80% of patients with initial shockable rhythm. The primary outcome was all-cause mortality, and the main secondary outcome was a composite of death or poor neurologic function (defined as CPC of 3 to 5). There were no differences in all-cause mortality [48% (33 °C) vs. 50% (36 °C),  $P = 0.5$ ] or in the secondary outcome [52% (33 °C) vs. 50% (36 °C),  $P = 0.2$ ]. It is important to highlight that this was not a trial comparing a strategy of no cooling with active cooling. Patients who were cooled to 36 °C actively received targeted temperature management. Hence, both arms in the clinical trial received “active temperature management” and there was no true normothermia/no-cooling arm. In contrast, in the control arm of the HACA trial, active temperature management of any sort was not performed, and hence patients' average temperature were significantly higher at 37.6 °C (compared with 36 °C) with a small number of patients with temperatures higher than 38 °C contributing to worse outcomes. Additionally, neurological outcomes in the 36 °C arm of the TTM trial were comparable to outcomes within the active treatment arms of the previous HACA trial and a trial by Bernard et al. (Fig. 2), thereby lending credence to the notion that 36 °C amounted to “active temperature management” and was not the same as no temperature control at all.

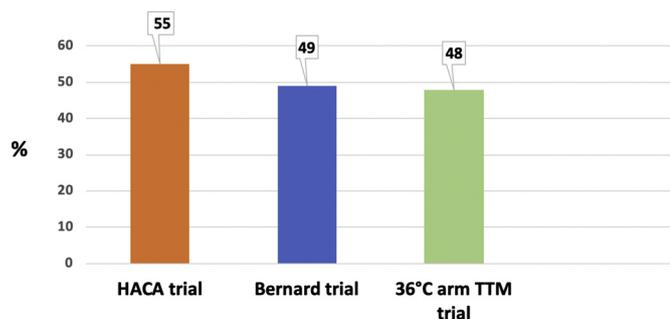


Fig. 2. Rate of good neurological outcomes in intervention arm of HACA and Bernard trial compared with 36 °C arm of TTM trial.

Overall, taking into consideration the results of this trial, the most recent AHA guidelines changed the target temperature for cooling from 32 °C–34 °C to a more liberal range from 32 °C–36 °C (Class I recommendation, Level of Evidence B).<sup>10</sup> However, there is concern in the resuscitation community that some will interpret this recommendation as saying that cooling is not really necessary. Indeed, there is some evidence this is already happening.<sup>17,18</sup>

### Timing of cooling

The optimal time to initiate cooling, and its impact on outcomes, remains uncertain. Early evidence from animal models demonstrated clear benefit of initiating hypothermia early and reaching the target temperature as rapidly as possible.<sup>19–21</sup> In contrast, data from human studies have been mixed.<sup>22–24</sup>

A number of randomized studies have studied initiation of hypothermia in the prehospital setting by rapid infusion of intravenous solutions. Bernard et al. performed the initial trial comparing outcomes among 264 survivors of OHCA with VF.<sup>25</sup> Patients in the early cooling group received a rapid infusion of two liters of ice-cold lactated Ringer's solution by paramedics, compared with routine in-hospital initiation of cooling. There was a significant difference in the core temperature of patients in the early cooling arm compared with routine hospital cooling arm on hospital arrival (34.6 °C vs. 35.4 °C,  $P = 0.01$ ). After admission, the early cooling arm continued to be cooled and the other arm had initiation of cooling. However, there was no difference in the primary outcome, defined as discharge to home or rehabilitation facility, between the two groups [47.5% (paramedic cooled) vs. 52.6% (hospital cooled), risk ratio 0.90, 95% C.I. 0.70–1.17,  $P = 0.43$ ]. There were no significant differences in adverse outcomes between the two arms either. This study was followed by a subsequent clinical trial by the same author group, employing a similar strategy in 163 patients successfully resuscitated from OHCA with non-shockable rhythms (i.e., pulseless electrical activity or asystole). Similar to the previous trial, there was no difference in the primary outcome of discharge to home or rehabilitation facility between the early-cooled and the standardly-cooled groups (12% vs. 9%,  $P = 0.5$ ). However, the overall trial was limited in power to detect any meaningful differences between the two groups given the small sample size.<sup>26</sup> This led to a larger randomized, clinical trial by Kim et al. that recruited 1364 survivors of OHCA in Seattle and King County, Washington. The study included patients with both shockable and non-shockable rhythms at the time of SCA.<sup>27</sup> They adopted a similar method of infusion of cold saline solution by paramedics to rapidly initiate cooling in the field, compared with initiation of routine cooling in the hospital. Similar to the previous studies, patients receiving early cooling with saline infusion had significantly lower core temperatures on hospital arrival, but there was no difference in survival rates [62.7% (paramedic cooled) vs. 64.3% (hospital cooled),  $P = 0.69$  in ventricular fibrillation group; 19.2% (paramedic cooled) vs. 16.3% (hospital cooled),  $P = 0.30$  in non-shockable group]. Additionally, safety concerns about this method of rapid cooling were raised, since patients in the intervention arm receiving rapid infusion of fluids had significantly higher rates of rearrests in the field as well as increased diuretic use and pulmonary edema on hospital presentation.

Alternative methods that achieve adequate prehospital cooling without rapid infusion of intravenous solutions have also been examined. In the Pre-ROSC IntraNasal Cooling Effectiveness (PRINCE) study, Castren et al. evaluated the feasibility of an intra-nasal cooling device among 200 survivors of OHCA to rapidly initiate intra-arrest cooling.<sup>28</sup> The study authors demonstrated that such a device is safe, and patients who were cooled with this device achieved target temperature numerically (but not statistically significantly) faster as compared with routine in-hospital cooling (155 versus 284 min,  $P = 0.13$ ). There was no difference in rates of ROSC or survival to discharge. However, this study was not powered to study survival outcomes. Subsequently, data from the Prehospital Resuscitation Intranasal Cooling Effectiveness Survival

Study (PRINCESS) were presented at Resuscitation Science Symposium 2018.<sup>29</sup> The authors examined differences in outcomes with the use of a transnasal cooling device to initiate intra-arrest cooling compared with standard application of TTM after hospital admission among >600 patients across seven European countries. While time to target temperature was significantly lower in the intervention arm as expected, there was no difference in survival at 90 days in the overall group (16.6% vs 13.5%;  $P = 0.26$ ) or in those with VF (34.8% vs 25.9%;  $P = 0.11$ ). With regard to survival with favorable neurological function (i.e., CPC 1 or 2), while there was no difference in the overall group (14.8% vs 10.5%;  $P = 0.09$ ), it was significantly higher among patients with VF (32.6% vs 20%;  $P = 0.02$ ). There were no significant differences in adverse events among the two arms. While these data suggest a potential benefit of an intranasal cooling device to provide expedited hypothermia among patients with shockable rhythms, the results of the trial are considered hypothesis generating at best especially given that the overall trial result was negative.

Taking into account the current data, the Guideline writing group recommends against the routine prehospital cooling of patients after ROSC with rapid infusion of cold intravenous fluids. (Class III recommendation, Level of Evidence A).<sup>10</sup> However, currently there is no guidance regarding alternative technologies of prehospital cooling.

### Duration of cooling

The current guidelines recommend an average duration of at least 24 h for TTM. This recommendation is derived from the landmark TTM trials that cooled patients for an average of 24 h.<sup>7,30</sup> Additionally, observational data suggest an optimal duration of 18–24 h for improved outcomes.<sup>31–33</sup> In 2017, Kirkegaard et al. conducted a randomized, multi-center study recruiting 355 patients from 6 European countries comparing a standard cooling duration of 24 h with a prolonged cooling duration lasting 48 h. There was no difference in the primary outcome of survival with favorable neurological function (defined as CPC of 1 or 2) at six months [64% (standard duration) vs. 69% (prolonged duration); relative risk: 1.08; 95% C.I. 0.93–1.25,  $P = 0.33$ ]. Similarly, no difference in mortality at 6 months was noted with standard cooling duration compared with prolonged duration of cooling (34% vs. 27%; relative risk, 0.81; 95% C.I. 0.59–1.11;  $P = 0.19$ ). The proportion of adverse events including hypotension was significantly higher in the prolonged cooling arm.

Overall, with data from this new clinical trial, we anticipate the guidelines will continue to recommend a cooling duration of an average of 24 h, especially given concern for increased adverse effects from prolonged cooling.

### Prevention of hyperthermia

There are observational data that have shown that fever is common among patients after they are rewarmed to normothermia,<sup>34</sup> and that the occurrence of fever is associated with worse neurological outcomes.<sup>35</sup> Hence, the recent guidelines state that it is reasonable to actively prevent fever in comatose patients after TTM (Class IIb recommendation; Level of Evidence C).<sup>10</sup> In most cases, this is achieved simply by leaving in place the device used to initiate TTM, though now set to maintain normothermia.

### Cooling methods

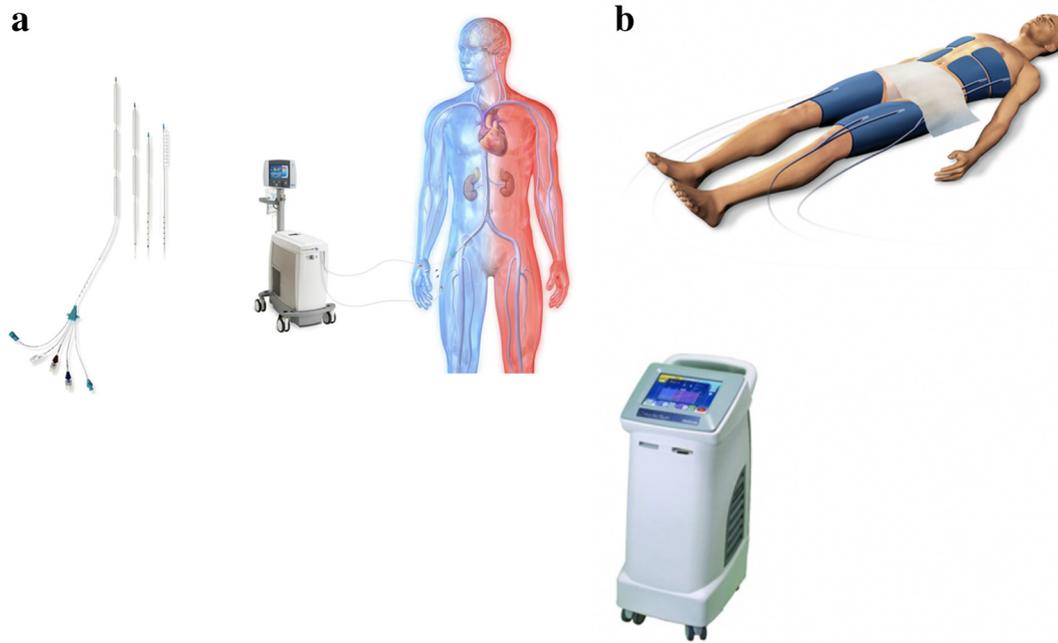
There currently are two methods of initiating targeted temperature management. While initial trials utilized ice bags, more modern TTM programs utilize specific tools to cool and maintain a target temperature. The first method consists of placement of an intravascular catheter that allows for circulation of blood through an external cooling device (Fig. 3A). This device allows for precise temperature control, which is imperative for proper application of TTM. The disadvantage of this

method is the need for expertise in obtaining central venous access, the risk of catheter infection, as well as difficulty in patient transportation while connected to the cooling device. Alternatively, patients can be cooled using surface cooling by application of large gel pads to the body that have cold saline circulating within them (Fig. 3B) ([www.medivance.com](http://www.medivance.com)). This has also shown to allow for precise temperature control. The advantages of this method include the ease of instituting TTM given the simple technique of gel pad application, ease of patient transportation to various procedures, and the ability to perform coronary angiography simultaneously (possible since the gel pads are radiolucent). Disadvantages include the risk of skin injury and the need for covering a large part of the body surface, thereby limiting access for nursing care. Outcome data comparing these two methods are scarce, and currently there are no studies suggesting a difference between the two methods.<sup>33</sup>

### Monitoring of the actively cooled patient

There are a number of patient care considerations that a clinician must be aware of during the application of TTM. They are as follows:

- **Sedation/Analgesia:** Adequate sedation/analgesia should be maintained throughout the duration of application of TTM including during active cooling phase, maintenance phase, and rewarming, until normothermia is achieved. “Sedation holidays” or spontaneous breathing trials should not be attempted while the patient is under TTM protocol.
- **Shivering:** Shivering is a physiological response that occurs from decreasing core temperatures. It increases metabolic activity and the patient’s oxygen requirement, potentially worsening underlying neurological damage. Therefore, attempts should be made to treat shivering whenever present. Non-pharmacological measures such as application of warm blankets based on the “skin counter warming” concept should be attempted first. Overall, skin temperature contributes about 20% (the core temperature contributes the other 80%) to the shivering threshold. Hence, increasing the skin temperature has been shown to decrease shivering without affecting core temperatures.<sup>36</sup> This can be followed by increasing sedation/analgesia as required. Finally, if shivering persists despite high levels of sedation, neuromuscular blockade can be attempted. However, the dose and the duration of neuromuscular blockade should be kept at a minimum, and the degree of neuromuscular blockage should be frequently assessed. Hence, the current guidelines consider it to be reasonable to consider the titrated use of sedation and analgesia in critically ill patients who require mechanical ventilation or shivering suppression during induced hypothermia after cardiac arrest. (Class IIb recommendation, Level of Evidence C).<sup>10</sup>
- **Hypotension:** Hypothermia has been shown to cause hypotension by causing vasodilatation and/or myocardial dysfunction. Currently, a mean arterial pressure goal of >65 mmHg, or systolic blood pressure > 80 mmHg, should be maintained to ensure adequate cerebral blood flow and minimize anoxic brain injury. The use of vasoactive agents is recommended if needed to achieve these blood pressure goals.
- **Oxygenation/Ventilation:** Hypoxic as well as hyperoxic episodes should be avoided since they are clearly associated with worse outcomes. Hence, the guidelines recommend that when resources are available to titrate FiO<sub>2</sub> and oxyhemoglobin saturation, it is reasonable to decrease the FiO<sub>2</sub> when oxygen saturation is 100% provided a saturation of ≥94% can be maintained.<sup>10,37</sup> PaCO<sub>2</sub> levels of 35–45 mmHg should be maintained, and excessive hyperventilation should be avoided to prevent cerebral vasoconstriction.<sup>10,38</sup>
- **Hypokalemia:** Decreasing the core temperature of the body leads to sequestration of potassium within the cells leading to significant hypokalemia. Conversely, during the rewarming phase, an efflux of intracellular potassium occurs, causing hyperkalemia. Hence, while



**Fig. 3.** A. Zoll intravascular targeted temperature management system. (Obtained with permission from Zoll Corporation). B. Bard artic sun targeted temperature management system which uses cooling pads on the skin attached to a module. Core temperature is generally taken via a foley catheter, and the module automatically adjusts based on this core temperature (Obtained with permission from BD Corporation).

aggressive potassium repletion is recommended during the cooling phase, potassium repletion should be stopped at the initiation of rewarming, to avoid rebound hyperkalemia.

- **Glucose control:** At lower body temperatures, there is decreased sensitivity towards insulin, and hence patients tend to have higher blood sugars during the cooling phase of TTM. Aggressive treatment of blood sugar did not show benefit in a small trial among survivors of VF, as well as potential harm in the broader intensive care unit population.<sup>39</sup> The guidelines acknowledge the uncertain benefit of tight glucose control, and do not recommend a specific target range.<sup>10</sup>

### Conclusion and future directions

The use of targeted temperature management has been shown to improve meaningful survival outcomes among OHCA survivors with shockable rhythms who are comatose. Its use is thus recommended in these patients. However, many questions persist regarding its therapeutic application, especially among patients with IHCA, or arrest with non-shockable rhythms, as well as the timing of hypothermia initiation. Patients with an unchangeably poor prognosis will not likely benefit from cooling. Accurate early prognostication strategies are thus keenly needed. Designing future studies focusing on patient populations that have the best prognosis (i.e. patients with initial shockable rhythms) would allow for efficient, high quality studies that could add much needed clarity to the field.

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