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Review

The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation: A systematic review\(^ \star \)

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A T I L E  I N F O

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A B S T R A C T

Objectives: To update a comprehensive systematic review of the use of therapeutic hypothermia after cardiac arrest that was undertaken initially as part of the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiac Care Science. The specific question addressed was: ‘in post-cardiac arrest patients with a return of spontaneous circulation, does the induction of mild hypothermia improve morbidity or mortality when compared with usual care?’

Methods: Pubmed was searched using (“heart arrest” or “cardiopulmonary resuscitation”) AND “hypothermia, induced” using ‘Clinical Queries’ search strategy; EmbASE was searched using (heart arrest) OR (cardiopulmonary resuscitation) AND hypothermia; The Cochrane database of systematic reviews; ECC EndNote Library for “hypothermia” in abstract OR title. Excluded were animal studies, reviews and editorials, surveys of implementation, analytical models, reports of single cases, pre-arrest or during arrest cooling and group where the intervention was not hypothermia alone.

Results: 77 studies met the criteria for further review. Of these, four were meta-analyses (LOE 1); seven were randomised controlled trials (LOE 1), although six of these were from the same set of patients; nine were non-randomised, concurrent controls (LOE 2); 15 were trials with retrospective controls (LOE 3); 40 had no controls (LOE 4); and one was extrapolated from a non-cardiac arrest group (LOE 5).

Conclusion: There is evidence supporting the use of mild therapeutic hypothermia to improve neurological outcome in patients who remain comatose following the return of spontaneous circulation after a cardiac arrest; however, much of the evidence is from low-level, observational studies. Of seven randomised controlled trials, six use data from the same patients.

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A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2011.01.021.
1. Background

Out-of-hospital cardiac arrest (OHCA) occurs in about 1 in 1500 adults in the developed world each year; this means that about 375,000 people in Europe have a sudden cardiac arrest each year. The number of patients surviving to hospital discharge remains low: in a recent meta-analysis the aggregate survival rate was recorded between 6.7 and 8.4%. Among survivors, anoxic neurological injury is an important cause of morbidity. Over the last few years, mild hypothermia (32–34 °C for 12–24 h) has been implemented in an attempt to improve neurological outcome in initially comatose survivors of cardiac arrest. The exact mechanism for the cerebral resuscitative effect of hypothermia is unclear but several potential mechanisms have been described. Many studies document apparent benefit from induced hypothermia after cardiac arrest.

The use of mild therapeutic hypothermia in comatose, post-cardiac arrest patients with a return of spontaneous circulation (ROSC) was evaluated as part of the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (2010 CoSTR). The aim of this study was to update the systematic review that provided evidence for the treatment recommendation on therapeutic hypothermia in 2010 CoSTR and to create a single, convenient source for all the available data on this topic.

2. Methods

The review was conducted in accordance with the International Liaison Committee on Resuscitation (ILCOR) 2010 evidence evaluation process, which has been well described. Expert review of the search strategy and findings were conducted by the worksheet evaluation experts who had been appointed specifically for this task. In keeping with all the ILCOR systematic reviews undertaken for 2010 CoSTR, a formal meta-analysis was not undertaken.

2.1. PICO question

This review sought to identify evidence to address the PICO (Patient/population, Intervention, Comparator, Outcome) question that had been formulated by the ILCOR Advanced Life Support Task Force12,13: “In post cardiac arrest patients with return of spontaneous circulation (P), does therapeutic hypothermia (I) compared with usual care (C), improve morbidity or mortality (O)?”

2.2. Search strategy

The electronic database PubMed was searched using the search terms (“heart arrest” or “cardiopulmonary resuscitation”) AND “hypothermia, induced” using the ‘Clinical Queries’ search strategy and the EMBASE database was searched using the terms “[heart arrest] OR [cardiopulmonary resuscitation] AND hypothermia” and was limited to title and abstract. The American Heart Association (AHA) Resuscitation EndNote library was searched using the term “hypothermia” in the title or abstract. The Cochrane database of systematic reviews was searched using the term “hypothermia”. Articles were excluded if they were animal studies, reviews and editorials, surveys of implementation, analytical models, reports of single cases, pre-arrest or during arrest cooling, intervention group not hypothermia alone (e.g. combined with haemofiltration or resuscitation with cardiopulmonary bypass instead of CPR).

The references of all included articles were reviewed to ensure no relevant articles had been missed.

2.3. Evidence appraisal

The studies were reviewed in detail and classified by level of evidence (LOE) for studies of therapeutic interventions (Table 1) and quality (rated poor, fair or good) (Table 2) according to agreed definitions.

2.4. Data presentation

Numerical data are reproduced directly from the respective papers. Parametric data are presented as mean (standard deviation) and non-parametric as median (interquartile range). Proportions are presented as a percentage. A p value of <0.05 is considered significant. No attempt was made to re-analyse these data.

3. Results

The search identified 2991 papers. Seventy-seven studies met with the criteria for further review. Of these, four were LOE 1 (meta-analyses)14-17; seven were LOE 1 (Randomized Controlled Trials),18-24 but six of these were from the same group of patients18; nine LOE 2 (non-randomized, concurrent controls)16,25-32; 15 LOE 3 (retrospective controls)7,8,33-45; 40 LOE 4 (no controls); and one LOE 5 (extrapolated from non-cardiac arrest group).

The level of evidence and quality of the papers are summarized in Tables 3-6.

3.1. Who to cool?

The data from trials reviewing who should be cooled are summarised in Table 6. The Hypothermia After Cardiac Arrest (HACA) Study Group performed a randomized controlled trial with blinded assessment of the outcome. Patients were included if they had a witnessed cardiac arrest, VF or nonperfusing VT as the initial cardiac rhythm and a presumed cardiac origin of the arrest. Of 3551 patients who were assessed, 275 (8%) were enrolled. The hypothermia group was sedated, paralysed, ventilated and cooled with surface cooling to 32–34 °C for 24 h. In the hypothermia group, 75 (55%) of 136 showed an improved neurological outcome at 6 months compared with 54 (39%) of 137 in the normothermia group (risk ratio (RR) 1.4, 95% confidence interval (CI) 1.08–1.81; number

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>LOE 1: Randomized controlled trials (or meta-analyses of RCTs)</td>
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<td>LOE 2: Studies using concurrent controls without true randomization (e.g. “pseudo”-randomized) or meta-analyses of such studies</td>
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<tr>
<td>LOE 3: Studies using retrospective controls</td>
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<td>LOE 4: Studies without a control group (e.g. cases series)</td>
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<tr>
<td>LOE 5: Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)</td>
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</table>
Evidence supporting therapeutic hypothermia following OHCA.

Table 3

<table>
<thead>
<tr>
<th>Quality factors for studies of each level of evidence.</th>
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<tbody>
<tr>
<td>Meta-analysis (of LOE 1 or LOE 2 studies)</td>
</tr>
<tr>
<td>• Were specific objectives of the review stated (based on specific clinical question in which patient, intervention, comparator, outcome (PICO) were identified)?</td>
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<tr>
<td>• Was the assignment of patients to treatment randomised?</td>
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<td>• Were comparison groups clearly defined?</td>
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<td>• Were outcomes measured in an objective way?</td>
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<td>• Were known confounders identified and appropriately controlled for?</td>
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<tr>
<td>• Was follow-up of patients sufficiently long and complete?</td>
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<tr>
<td>• Studies related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.) should have their methodological quality allocated to the type of study, i.e.</td>
</tr>
<tr>
<td>• RCT = good</td>
</tr>
<tr>
<td>• Studies without randomised controls = fair</td>
</tr>
<tr>
<td>• Studies without controls = poor</td>
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<td>Animal studies should also be designated using italics</td>
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Good studies = have most/all of the relevant quality items. Fair studies = have some of the relevant quality items. Poor studies = have few of the relevant quality items (but sufficient value to include for further review).

needed to treat (NNT = 6). Mortality at 6 months was 41% (56/137) in the hypothermia group compared with 55% (76/138) in the normothermia group (RR 0.74, 95% CI 0.58–0.95; NNT = 7). There were more complications in the hypothermia group (22% overall) but these, individually or collectively, were not statistically significant. These included pneumonia (number needed to harm (NNH) = 12), bleeding (NNH = 14) and sepsis (NNH = 16).

Another study enrolled 77 patients who had ROSC following a VF cardiac arrest. The hypothermia group was sedated, paralysed, ventilated and cooled to 33°C for 12 h using surface cooling. There was a benefit for the hypothermia group both in terms of neurological outcome and mortality although the trial was statistically underpowered to confirm the measured benefit. There was good neurological outcome at hospital discharge in 49% (21/43) of the hypothermia group compared with 26% (9/34) of the normothermia group (odds ratio 2.7 [1.0–7.0]; NNT = 4.5 [2.3–7.6]; Chi square p = 0.046). Mortality was 51% (22/43) in the hypothermia group compared with 68% (23/34) in the normothermia group (Chi-square p = 0.145; NNT = 6).

The mortality and neurological outcome of patients with signs of a ST-elevation myocardial infarction (STEMI) following ROSC after a VF cardiac arrest who underwent primary percutaneous coronary intervention (PCI) with therapeutic hypothermia were compared to a historical control group. The hypothermia group underwent surface cooling either before, during or after PCI was performed. There was a significant increase in those surviving with a good neurological outcome in the hypothermia group 22 (55%) vs 5 (16%) in the control (p = 0.001) and...
Table 4
Evidence neutral to therapeutic hypothermia following cardiac arrest.

| Good | Trainen, D 19 |
| Fair | Bernard, C 25 |
| Poor | Hachimi-Idrissi, C 20 |

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = Return of spontaneous circulation; B = Survival of event; C = Survival to hospital discharge; D = Intact neurological survival; E = Other endpoint.</td>
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this was sustained at 6 months. Mortality was also improved in the hypothermia group 30 (75%) vs 14 (44%) in the control (p = 0.0014).

Other studies with historical control groups have shown a significantly improved neurological outcome35,41 or mortality35 after therapeutic hypothermia for comatose survivors of VF cardiac arrest. There were six studies with historical controls (LOE 3) that showed benefit from therapeutic hypothermia after OHCA after all rhythm arrests.8,34,36–39 The majority of these still had a higher percentage of VF as the presenting arrhythmia (61–87%) except in one39 where only 35% presented with VF. However, this study included all patients presenting to the Emergency Department (ED) with ROSC before and after the introduction of a therapeutic hypothermia protocol, whereas other studies included only those who reached ICU and had hypothermia induced. Because of this, therapeutic hypothermia was achieved in 65% of the ‘hypothermia’ group. One study with a historical control group showed better neurological outcome after VF cardiac arrest but did not assess this after cardiac arrest from other arrhythmias,40 whilst two non-randomized studies with concurrent controls indicated possible benefit of hypothermia following cardiac arrest from other initial rhythms in- and out-of hospital.

3.2. How to cool?

There are several different methods described for the induction of cooling. Intravenous infusion of ice-cold fluids (30 ml kg⁻¹ of saline 0.9% or Ringer’s lactate) has been shown to adequately induce hypothermia46–53 as has the use of ice packs placed in the groins, armpits and around the head and neck. Cooling can be initiated in the pre-hospital phase with intravenous cold saline28,54–56 or cooling pads.57 Bernard et al.52 showed that the infusion of large volume (30 ml kg⁻¹), ice-cold (4°C) fluid reduced core temperature rapidly (mean 1.6°C decrease; p < 0.01) and increased mean arterial blood pressure (mean increase 10 mmHg; p = 0.012), improved renal function (mean creatinine decrease 20 μmol L⁻¹; p = 0.002), and increased pH (mean increase 0.04; p = 0.014).

Cold intravenous fluid and/or cooling pads can also be used to maintain hypothermia if transfer to the angiography laboratory is required,32,37,57 and can be used in conjunction with surface or internal cooling devices to facilitate induction of hypothermia.56,58

Ice cold fluids alone cannot maintain hypothermia59 but the addition of ice packs can keep the temperature in the target range.46 Temperature charts of patients receiving surface cooling with a cooling blanket/mattress or ice bags were reviewed60 with overcooling being documented in many: in 20/32 (63%) the temperature was below 32°C for more than an hour. To try and reduce the episodes of overcooling some devices include continuous temperature feedback to achieve a set target temperature.

Table 5
Evidence opposing hypothermia following OHCA.

| Good | Nielsen, CE 73 |
| Fair | Yanagawa, E 7 |
| Poor | Fries, E 31 |

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>A = Return of spontaneous circulation; B = Survival of event. C = Survival to hospital discharge; D = Intact neurological survival; E = Other endpoint.</td>
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* Overlapping patients.
Typical external cooling devices are cooling blankets or pads with water filled circulating systems. One study compared the efficiency of various cooling methods in maintaining a target temperature and documented that intravascular cooling was significantly more reliable in keeping patients within the target range. In the hypothermia group the intravascular catheter was significantly more reliable in keeping patients within the target temperature and documented that intravascular cooling was equally effective using device, 74.1 ± 4.8% of the time compared with 69.8 ± 3.7% when compared with a water-circulating device but they used only a single cooling blanket. One water-cooling device uses convective-immersion by circulating ice water from a perforated top sheet and an under-blanket across the skin surface at a rapid rate achieving cooling rates of 3 °C h⁻¹ (more than double those of the first study), the target temperature being reached in an average of 37 min and within an hour in 87% of patients. A recent study of a new cooling method comprising the transnasal delivery of 37 min and within an hour in 87% of patients. A recent study of a new cooling method comprising the transnasal delivery of 3.3. When to cool?

A recent randomized controlled trial has studied paramedic initiated cooling. The study included patients with a ROSC following a VF cardiac arrest. The trial arm received 2 L of ice-cold Ringer’s solution from the paramedics whilst the control arm received cooling on arrival to hospital using the same method. Although there was no difference in neurological outcome, there were several limitations to the study. There was a significant difference in temperature on arrival at hospital, but after 30 min the two groups had similar temperatures. By 1 h, the temperature in the paramedic group, was higher than it had been on hospital arrival. In one case series of patients cooled intravascularly, the time to coldest temperature (TCT) was an independent predictor of good neurological outcome (OR for every hour TCT: 0.72 ± 0.02. p = 0.009).

3.4. Safe with PCI?

Patients who achieve ROSC following out-of-hospital cardiac arrest often require intervention in the angiography laboratory. Three studies with historical controls has shown that the combination of therapeutic hypothermia and primary PCI is feasible and safe after cardiac arrest caused by acute myocardial infarction.
3.5. Harm from cooling?

A large prospective, observational, registry based study of 22 hospitals in Europe and the United States reviewed the adverse events that occurred in all patients treated with therapeutic hypothermia following OHCA. As there was no control group it was difficult to ascertain which complications were due to the hypothermia and which were due to the OHCA itself. Complications were common but the only ones associated with increased mortality were sustained hyperglycaemia and seizures treated with anti-convulsants. Other complications included arrhythmias (7–14%), pneumonia (48%) and metabolic and electrolyte disorders (5–37%). Sepsis (4%) and bleeding (6%) were less common overall but occurred more frequently when an intravascular device was used. This was for all intravascular devices, e.g. cooling devices, intra-aortic balloon pumps or angiography but was not associated with an increase in mortality.

One study showed that significantly more patients who were cooled for 48 h developed pneumonia compared with a control group (11/13 (85%) vs 5/15 (33%) (p = 0.02)). Although four patients in the hypothermia group and two in the control group with pneumonia died, in no case was the pneumonia a direct cause of death. Other studies have shown no difference in pneumonia or sepsis rates. Another study documented the inflammatory response after hypothermia. The authors reported that interleukin-6 levels were significantly elevated in the hypothermia group compared with controls, as was the rate of bacterial colonisation (64.1 vs 12.5%; p < 0.01), which was found predominantly in broncho-alveolar lavage (48.8%), blood cultures (30.2%) and urine (11.6%). The hypothermia group was also significantly more likely to require catecholamines to maintain the mean arterial pressure higher than 65 mmHg (p < 0.05). However, none of these changes appeared to affect mortality, with the hypothermia group trending towards reduced mortality. Increased catecholamines were also required in another study, which also found an increase in intra-aortic balloon pump use. Again, mortality appeared unaffected, as survival was significantly higher in the treatment arm.

A study that described 11 patients with traumatic brain injuries cooled with an intravascular device for 3–8 days documented a 50% incidence of deep vein thrombosis. In the last five patients the intravascular device was removed within 5 days and the incidence reduced from 75% to 33.3%. Shivering is common, particularly in the induction phase, and has the potential to cause harm because it increases metabolic rate and oxygen demand and may actually increase the incidence of myocardial infarction. But when hypothermia is used in the clinical setting, patients are sedated and often paralysed to abolish shivering. In this setting the heart rate is reduced and systemic vascular resistance increased, leading to a reduction in cardiac output. Arrhythmias are also described with hypothermia, with bradycardia the most common. Some investigators report more arrhythmias with hypothermia in comparison with controls, whilst others document no difference. Other complications include the induction of a diuresis leading to hypovolaemia and potential haemodynamic instability, as well as hypophosphataemia, hypokalaemia, hypomagnesaemia and hypocalcaemia. Hypothermia also reduces insulin sensitivity and insulin secretion, causing hyperglycaemia.

Hypothermia can lead to increased concentrations of sedative and neuromuscular drugs because their clearance is reduced by 30% at 34 °C.

4. Discussion

This review has identified some evidence that therapeutic hypothermia following cardiac arrest in comatose patients with ROSC improves mortality and neurological outcome. The strongest data remain those provided by the HACA Study Group, which showed both a reduction in mortality and improved neurological outcome at 6 months following out-of-hospital cardiac arrest where the initial rhythm was VF. These findings are supported by other, lower level, studies. The extrapolation of these data to other cardiac arrests (e.g. other initial rhythms) is hospital arrests, cardiac arrest in children seems reasonable but is supported by only lower level data. There is a need for randomised controlled trials of hypothermia in these other groups and a few such studies are underway (see below).

5. Authors conclusion and recommendation

This review has identified data on the use of therapeutic hypothermia to improve neurological outcome in comatose patients with ROSC after cardiac arrest. There is reasonable evi-
dence that this therapy is effective for comatose survivors of VF/VT out-of-hospital cardiac arrest but there are only observational data to support its use after cardiac arrest from non-shockable rhythms or after in-hospital cardiac arrest. Cooling can be achieved in both the pre- and in-hospital setting and it can be done in conjunction with other interventions such as PCI. Whilst devices with temperature feedback appear to provide better temperature control, the lack of this equipment should not prevent the use of therapeutic hypothermia because this can be achieved with equipment readily available in all hospital settings, e.g. ice-cold fluid, ice-packs and cold, wet blankets. If therapeutic hypothermia is not feasible then, at a minimum, pyrexia must be prevented.

Disclaimer

This review includes information on resuscitation questions developed through the C2010 Consensus on CPR and ECC Science with Treatment Recommendations (CoSTR) process managed by the International Liaison Committee on Resuscitation.1 The questions were developed by ILCOR Task Forces, using strict conflict of interest guidelines.2,3 In general, each question was assigned to two experts to complete a detailed structured review of the literature, and complete a detailed worksheet. Worksheets were discussed at ILCOR meetings to reach consensus and were published in the 2010 CoSTR.4 The conclusions published in the final CoSTR consensus document may differ from the conclusions of in this review because the CoSTR consensus reflected input from other worksheet authors and discussants at the conference, and took into consideration implementation and feasibility issues as well as new relevant research.

Conflict of interest

JW – none; PM is a reimbursed consultant for Evidence Evaluation Expert position with ILCOR/AHA; and JN is Co-chair ILCOR and Editor-in-Chief of Resuscitation.

References


