Resuscitation 82 (2011) 508–516

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation: A systematic review☆

James H. Walters[a,*], Peter T. Morley[b], Jerry P. Nolan[c]

[a] Intensive Care Medicine, Royal United Hospital, Bath BA1 3NG, UK
[b] Director of Medical Education, Royal Melbourne Hospital, University of Melbourne, Australia
[c] Anaesthesia and Intensive Care Medicine, Royal United Hospital, Bath BA1 3NG, UK

ARTICLE INFO

Article history:
Received 24 August 2010
Received in revised form 23 January 2011
Accepted 26 January 2011

Keywords:
Hypothermia
Cardiac arrest
Outcome

ABSTRACT

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 Cardiovascular 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.

Contents

1. Background 509
2. Methods 509
   2.1. PICO question 509
   2.2. Search strategy 509
   2.3. Evidence appraisal 509
   2.4. Data presentation 509
3. Results 509
   3.1. Who to cool? 509
   3.2. How to cool? 511
   3.3. When to cool? 512
   3.4. Safe with PCI? 512
   3.5. Harm from cooling? 513

☆ 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.

* Corresponding author.
E-mail addresses: james@drwalters.co.uk (J.H. Walters), peter.morley@mh.org.au (P.T. Morley).

0300-9572/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2011.01.021

4. Discussion 513
5. Authors conclusion and recommendation 513
Disclaimer 514
Conflict of interest 514
References 514

1. Background

Out-of-hospital cardiac arrest (OHCA) occurs in about 1 in 1500 adults in the developed world each year[1]; this means that about 375,000 people in Europe have a sudden cardiac arrest each year.[2] 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%.[3] Among survivors, anoxic neurological injury is an important cause of morbidity.[4] 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.[5]

The exact mechanism for the cerebral resuscitative effect of hypothermia is unclear but several potential mechanisms have been described.[6] Many studies document apparent benefit from induced hypothermia after cardiac arrest.[5,7–9]

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).[10] 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.[11] 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 Force[12,13]: "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.[11]

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 patients[18]; 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.[18] 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 1
ILCOR level of evidence for therapeutic interventions.

LOE 1: Randomized controlled trials (or meta-analyses of RCTs)
LOE 2: Studies using concurrent controls without true randomization (e.g. "pseudo"-randomized) or meta-analyses of such studies)
LOE 3: Studies using retrospective controls
LOE 4: Studies without a control group (e.g. cases series)
LOE 5: Studies not directly related to the specific patient/population (e.g. different patient/population, animal models, mechanical models etc.)

Table 2
Quality factors for studies of each level of evidence.

Meta-analysis (of LOE 1 or LOE 2 studies)	Randomised controlled Trials (LOE 1)	Studies using controls without randomisation (concurrent LOE 2, or retrospective LOE 3)	Studies without controls (LOE 4)	Studies not directly related to the specific patient/population (LOE5)
• Were specific objectives of the review stated (based on specific clinical question in which patient, intervention, operator, comparator, outcome (PICO) were identified)?	• Was the assignment of patients to treatment randomised?	• Were comparison groups clearly defined?	• Were outcomes measured in an objective way?	Studies not 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.
• Was study design defined?	• Was the randomisation list concealed?	• Were outcomes measured in the same (preferably blinded) objective way in both groups?	• Were known confounders identified and appropriately controlled for?	• RCT = good
• Were selection criteria stated for studies to be included (using appropriately crafted search strategies)?	• Were all patients who entered the trial accounted for in its conclusions?	• Were known confounders identified and appropriately controlled for?	• Was follow-up of patients sufficiently long and complete?	• Studies without randomised controls = fair
• Were characteristics and methodological quality of each trial identified?	• Were the patients analysed in the groups to which they were randomised? • Were patients and clinicians "blinded to which treatment was being received? • Aside from the experimental treatment, were the groups treated equally? • Were the groups similar at the start of the trial?	• Was follow-up of patients sufficiently long and complete?		• Studies without controls = poor Animal studies should also be designated using *italics*

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.[25] 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.[33] 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 3
Evidence supporting therapeutic hypothermia following OHCA.

Good	Arrich, CD[a,16] HACA study group, CD[b,18] Tiainen, E[b,19] Nielsen, D[17]		Bernard, CD[8]	Hovdenes, CD[71] Wolff, DE[69] Nielsen, CD[70]	
Fair	Holzer, CD[a,14]	Bernard, D[25] Holzer, CD[26] Kagawa,[32] D	Knafelj, CD[33] Busch, C[34] Belliard, CD[35] Oddo, D[36] Sunde, CD[37] Storm, CDE[38] Don, CD[39] Bro-Jeppesen, D[40]	Oksanen, C[84] Sagalyn, [a,85]	
Poor	Hachimi-Idrissi, E[20] Cheung, CD[a,15]	Arrich, CD[67]	Castrejon, D[41]	Williams, D[86]	
Level of evidence	1	2	3	4	5

A = return of spontaneous circulation; B = survival of event; C = survival to hospital discharge; D = intact neurological survival; E = other endpoint.
[a] Meta-analysis.
[b] Overlapping patients

Table 4
Evidence neutral to therapeutic hypothermia following cardiac arrest.

Good	Trainen, D[a,19] Tiainen, E[a,21] Tiainen, DE[a,22] Koreny, E[a,23] Nielsen, C[17]			Damian, CD[87] Cronberg, D[80]
Fair	Zeiner, E[a,24]	Bernard, C[25] Doherty, CDEP[27] Hammer, CD[28]	Yanagawa, CDE[7] Oddo, C[36] Wolfrum, CDE[42] Gaieski, CD[43] Bro-Jeppesen, C[40] Busch, D[34]	Bernard, E[52] Merchant, C[60] Virkkunen, E[48] Kliegel, CDE[53] Kliegel, CDE[59] Haugk, E[58] Pichon, CDE[88] Kim, E[89] Kim, C[51] Uray, CDE[57] Skulec, D[90] Jimmink, E[91] Heard, E[62] Larsson, E[46] Jacobshagen, E[50] Spiel, E[47] Gal, CD[61] Kamarainen, CDE[56] Dumas, CDE[72]
Poor	Hachimi-Idrissi, C[20]	Benson, C[29] Derwall, E[30] Fries, CD[31]	Werling, CD[44] Borgquist, CD[45] Castrejon, C[41]	Al-Senani, CDE[92] Felberg, CD[93] Nagao, 200 CD[94] Silfvast, CD[95] Zeiner, 200 CD[9] Scott, CD[96] Hoedemaekers, E[63] Flint, E[97] Hay, D[98] Kamarainen, CE[55] Kamarainen, CE[54] Kilgannon, E[49]
Level of evidence	1	2	3	4 5

A = Return of spontaneous circulation; B = survival of event; C = Survival to hospital discharge; D = Intact neurological survival; E = Other endpoint; P = pediatric patients.
[a] Overlapping patients.

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 outcome[35,41] or mortality[35] 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 one[39] 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.

Table 5
Evidence opposing hypothermia following OHCA.

Good				Nielsen, CE[73]	
Fair			Yanagawa, E[7]		
Poor		Fries, E[31]			Simosa, E[74]
Level of evidence	1	2	3	4	5

A = return of spontaneous circulation; B = survival of event. C = survival to hospital discharge; D = intact neurological survival; E = other endpoint.

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 hypothermia[46–53] 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 saline[28,54–56] 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,[33,37,57] and can be used in conjunction with surface or internal cooling devices to facilitate induction of hypothermia.[26,58]

Ice cold fluids alone cannot maintain hypothermia[59] 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 reviewed[60] 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 6
Who to cool.

Study	Study design	Number	Cooling mechanism	Arrhythmias included	Survival[a] (hypothermia vs control)	Neurological outcome[a] (hypothermia vs control)
HACA Study Group[18]	Randomized, controlled	275	CAM	VF/VT	59% vs 45% (6 months) $p = 0.02$	CPC score 1–2 55% vs 39% (6 months) $p = 0.009$
Bernard[25]	Pseudo-randomized controlled	77	IP - initiated in ambulance	VF	49% vs 32% $p = 0.145$	CPC score 1–2 49% vs 26% $p = 0.046$
Knafelj[33]	Historical control	72	CSI plus IP	VF with STEMI	75% vs 14% $p = 0.0014$	CPC score 1–2 55% vs 16% $p = 0.001$
Belliard[35]	Historical control	68	IP and WC	VF	56% vs 36% $p = 0.04$	GOS score 5 72% vs 46% $p = 0.02$
Castrejon[41]	Historical control	69	IP, CSI and CB	VF/VT	56% vs 39% $p = 0.17$	CPC score 1–2 44% vs 18% $p = 0.029$
Bernard[8]	Historical control	44	IP	All (77% VF)	55% vs 23% $p = 0.06$[b]	CPC score 1–2 50% vs 14% $p = 0.02$[b]
Oddo[36]	Historical control	109	IP and CB	All (79% VF)	VF 60% vs 44% $p = 0.28$ Other – 17% vs 9%	CPC score 1–2 VF 56% vs 26% $p = 0.004$. Other 17% vs 0%
Busch[34]	Historical control	61	IP and WB	All (69% VF)	59% vs 32% $p = 0.05$	CPC score 1–2 41% vs 26% $p = 0.21$
Sunde[37]	Historical control	119	EC ± IP and CSI or CB, IP + WB	All (87% VF)	56% vs 31% $p = 0.007$	CPC score 1–2 56 vs 26% $p < 0.001$
Storm[38]	Historical control	126	CSI and CB	All (61% VF)	71% vs 58% $p = 0.19$	CPC score 1–2 62% vs 23% $p = <0.001$
Don[39]	Historical control	491	IP, CB or CP	All (35% VF)	VF/VT 54% vs 39% $p = 0.04$ Other 21% vs 19% $p = 0.65$	CPC score 1 VF 35% vs 15% $p < 0.01$ Other 12% vs 9% $p = 0.44$
Bro-Jeppesen[40]	Historical control	156	IP, CSI and CB	All (69% VF)	VF/VT 65% vs 68% $p = 0.79$ Other 26% vs 24% $p = 0.87$	CPC score 1–2 VF 97% vs 71% (of survivors) $p = 0.003$

CAM, cold air mattress; IP, ice packs; CSI, cold saline infusion; WC, wet cloths; CB, cooling blankets; EC, endovascular cooling; CP, cooling pads; VF, ventricular fibrillation; VT, ventricular tachycardia; STEMI, ST-elevation myocardial infarction; GOS, Glasgow outcome score; CPC, cerebral performance categories.

[a] At hospital discharge unless otherwise stated.

[b] *p*-Values recalculated using Chi-squared analysis.

Typical external cooling devices are cooling blankets[61] or pads with water filled circulating systems.[58,62] 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.[63] In the hypothermia group the intravascular catheter was out of range for 3.2 ± 4.8% of the time compared with 69.8 ± 37.6% with conventional cooling, 50.5 ± 35.9% with the water circulating device, 74.1 ± 40.5% with the air-circulating cooling device and 44.2 ± 33.7% with the gel-coated external cooling system ($p < 0.05$). They found that induction of cooling was equally effective using the water-circulating cooling device, the gel-coated external device and the intravascular catheter. Another study found that intravascular cooling was significantly faster at inducing hypothermia when compared with a water-circulating device but they used only a single cooling blanket.[64] 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.[65] A recent study of a new cooling method comprising the transnasal delivery of perflurocarbon nebulised with oxygen was excluded from our review because cooling was started during cardiac arrest.[66] Rewarming can be achieved with either the same external or internal temperature control used to cool the patient, or with another temperature control device. The optimal rate of warming is not known but the consensus is currently about 0.25–0.5 °C of warming per hour.[67]

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.[68] 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 [95% CI 0.56–0.94]).[69] In contrast, one registry-based case series of 986 comatose post-cardiac arrest patients documented that time to initiation of cooling (median 90 min; interquartile range 60–165 min) was not associated with improved neurological outcome post discharge.[70]

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[33,37,42] and three case series[70–72] have 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.[73] 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%) ($p = 0.02$)].[7] 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[41] or sepsis[18] rates. Another study documented the inflammatory response after hypothermia.[31] 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 bronchoalveolar 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,[37] 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%.[74]

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.[75] 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.[76] Arrhythmias are also described with hypothermia, with bradycardia the most common. Some investigators report more arrhythmias with hypothermia in comparison with controls[40] whilst others document no difference.[33,34] Other complications include the induction of a diuresis leading to hypovolaemia and potential haemodynamic instability, as well as hypophosphataemia, hypokalaemia, hypomagnesaemia and hypocalcaemia.[34,77,78] Hypothermia also reduces insulin sensitivity and insulin secretion, causing hyperglycaemia.[25,34,37]

Hypothermia can lead to increased concentrations of sedative and neuromuscular drugs because their clearance is reduced by 30% at 34 °C.[79]

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,[18] 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.[25,33,35,41] The extrapolation of these data to other cardiac arrests (e.g. other initial rhythms,[8,34,36–39] in-hospital arrests,[80] cardiac arrest in children[27]) 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).

To date, most clinical data have been derived from studies that have used a target temperature of 32–34 °C for 24 h. Although this is the generally accepted optimal target temperature and duration for cooling, the optimal cooling strategy remains unknown. It is even possible that simply avoiding hyperthermia would confer as much benefit as mild hypothermia.[81] No study has compared hypothermia with strict normothermia; they have generally compared hypothermia with best practice.

Practically, therapeutic hypothermia can be divided into three parts: induction, maintenance and rewarming. The induction of cooling has a benefit even if delayed. Although not included in this systematic review, there are animal data indicating a greater benefit the earlier hypothermia is initiated.[82] However, the human data supporting earlier cooling are not very convincing.[68–70]

Although the role for therapeutic hypothermia after resuscitation from cardiac arrest is generally accepted, there are many gaps in our knowledge and further research is essential. There remains just one LOE 1 study showing improved long-term survival with therapeutic hypothermia;[18] although there are several other LOE 1, supportive studies, these have used data from the same study.[19,21–24] Based on the criteria defined in the 2010 CoSTR, we have classified the HACA study as good quality; however, others have challenged this and suggested that even this study has a significant risk of bias.[17] These same authors have initiated a randomised trial that is currently recruiting patients (NCT01020916). The use of therapeutic hypothermia when the initial rhythm is not VF or non-perfusing VT should ideally be studied with a prospective randomised trial, rather than relying on sub-group analysis or extrapolation of data derived from shockable rhythms. The impact of very early cooling, including during cardiac arrest, should be further investigated. Although a recent trial appeared to show no benefit from paramedic-initiated cooling there were several limitations to the study. The use of a transnasal device is promising and would allow intra-arrest cooling. Although no significant difference in mortality or neurological outcome was demonstrated, the trial was not powered for this and further, larger trials are needed.

Trials should also be undertaken to determine the optimum length of cooling, the speed of cooling, the cooling technique and the rate of re-warming. Some of these knowledge gaps are being addressed with ongoing clinical trials (e.g. "Intra-Arrest Therapeutic hypothermia in Prehospital cardiac arrest" (NCT00886184), "Therapeutic Hypothermia to Improve Survival After Cardiac Arrest in Pediatric Patients" (The THAPCA_IH [In Hospital] (NCT00880087) and OH [Out of Hospital] (NCT00878644) Studies), and "Trial of Different Hypothermia Temperatures in Patients Recovered From Out-of –Hospital Cardiac Arrest" (NCT01155622) as well as a number of trials comparing various devices).

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.[11] The questions were developed by ILCOR Task Forces, using strict conflict of interest guidelines.[83] 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.[10] 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

1. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104:2158–63.
2. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol 1997;30:1500–5.
3. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2010;3:63–81.
4. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 1994;343:1055–9.
5. Holzer M. Targeted temperature management for comatose survivors of cardiac arrest. N Engl J Med 2010;363:1256–64.
6. Schneider A, Bottiger BW, Popp E. Cerebral resuscitation after cardiocirculatory arrest. Anesth Analg 2009;108:971–9.
7. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation 1998;39:61–6.
8. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 1997;30:146–53.
9. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. Stroke 2000;31:86–94.
10. Nolan JP, Hazinski MF, Billi JE, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Resuscitation 2010;81:e1–25.
11. Morley PT, Atkins DL, Billi JE, et al. Part 3: Evidence evaluation process: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2010;81:e32–40.
12. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club 1995;123:A12–3.
13. Deakin CD, Morrison LJ, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2010;81:e93–174.
14. Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Mullner M. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med 2005;33:414–8.
15. Cheung KW, Green RS, Magee KD. Systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. CJEM 2006;8:329–37.
16. Arrich J, Holzer M, Herkner H, Mullner M. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2009:CD004128.
17. Nielsen N, Friberg H, Gluud C, Herlitz J, Wetterslev J. Hypothermia after cardiac arrest should be further evaluated-A systematic review of randomised trials with meta-analysis and trial sequential analysis. Int J Cardiol 2010.
18. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
19. Tiainen M, Roine RO, Pettila V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003;34:2881–6.
20. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation 2001;51:275–81.
21. Tiainen M, Poutiainen E, Kovala T, Takkunen O, Happola O, Roine RO. Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia. Stroke 2007;38:2303–8.
22. Tiainen M, Parikka HJ, Makijarvi MA, Takkunen OS, Sarna SJ, Roine RO. Arrhythmias and heart rate variability during and after therapeutic hypothermia for cardiac arrest. Crit Care Med 2009;37:403–9.
23. Koreny M, Sterz F, Uray T, et al. Effect of cooling after human cardiac arrest on myocardial infarct size. Resuscitation 2009;80:56–60.
24. Zeiner A, Sunder-Plassmann G, Sterz F, et al. The effect of mild therapeutic hypothermia on renal function after cardiopulmonary resuscitation in men. Resuscitation 2004;60:253–61.
25. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.
26. Holzer M, Mullner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. Stroke 2006;37:1792–7.
27. Doherty DR, Parshuram CS, Gaboury I, et al. Hypothermia therapy after pediatric cardiac arrest. Circulation 2009;119:1492–500.
28. Hammer L, Vitrat F, Savary D, et al. Immediate prehospital hypothermia protocol in comatose survivors of out-of-hospital cardiac arrest. Am J Emerg Med 2009;27:570–3.
29. Benson DW, Williams Jr GR, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. Anesth Analg 1959;38:423–8.
30. Derwall M, Stoppe C, Brucken D, Rossaint R, Fries M. Changes in S-100 protein serum levels in survivors of out-of-hospital cardiac arrest treated with mild therapeutic hypothermia: a prospective, observational study. Crit Care 2009;13:R58.
31. Fries M, Stoppe C, Brucken D, Rossaint R, Kuhlen R. Influence of mild therapeutic hypothermia on the inflammatory response after successful resuscitation from cardiac arrest. J Crit Care 2009;24:453–7.
32. Kagawa E, Inoue I, Kawagoe T, et al. Who benefits most from mild therapeutic hypothermia in coronary intervention era? A retrospective and propensity-matched study. Crit Care 2010;14:R155.
33. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. Resuscitation 2007;74:227–34.
34. Busch M, Soreide E, Lossius HM, Lexow K, Dickstein K. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. Acta Anaesthesiol Scand 2006;50:1277–83.
35. Belliard G, Catez E, Charron C, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. Resuscitation 2007;75:252–9.
36. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med 2006;34:1865–73.
37. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation 2007;73:29–39.
38. Storm C, Steffen I, Schefold JC, et al. Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls. Crit Care 2008;12:R78.
39. Don CW, Longstreth Jr WT, Maynard C, et al. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. Crit Care Med 2009;37:3062–9.
40. Bro-Jeppesen J, Kjaergaard J, Horsted TI, et al. The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. Resuscitation 2009;80:171–6.
41. Castrejon S, Cortes M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. Rev Esp Cardiol 2009;62:733–41.

42. Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. Crit Care Med 2008;36:1780–6.
43. Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. Resuscitation 2009;80:418–24.
44. Werling M, Thoren AB, Axelsson C, Herlitz J. Treatment and outcome in post-resuscitation care after out-of-hospital cardiac arrest when a modern therapeutic approach was introduced. Resuscitation 2007;73:40–5.
45. Borgquist O, Friberg H. Therapeutic hypothermia for comatose survivors after near-hanging-a retrospective analysis. Resuscitation 2009;80:210–2.
46. Larsson IM, Wallin E, Rubertsson S. Cold saline infusion and ice packs alone are effective in inducing and maintaining therapeutic hypothermia after cardiac arrest. Resuscitation 2010;81:15–9.
47. Spiel AO, Kliegel A, Janata A, et al. Hemostasis in cardiac arrest patients treated with mild hypothermia initiated by cold fluids. Resuscitation 2009;80:762–5.
48. Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation 2004;62:299–302.
49. Kilgannon JH, Roberts BW, Stauss M, et al. Use of a standardized order set for achieving target temperature in the implementation of therapeutic hypothermia after cardiac arrest: a feasibility study. Acad Emerg Med 2008;15:499–505.
50. Jacobshagen C, Pax A, Unsold BW, et al. Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors. Resuscitation 2009;80:1223–8.
51. Kim F, Olsufka M, Longstreth Jr WT, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation 2007;115:3064–70.
52. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 2003;56:9–13.
53. Kliegel A, Losert H, Sterz F, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest: a feasibility study. Resuscitation 2005;64:347–51.
54. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. Resuscitation 2008;79:205–11.
55. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital induction of therapeutic hypothermia during CPR: a pilot study. Resuscitation 2008;76:360–3.
56. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta Anaesthesiol Scand 2009;53:900–7.
57. Uray T, Malzer R. Out-of-hospital surface cooling to induce mild hypothermia in human cardiac arrest: a feasibility trial. Resuscitation 2008;77:331–8.
58. Haugk M, Sterz F, Grassberger M, et al. Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. Resuscitation 2007;75:76–81.
59. Kliegel A, Janata A, Wandaller C, et al. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation 2007;73:46–53.
60. Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Crit Care Med 2006;34:S490–4.
61. Gal R, Slezak M, Zimova I, Cundrle I, Ondraskova H, Seidlova D. Therapeutic hypothermia after out-of-hospital cardiac arrest with the target temperature 34–35 °C. Bratisl Lek Listy 2009;110:222–5.
62. Heard KJ, Peberdy MA, Sayre MR, et al. A randomized controlled trial comparing the Arctic Sun to standard cooling for induction of hypothermia after cardiac arrest. Resuscitation 2010;81:9–14.
63. Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. Crit Care 2007;11:R91.
64. Keller E, Imhof HG, Gasser S, Terzic A, Yonekawa Y. Endovascular cooling with heat exchange catheters: a new method to induce and maintain hypothermia. Intensive Care Med 2003;29:939–43.
65. Howes D, Ohley W, Dorian P, et al. Rapid induction of therapeutic hypothermia using convective-immersion surface cooling: safety, efficacy and outcomes. Resuscitation 2010;81:388–92.
66. Castren M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation 2010;122:729–36.
67. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 2007;35:1041–7.
68. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation 2010;122:737–42.
69. Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol 2009;133:223–8.
70. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926–34.
71. Hovdenes J, Laake JH, Aaberge L, Haugaa H, Bugge JF. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. Acta Anaesthesiol Scand 2007;51:137–42.
72. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv 2010;3:200–7.
73. Nielsen N, Sunde K, Hovdenes J, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2010.
74. Simosa HF, Petersen DJ, Agarwal SK, Burke PA, Hirsch EF. Increased risk of deep venous thrombosis with endovascular cooling in patients with traumatic head injury. Am Surg 2007;73:461–4.
75. Bernard SA, Buist M. Induced hypothermia in critical care medicine: a review. Crit Care Med 2003;31:2041–51.
76. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350–79.
77. Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality. Part 2: Practical aspects and side effects. Intensive Care Med 2004;30:757–69.
78. Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurg 2001;94:697–705.
79. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: a focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med 2007;35:2196–204.
80. Cronberg T, Lilja G, Rundgren M, Friberg H, Widner H. Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. Resuscitation 2009;80:1119–23.
81. Nolan JP, Soar J. Mild therapeutic hypothermia after cardiac arrest: keep on chilling. Crit Care Med 2011;39:206–7.
82. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 1993;21:1348–58.
83. Shuster M, Billi JE, Bossaert L, et al. Part 4: Conflict of interest management before, during, and after the 2010 International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2010;81:e41–7.
84. Oksanen T, Pettila V, Hynynen M, Varpula T. Therapeutic hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. Acta Anaesthesiol Scand 2007;51:866–71.
85. Sagalyn E, Band RA, Gaieski DF, Abella BS. Therapeutic hypothermia after cardiac arrest in clinical practice: review and compilation of recent experiences. Crit Care Med 2009;37:S223–6.
86. Williams Jr GR, Spencer FC. The clinical use of hypothermia following cardiac arrest. Ann Surg 1958;148:462–8.
87. Damian MS, Ellenberg D, Gildemeister R, et al. Coenzyme Q10 combined with mild hypothermia after cardiac arrest: a preliminary study. Circulation 2004;110:3011–6.
88. Pichon N, Amiel JB, Francois B, Dugard A, Etchecopar C, Vignon P. Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. Crit Care 2007;11:R71.
89. Kim F, Olsufka M, Carlbom D, et al. Pilot study of rapid infusion of 2 L of 4 °C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. Circulation 2005;112:715–9.
90. Skulec R, Kovarnik T, Dostalova G, Kolar J, Linhart A. Induction of mild hypothermia in cardiac arrest survivors presenting with cardiogenic shock syndrome. Acta Anaesthesiol Scand 2008;52:188–94.
91. Jimmink JJ, Binnekade JM, Paulus F, Mathus-Vliegen EM, Schultz MJ, Vroom MB. The influence of body composition on therapeutic hypothermia: a prospective observational study of patients after cardiac arrest. Crit Care 2008;12:R87.
92. Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. Resuscitation 2004;62:143–50.
93. Felberg RA, Krieger DW, Chuang R, et al. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. Circulation 2001;104:1799–804.
94. Nagao K, Hayashi N, Kanmatsuse K, et al. Cardiopulmonary cerebral resuscitation using emergency cardiopulmonary bypass, coronary reperfusion therapy and mild hypothermia in patients with cardiac arrest outside the hospital. J Am Coll Cardiol 2000;36:776–83.
95. Silfvast T, Tiainen M, Poutiainen E, Roine RO. Therapeutic hypothermia after prolonged cardiac arrest due to non-coronary causes. Resuscitation 2003;57:109–12.
96. Scott BD, Hogue T, Fixley MS, Adamson PB. Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. Clin Cardiol 2006;29:525–9.

97. Flint AC, Hemphill JC, Bonovich DC. Therapeutic hypothermia after cardiac arrest: performance characteristics and safety of surface cooling with or without endovascular cooling. Neurocrit Care 2007;7:109–18.

98. Hay AW, Swann DG, Bell K, Walsh TS, Cook B. Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest. Anaesthesia 2008;63:15–9.