Clinical question.
In post-cardiac arrest patients with ROSC (P), does therapeutic hypothermia (I) compared with usual care (C), improve morbidity or mortality (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis: Intervention/therapy.
State if this is a proposed new topic or revision of existing worksheet: Revision.

Search strategy (including electronic databases searched).
PubMed (“heart arrest” or “cardiopulmonary resuscitation”) AND “hypothermia, induced” using ‘Clinical Queries’ search strategy = 1185 hits
EMBASE (heart arrest) OR (cardiopulmonary resuscitation) AND hypothermia (limited to Title and abstract) – 692 hits – just 3 new relevant reference
ECC EndNote Library 4Nov09: “hypothermia” in abstract OR title = 1016 hits
Cochrane database for systematic reviews “hypothermia” = 1 review (Arrich 2009).
Review of references from articles.
References from pdfs stored by Nolan and Morley.

State inclusion and exclusion criteria
The following studies were excluded: 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 (eg. combined with haemofiltration or resuscitation with cardiopulmonary bypass instead of CPR).

Number of articles/sources meeting criteria for further review:
72 studies met criteria for further review. Of these three were Level 1 (meta-analyses), seven were Level 1 (RCTs), eight Level 2 (non-randomised, concurrent controls), fifteen Level 3 (retrospective controls), thirty-eight Level 4 (no controls) and one Level 5 (extrapolated from non-cardiac arrest group).

Summary of evidence
Evidence Supporting Clinical Question

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Level of evidence
A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
* = overlapping patients
# = meta-analysis
## Evidence Neutral to Clinical question

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<tr>
<td><strong>A</strong> = Return of spontaneous circulation</td>
<td>Tiainen, 2003 D*</td>
<td>Bernhard, 2002 C</td>
<td>Hachimi-Idrissi, 2001 C</td>
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<tr>
<td><strong>B</strong> = Survival of event</td>
<td>Tiainen, 2007 E*</td>
<td>Doherty, 2009 CDE (P)</td>
<td>Benson, 1959 C</td>
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<td><strong>C</strong> = Survival to hospital discharge</td>
<td>Tiainen, 2009 D, E*</td>
<td>Hammer, 2009 CD</td>
<td>Derwall, 2009 E (S100)</td>
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<td><strong>D</strong> = Intact neurological survival</td>
<td>Koreny, 2009 E*</td>
<td>Yanagawa, 1998 CDE</td>
<td>Fries, 2009 E</td>
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<td><strong>E</strong> = Other endpoint</td>
<td>Damian, 2004 CD</td>
<td>Oddo, 2006 C</td>
<td>Werling, 2007 CD</td>
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<td><strong>(P)</strong> = paediatric patients</td>
<td>Cronberg, 2009 D</td>
<td>Wolfrum, 2008 CDE</td>
<td>Borgquist, 2009 CD</td>
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<td>* = overlapping patients</td>
<td>Bernard, 2003 E</td>
<td>Gaieski, 2009 CD</td>
<td>Castrejon, 2009 C</td>
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<td>Merchant, 2006 C</td>
<td>Bro-Jeppesen, 2009 C</td>
<td>Al-Senani, 2004 CDE</td>
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<td>Virkkunen, 2004 E</td>
<td>Busch, 2006 D</td>
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<td>Scott, 2006 CD</td>
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<td>Kim, 2005 E</td>
<td>Kliegel, 2005 CDE</td>
<td>Hoedemaekers, 2007 E</td>
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<td>Uray, 2008 CDE</td>
<td>Jacobshagen, 2009 E</td>
<td>Hay, 2008 D</td>
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<td>Jimmink, 2008 E</td>
<td>Gal, 2009 CD</td>
<td>Kamarainen, 2008b CE</td>
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<td>Heard, 2010 E</td>
<td>Kamarainen, 2009 CDE</td>
<td>Kilgannon, 2008 E</td>
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<td>Larsson, 2010 E</td>
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## Evidence Opposing Clinical Question

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<td>Fries, 2009 E (bact. colon.)</td>
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<td>3</td>
<td>Yanagawa, 1998 E</td>
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<td>Simosa, 2007 E (DVT with intravasc. cooling)</td>
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**Level of evidence:***

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint
## DISCUSSION:

**Who to cool?**

The definitive study to date is that performed by the Hypothermia After Cardiac Arrest (HACA) Study Group (HACA, 2002) which performed a methodologically good prospective randomized study, and confirmed that the induction of hypothermia in comatose survivors of out-of-hospital cardiac arrest caused by ventricular fibrillation (VF) improves neurological outcome and mortality at 6 months. Hypothermia patients were sedated, paralysed, ventilated and cooled with surface cooling to 32-34°C for 24 hours. Major limiting factors include the inability of the investigators to blind the treating team to the study group, the limited proportion of patients finally included (8% of those assessed; limiting extrapolations), and the relative hyperthermia in the control group. There were more complications in the hypothermia group but these (individually or collectively) were not statistically significant.

The other landmark study was performed in Melbourne Australia, also in comatose survivors of out-of-hospital cardiac arrest caused by VF, was statistically underpowered to confirm the measured benefit (Bernard, 2002). Hypothermia patients were sedated, paralysed, ventilated and cooled with surface cooling to 33°C for 12 hours. Major limitations of this study included the pseudo-randomisation of patients, the inability of the investigators to blind the treating team to the study group, and the limited number of patients finally included.

In a Level 3 study of patients with out-of-hospital VF cardiac arrest associated with ST-elevation MI, the neurological outcome of patients treated with primary PCI and cooling after was improved compared with an historical control group treated with primary PCI alone (Knafleji, 2007).

There is good evidence supporting the use of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest caused by VF.

Two studies with historical control groups (Level 3) showed improvement in neurological outcome after therapeutic hypothermia for comatose survivors of VF cardiac arrest (Belliard, 2007, 252; Castrejon, 2009, 733). Extrapolation of these data to other cardiac arrests (e.g., other initial rhythms, in-hospital arrests, paediatric patients) seems reasonable but is supported by only lower level data:

Six studies with historical control groups (Level 3) showed benefit after therapeutic hypothermia in comatose survivors of OHCA after all rhythm arrests (Bernard, 2007; Oddo, 2006; Busch, 2006; Sunde, 2007; Storm, 2008; Don 2009). One studies with historical controls showed better neurological outcome after VF cardiac arrest but no difference after cardiac arrest from other rhythms (Bro-Jeppesen, 2009). Two non-randomised studies with concurrent controls (Arrich, 2007; Holzer, 2006) indicate possible benefit of hypothermia following cardiac arrest from other initial rhythms in- and out-of-hospital.

## Statistical summary of critical studies: HACA 2002; Bernard 2002

### Summary of HCASG 2002:

- 3551 assessed 275 enrolled
- Good neurological outcome at 6 months 75/136 [55% in hypo group] vs 54/137 [39%] (RR 1.40, 95% CI 1.08-1.81; Number Needed to Treat = 6)
- Deaths by 6 months 56/137 [41% in hypothermia group] vs 76/138 [55%] (RR 0.74, 95% CI 0.58-0.95; NNT = 7)
- Non-significant trend to more complications in hypothermia group (22% more overall): more pneumonia (NNH = 12), bleeding (NNH = 14) and sepsis (NNH = 16).

### Summary of Bernard 2002:

- Unknown number assessed, 77 enrolled
- Good neurological outcome at discharge 21/43 [49%] vs 9/34 [26%]
  - (OR 2.7 [1.0-7.0]; NNT 4.5 [2.3 - 76]; Chi square P=0.046; FE, P=0.061)
- Mortality 22/43 [51% in hypo group] vs 23/34 [68%]
  - (Chisq P=0.145) (NNT = 6)

### How to cool?

Cooling should be initiated as soon as possible after return of spontaneous circulation (Wolff, 2008), but appears successful even if it is delayed (e.g., 4-6 hours). Cooling should be to 32-34°C for 24 hours, and rewarming should be passive over at about 0.25°C h⁻¹. The practical approach of therapeutic hypothermia can be divided into three parts: induction, maintenance, and rewarming. Induction can be induced easily and inexpensively with intravenous ice-cold fluids (30 ml/kg of saline 0.9% or Ringer’s lactate)
In the maintenance phase, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferred. This is best achieved with external or internal cooling devices that include continuous temperature feedback to achieve a set target temperature (Hoedemaekers, 2007). Typical external devices are cooling blankets (Gal, 2009) or pads with water-filled circulating systems (Haugk, 2007; Heard, 2010). Typical internal cooling devices include intravascular cooling catheters (Al-Senani, 2004; Pichon, 2007), placed usually in the femoral or subclavian veins. However, less sophisticated methods such as cold wet, blankets on the torso and around the extremities, or icepacks, combined with ice cold fluids, can also be effective; however, these methods may be more time consuming for nursing staff, may result in greater temperature fluctuations, and do not enable controlled rewarming (Merchant, 2006). Ice cold fluids alone cannot be used to maintain hypothermia (Kliegel, 2007), but even the addition of simple ice packs may control the temperature adequately (Larsson, 2010).

The rewarming phase can be achieved with either external or internal cooling devices (if these are used), or with other heating systems. The optimal rate of rewarming is not known, but the consensus is currently about 0.25-0.5 ºC of warming per hour (Arrich, 2007). Particular care should be taken during the cooling and rewarming phases because metabolic rate, plasma electrolyte concentrations and haemodynamics may change rapidly.

If therapeutic hypothermia is not feasible or contraindicated, then, at a minimum, pyrexia must be prevented.

Harm from cooling?
One study (Yanagawa, 1998) reported more pneumonia in a 48-hour hypothermia group and another reported higher levels of inflammatory markers (IL-6) and bacterial colonization with hypothermia compared with controls (Fries, 2009).

REVIEWER’S CONFLICTS OF INTEREST:

Peter Morley - Intensive Care Specialist/Internist/Anesthesiologist. No intellectual or commercial conflicts. Reimbursed consultant for E3 position with ILCOR/AHA. No other conflicts.
Jerry Nolan - Consultant in Anaesthesia and Critical Care Medicine. Co-chair ILCOR, Chair Resuscitation Council (UK) and member of the Executive Committee of the ERC. No other conflicts.

Acknowledgements:
Nil
Citation List


Level 4, poor, neutral. Case series of 20 patients cooled on ITU – no outcome data but full paper not reviewed (German)


Level 4 study, neutral. Intravascular cooling with this device resulted in very tight control of body temperature.


Level 2 Study, poor, supportive. Patients entered on to cardiac arrest registry run by Alsius and ERC. A few centres contributed most patients. Most of those cooled were cooled endovascularly. Controls not matched and significant baseline differences (e.g. far more in-hospital, non-cardiac aetiology arrests in normothermic group. Survival to discharge hypothermia 267 (57%) versus normothermia 39 (52%) but impossible to draw conclusions because of selection bias. 16 patients who were cooled in the PEA/Asystole group survived with a CPC of > 2. All those with PEA/asystole in the normothermia group who survived had a favourable CPC.


LOE 1, good, supportive (survival, neurology). Meta-analysis of RCTs. Search to Jan 2007. Included Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005 (no hypothermia group by itself; only combined with haemofiltration); Mori 2000 (abstract only). Results :
- Survival: Conventional cooling without extracorporal methods (survival to discharge) N = 383. Risk Ratio (M-H, Fixed, 95% CI) 1.35 [1.10, 1.65]
- Good neurological outcome: Conventional cooling without extracorporal methods: N = 383. Risk Ratio (M-H, Fixed, 95% CI) 1.55 [1.22, 1.96]
- No significant differences between groups for adverse effects.


Level 3 study, fair, supportive. 76 patients after OHCA from VF. 8 moribund patients excluded from the analysis (4 in control and 4 in hypothermia group) – validity of this? Survival to discharge: historical 13/36 (36%) versus hypothermia 18/32 (56%) P = 0.04. Neurological status at least 1 year after discharge was good (GOS 5) in 6/13 in historical versus 13/18 in hypothermia group (P=0.02)

No abstract available.
Level 2. Poor. Neutral (underpowered).
27 in-hospital arrests at Johns Hopkins University (Baltimore), excluded 2 failed resuscitations and 6 good neurological outcome. 19 patients with neurological insult after successful resuscitation (internal cardiac massage) were either cooled or not. Concurrent controls. Not randomised. 12 cooled to 30-32°C within 1 to 6 hours (for 3hrs to 8 days). 7 not cooled. Survival in 1/7 vs 6/12 (FE, P=0.17). Included all four cases reported in Williams and Spencer Ann Surg 1958.


Prospective interventional study of hypothermia using retrospective controls, single centre, Melbourne Australia. Consecutive patients comatose on arrival at ED, after out-of-hospital cardiac arrest (but not hypotensive despite dopamine/adrenaline, other causes of coma, <16 years or possibly pregnant). Surface cooled with ice packs and paralysed, maintained at 33°C for 12 hours then actively rewarmed over 6 hours. Goals of PaCO2 of 40 mmHg, MAP 90-100, lidocaine if VF. 22 consecutive historical controls, same inclusion and exclusion criteria. Similar groups (17/22 in each group initially VF)). Similar protocols for therapy and
withdrawal. Better good Glasgow Outcome Coma Scale (1 or 2: 11/22 [50%] vs 3/22 [14%], FE P=0.02) and mortality (10/22 [45%] vs 17/22 [77%], Chi square P = 0.03; FE P=0.06). No increased bleeding, sepsis, coagulopathy, thrombocytopenia.


Level 2, supportive (intact neurology), neutral (mortality). Fair. Underpowered, stopped early, unadjusted P value, not randomised, randomisation not blinded, treatment (incl. withdrawal) not blinded, ? other treatment not same [admitted] (eg. paralysis), no control for baseline differences. Positive (discharge destination) Multicentre study of out-of-hospital cardiac arrest in Melbourne Australia. Patients in VF at arrival of ambulance, ROSC and persistent coma, but not age < 18 (men) or < 50 (women, as ? pregnant), hypotension (SBP < 90 despite epinephrine infusion), or other causes of coma. Allocated according to day of month (ie. not randomised, not blinded; but ? authors "not aware of eligible patients who were not included in the outcome analysis"). 84 eligible over 33 months, 7 excluded. Standard management included midazolam and vecuronium, temperature corrected CO2 of 40, MAP 90-100 (with epinephrine or GTN), lignocaine infusion and glucose < 10 mmol/L.

Normothermia passively rewarmed to target of 37°C, sedated and paralysed as needed. Hypothermia group had clothing removed, and ice-packs to head and torso (paramedics), then sedated and paralysed as needed to prevent shivering; target temperature 33°C for 12 hours after hospital arrival then actively rewarmed over 6 hours. Treatment group obvious to treating physicians; 2/3 to 3/4 received PA catheters; most deaths as a result of withdrawal of therapy. Outcome assessment (by specialist "unaware" of treatment group) = death or discharge destination (home/rehab facility vs nursing home/death in hospital). Power analysis based on retrospective data (14% to 50%; p<0.05, power 80%; 31 in each group), but study continued because of trend until positive! More discharged home/rehab with hypothermia (26% vs 49%, OR 2.7 [1.0-7.0]; NNT 4.5 [2.3 - 76]; Chi square P=0.046; FE, P=0.061. Not adjusted for repeat/multiple looks.) Power calculations on 26% and 49% give 70 in each group!!! Adjusted for baseline differences (in age and time collapse to ROSC) OR for good outcome 5.25 [1.5 to 18.8; p=0.011). No adjustment made for differences in bystander CPR (71% in normo vs 49%) and male sex (71% in normo vs 49%). Difference in home discharge not significant. No mortality difference (hypo 22/43 [51%] vs 23/34 [68%], ChiSq P=0.145; NNT=6.1). Decreased pulse rate and increased SVR, but no effects on white cells, platelets of obvious sepsis.


Level 4, neutral. Fair. Used 30 mL/kg cold fluids (4C) to decrease core temperature.


Level 3, neutral, poor. Very small retrospective study of cardiac arrests secondary to hanging.


Level 3, supportive, fair. Better neurological function at discharge but no difference when assessed at 30 months. No significant differences were found in long-term survival (57% vs. 56% alive at 30 months), MMSE, or SF-36.


Level 3, supportive (hospital discharge), neutral (neurological outcome), fair. Historical controls. Survival to discharge 11/34 (32%) versus 16/27 (59%) P = 0.036; CPC 1 or 2 = 9/34 (26%) versus 11/27 (41%) P =0.21


Level 3, supportive (neurological outcome), neutral (hospital discharge), poor. Retrospective control and study groups. No significant difference in survival to discharge but better neurological outcome at 6 months in cooled group.
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.

Level 1. Poor. Adds nothing further to the Holzer meta-analysis. The only other study that was included (Mori K, Takeyama Y, Itoh Y, et al. Multivariate analysis of prognostic factors in survivors of out-of-hospital cardiac arrest with brain hypothermia therapy. Crit Care Med 2000;28:A168.) was an abstract that has not been published in full.


Level 4, good, neutral. 36/43 (84%) of survivors that were assessed were CPC 1, but 37/43 had a mild cognitive deficit.


Level 4, good, neutral. Although this is a level 1 study, both groups were cooled – the CoQ10 was randomly assigned. Therefore included as case series. Hypothermia target range was 35-36°C.


Level 2, Neutral (outcome E: S-100), poor. Prospective, observational study. Physicians decided whether or not to cool.


Level 2, fair, neutral. Retrospective study, but concurrent controls. Although unadjusted mortality was higher in the hypothermia group, the outcomes were not significantly different when adjusted for multiple confounders. Relatively rare paediatric data on this topic.


Level 3, fair, supportive (overall for hospital discharge and neurological outcome [all rhythms combined; only univariate analysis reported] Subsequent analysis: VF supportive for neurological outcome (multivariate) but neutral for non-VF.


Level 4, neutral. Feasibility study.
Safety and feasibility study from Houston, Texas. Out-of-hospital cardiac arrest, with ROSC ≥ 90 within 60 min, 18-85, GCS ≤8, but not cardiac instability, ongoing myocardial ischemia, sepsis, need for vasoactive drugs, coagulopathy or thrombocytopenia, QTc > 470 msec. 9 patients enrolled in 15 months. Sedated (propofol) and paralysed, cooled to 33°C for 24 hours, then rewarmed at 1°C every 4 hours. Cooled with cooling blankets and ice packs (axillae, groin) and iced saline gastric lavage. ACLS to initiation of hypothermia 78 (40 to 109 min). Time to goal temp 391 min (167 to 770), 301 (90 to 690) min after initiation (goal was 120 minutes!). Rewarmed quicker than expected 645 min (330-990), and all overshoot (≥38°C). Survival in 4/9; pneumonia occurred in 5/9, but coagulopathy in only 1/9. Only 28/110 OOH cardiac arrests had ROSC, and only 9/28 ROSC enrolled (13 not eligible, 6 eligible but not enrolled).


Level 4, fair, neutral. Cooling attempted in all patients. This is actually a study comparing surface cooling with endovascular cooling. The outcome is neutral for the question. However, very few of the historical group reached target temperature (mean core temp = 36.1°C).


Level 4, poor, neutral. Neutral for clinical question but another study indicating better temperature control with endovascular cooling.

Level 2, neutral (survival, neurology), opposing (E = bacterial colonization), poor. Physicians chose whether to cool or not. IL-6 and bacterial colonization higher in cooled group but trend to reduced mortality 74% versus 53% (P = 0.053)


Level 4, neutral, fair. Full paper not studied.


Level 3, fair, neutral. Combination of early goal directed therapy and hypothermia, therefore difficult to tease out the impact of TH alone.


Level 1 (small study). Poor, neutral (survival), supportive (E =lactate, O2 extraction, CvO2).
"Feasibility" trial from Brussels. Patients who achieved ROSC after asystole or PEA (presumed cardiac origin), > 18 yrs, tympanic T>30°C on admission to ER, GCS < 7, not pregnant, no known coagulopathy, no CNS depressant drugs, haemodynamically stable (MAP>60, SBP>100). All PaCO2 40-45 mmHg, MAP >60, no glucose solutions, 30° head up, paralysed with pancuronium. Blindly randomised. Hypothermic group had refrigerated helmet device (-4°C; Frigicap), replaced hourly until bladder temperature 34°C or 4 hrs reached. 30 consecutive patients included (unable to exclude any significant baseline differences between groups). Able to cool tympanic to 34°C in median 60 min (15-240 min), and bladder in 180 (70-240 min). After 4 hours (presumably not blinded assessor and treating doctor not blinded), hypothermia group had significantly higher CvO2, with a lower O2 extraction ratio, and a lower arterial lactate (P<0.05). 13/16 hypothermia died, vs 13/14 normothermia (P = NS).


Level 2 (concurrent controls), fair, neutral (survival, neurology). Trend towards better neurological outcome in control group.


Level 4, fair, neutral. A feasibility study using the Artic Sun system.


Level 1 study. Good, supportive. Positive neurological outcome.
Randomised controlled multicentre European study with blinded assessment of outcome. Consecutive cases considered for inclusion if initial VF/pulseless VT with witnessed, presumed cardiac cause, collapse-EMS resuscitation attempt time 5-15 min, ROSC within 60 min of collapse, no subsequent prolonged hypotension or hypoxia before cooling, temperature not <30°C on admission, or pre-existing malignancy/pregnancy/coma/CNS depression with drugs/known coagulopathy. Family informed about trial, but no withdrawals. Random numbers, blocks of 10, stratified by centre, sealed envelope. Treating personnel not blinded, neurologic assessors "unaware". All sedated and paralysed (midazolam & fentanyl infusions, and pancuronium boluses) for 32 hours. Cooling group used special mattress/blanket delivering cold air to reach 32-34°C (bladder) within 4 hours and maintained for 24 hours then passively rewarming. Control group had "normothermia" maintained.
3551 patients assessed, 275 enrolled (137 hypo, 138 normothermia). No sample size calculation. All included in mortality. One in each group lost to follow up (ie. neurology). Baseline: more in normothermia group with diabetes (26/138 19% vs 11/135 8% Chi2=0.01) and coronary heart disease (59/138 43% vs 43/135 32% Chi2 = 0.05). Cooling achieved in 8 hrs (IQR 4-16); 19 not reached desired temperature, 70% required ice packs; maintained for 24 hours (IQR 12-29). Control group temperature high (37-38°C for 40 hours).
Pittsburgh Cerebral Performance Category assessed at 6 months: more favorable in hypothermia (75/136 55% vs 54/137 39%; RR 1.40 [1.08-1.81], p=0.009). Adjusted for all of table 1 (1.47 [1.09-1.82]), but decreased (not shown) by adjust for diabetes, coronary disease and bystander BLS. NNT = 6 [4-25].

Deaths by 6 months more favorable in hypothermia (56/137 41% vs 76/138 55%; RR 0.74 [0.58-0.95], p=0.02). NNT = 7 [4-33]. Adjusted RR similar.

Complications occurred 22% more in Hypothermia group (NS), with more pneumonia (37 vs 29%, NS, NNH 12), and bleeding (26 vs 19%, NS, NNH 14) and nearly twice as much sepsis (13 vs 7%, p=0.08, NNH 16)


Level 4, neutral for the question, fair. This is an RCT comparing Arctic Sun with standard external cooling. Essentially, no difference in proportion of patients reaching target temperature by 4 h.


Level 4 study, poor, neutral. Case series but because only 100/139 sets of notes were available (typical of the UK) we have no idea how many were cooled overall!!


Level 4, poor, neutral. A study comparing cooling techniques – randomly assigned to technique. No survival data. Endovascular cooling enabled tighter temperature control.


Level 1, fair, supportive. Meta-analysis using individual patient data from HACA, Bernard and Hachimi-Idrissi. NNT for favourable outcome (95% CI) was 4-13.


Level 2, fair, supportive. Concurrent controls but strong possibility of selection of bias although statistical methods used in attempt to adjust for baseline differences. Odds ratio for survival 1.96 (1.19 -3.23) after adjustment for baseline differences. No differences in complication between frequency-matched groups except for more bradycardia in cooled group.


Level 4, good, supportive. 50 patients cooled after OHCA from VF. 72% had PCI and 46% had IABP. At 6 months 41/50 (82%) survival and 34/50 (78%) = CPC 1 or 2.


Level 4, neutral, fair. Retrospective study showing no change in respiratory function after infusion of 3500 ml of ice cold fluid.


Level 4, neutral, fair – indicating influence of body composition on ability to cool.

Level 4, neutral, poor. Pilot showing feasibility of prehospital cooling with cold fluid.


Level 4, neutral, poor. Small study showing feasibility of prehospital cooling with cold fluid – includes 5 patients from the pilot study from the same group.


Level 4, neutral (mortality and neurology), fair. Small RCT of prehospital cooling. No control of in-hospital cooling (not all patients cooled in hospital, but outcomes not described for these, so unable to compare cooling with no cooling). Includes subjects from previous study??


Level 4, neutral, poor. Simply indicating that hypothermia can be implemented.


Level 4, fair, neutral. Efficacy study of hypothermia induced with cold IV saline.


Level 4, fair, neutral (survival). RCT of prehospital cooling. No control of in-hospital cooling (not all patients cooled in hospital, but outcomes not described sufficiently, so unable to compare cooling with no cooling). “60 of 97 admitted patients (62%) received hospital cooling regardless of field cooling. Our preliminary analyses did not suggest that the effect of field cooling on outcomes was either confounded or modified by hospital cooling, although these questions need to be addressed in larger studies”. “When we adjusted for the effects of hospital cooling, the odds ratio for survival to hospital discharge for the field cooling group increased slightly from 1.25 to 1.38 (95% CI, 0.58 to 3.29)”. Prehospital cooling successfully reduced core temperature but survival to discharge was cooled: 21/63 (33%) versus normothermia 18/62 (29%) NS.


Level 4, fair, neutral. Feasibility study of IV fluid for cooling.


Level 4, fair, neutral. Case series of cooling technique – ice cold IV fluid to maintain hypothermia. Of all patients, 8 (40%) survived to discharge and 7 (35%) had a favourable neurological outcome (CPC 1 or 2).


Level 3, fair, supportive. 40 patients treated with PCI and hypothermia compared with historical control of 32 patients with primary PCI but no hypothermia. 6-month survival 27/40 (68%) versus 12/32 (38%) P=0.021; CPC 1 or 2 = 21/40 (53%) versus 6/32 (19%) P = 0.007.


Level 1, neutral, good. Cooling did not influence infarct size.

Level 4, neutral, fair. Demonstrates that hypothermia can be achieved with simple techniques.


Level 4, fair, neutral. Shows problems associated with external cooling but neutral for the clinical question.


Level 4, fair, neutral. No real control group (as others were excluded as unstable). Not excluded as not all patients had CPB. Extra-ordinarily aggressive interventions to support circulation and brain preservation after out-of-hospital cardiac arrest in Tokyo. Inclusions age 18-74, witnessed CPR, BLS within 15 min, or VF; no aortic dissection or intracranial haemorrhage, GCS 3-5 on arrival in ED. Resistant VF or after second dose of adrenaline in other rhythms, emergency cardiopulmonary bypass and intra-aortic balloon pump. If ROSC just intra-aortic balloon pump. Then angiography if suspected acute coronary syndrome. When SBP > 90 and GCS 3-5, mild hypothermia induced (direct blood cooling in two stages to 34° [in 6.3±3.4 h], maintained for 2-3 days, and slowly up to 36°C). SBP goal >90 mmHg, sedated and paralysed, mildly anticoagulated. 50 patients treated, 46 had ROSC for more than 1 hour, and hypothermia able to be induced in 23 of these (ie. SBP good enough). Good cerebral performance category in 12/23 (52%) and survival to discharge in 15/23 (65%).

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Level 4, good, supportive. Registry data – no controls. 50% survival and 90% good neurological recovery.


Level 3, fair, supportive for neurological outcome (neutral [underpowered] for hospital discharge) . 55 cooled OHCA patients compared with 54 historical controls. Overall survival to discharge = 28/55 (51%) versus 20/54 (37%) (p=0.15). After VF CPC 1 or 2 = 55.8% versus 25.6% (p=0.004)


Level 4, poor, supportive. Six-month survival data collected by 10 of 19 ICUs: 93/178 (52.5%)


Level 4 and 3 (multiple studies – 6 with retrospective controls), fair, supportive. OR for survival among the 6 LOE 3 studies was 2.5 (1.8 – 3.3).

Level 4, poor, neutral.


Level 4, fair, neutral. This study was actually comparing outcomes of those in cardiogenic shock with those were not (retrospectively analysed) – all patients were cooled. Although there is a control group it was not comparing cooled versus not cooled.


Level 4, fair, neutral.


Level 5, poor, against. Study indicating risk of DVT with intravascular cooling – in head-injured patients –not cardiac arrest.


Level 4, neutral, fair. 18 post cardiac arrest patients cooled – slightly prolonged clotting time, otherwise no significant change in clotting.


Level 3, fair supportive. Historical control group; reduced ITU LOS and improved 1-year survival.


Level 3, fair, supportive. This study compares a package of care (including hypothermia) with historical controls. 77% of the study group were cooled. Survival to discharge with CPC 1 or 2 = 34/61 (56%) versus 15/58 (26%); (OR 3.61, CI 1.66-7.84, p=0.001).


Level 1 study, good, supportive – NSE was reduced in the hypothermia group. Neutral for neurologically intact survival. Patients from the HACA trial. At 6 months, good neurological outcome was achieved in 69% (25/36) of hypothermia-treated patients (CPC 1, 22; CPC 2, 3) and in 47% (16/34) of normothermia-treated patients (CPC 1, 11; CPC 2, 5) (FE = 0.089)


Level 1, good, neutral. Same cohort as the paper from the same group above. No significant differences reflecting small groups.


Level 1, neutral (neurology), good. Subset of the HACA study. Only minor arrhythmias in cooled group (not considered clinically significant: ie. not “opposing”).


Level 4, fair, neutral. Feasibility trial for out-of-hospital use of EMCOOLS external cooling system

Level 4, fair, neutral. Feasibility trial for using ice-cold saline to induce hypothermia in the field.


Level 3, poor, neutral. 85 patients from 2003-2005 compared with 1310 patients from 1980-2000. Survival to discharge was 32% versus 36% (NS). CPC 1 or 2 was 85% for current cohort of survivors (CPC 3 = 15%). Same group reported in 1997 a CPC of 1 in 56% of survivors.


Level 4. Case series. poor, supportive. Case report of 4 cases of good neurological outcome after in-hospital cardiac arrest. All had open cardiac massage, 3/4 had fixed dilated pupils, all cooled after ROSC to 30-34°C with water cooled mattress for 24-72 hours. Also level 6 but excluded as great vessel occlusion model (brief report with table). Positive. Mortality. 10 minutes of circulatory arrest in dogs, hypothermia instituted after anoxic injury (18-36 hours of 32-34°C), had better survival 10/12 vs 4/12 controls (FE, P=0.036). "Zimmerman J.McK. and Spencer F.C" to be published. Referred to in Wolfe 1960.


Level 4. Good, supportive. Case series of 49 patients all cooled endovascularly – the first human data to show that time to target temperature is an independent predictor for good outcome.


Level 3, neutral, fair. Compared PCI with MTH versus PCI only group (historical).


Level 3. Fair, neutral (type II error survival/GOS) to opposing (worse outcome = pneumonia). Prospective study from Tokyo using matched retrospective controls (1995). 13 consecutive patients after cardiopulmonary arrest, not due to trauma/CNS/terminal disease, < 70 and < 0.3 mg(/)kg/min adrenaline. Core temperature (bladder/PA catheter) maintained at 33-34°C for 48 hrs then slowly rewarmed (1°C/day). Cooled with blankets and topical alcohol(!), and sedated/paralysed throughout (CO2 30-40 mmHg; MAP > 70, SBP 90-170; PaO2 100-150; glucose 100-200 mg/dL). No discussion about control group management. Similar causes of arrest (small numbers) and baseline characteristics except more witnessed collapse in control group. Survival to discharge (7/13 vs 5/15) and Glasgow Outcome score at discharge not significantly different (3/13 good vs 1/15). Primary outcome variable not reported (6 month GOS). Significantly more pneumonia in cooling group (11/13 vs 6/15, FE p = 0.024).


Level 4, fair, neutral. Safe and feasible. Case series (pilot study) from Austria of 27 patients (April 95 - Jan 96) with out-of-hospital cardiac arrest. Consecutive cases (with multiplicity of exclusions; only 31 of 153 eligible, and 4 subsequently excluded): initial VF with, witnessed, non-traumatic, no-flow time 5-15 min, ROSC within 60 min, no subsequent prolonged hypotension or hypoxia before cooling, or malignancy/pregnancy/unfavorable CPC/OPC before, additional arrest within 6 months. Managed with standard protocols except for cooling (with blankets and cold air) on arrival in ED to 33±1°C (typanic then PA catheter) for 24 hours (then passive rewarming with midazolam/fentanyl/pancuronium infusions. No complications (renal failure, sepsis, coagulopathy, neutropenia, thrombocytopenia, frostbite). 6 month neurologic outcome Cerebral Performance Category of 1/2 (good) in 14/27, poor in 2/27,
and 11/27 died. Demonstrated safe and feasible. Passing reference to historic outcomes (2-fold improvement in outcome) but no true control group (ie. Level 4 not 3).


Level 1 study, fair, neutral, but used the patients from the HACA study.