WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)
Peter Morley, Jerry Nolan

Date Submitted for review: 4 April 2006

Clinical question.
Does the use of induced hypothermia (I) improve survival (O) in patients after cardiac arrest (P)?

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” as MESH (headings) AND “Hypothermia” textword in abstract.
EMBASE search using text words (all fields) hypothermia AND (cardiac arrest OR resuscitation)
AHA EndNote Master library, Cochrane database for systematic reviews, Central Register of Controlled Trials, Review of references from articles.
Forward search using SCOPUS and Google scholar.

State inclusion and exclusion criteria
The following studies were excluded: Not true cardiac arrest models (eg. exsanguinations, great vessel occlusion [x], carotid artery occlusion [y]), pre-arrest [z] or during arrest cooling [a], resuscitation with cardiopulmonary bypass instead of CPR [b], reports of single cases.

Number of articles/sources meeting criteria for further review:
28 studies met criteria for further review. Of these 5 were LOE 1 (RCTs), two LOE 2 (non-randomised, concurrent controls), two LOE 3 (retrospective controls), eight LOE 4 (no controls), and eleven LOE 5 (not directly related; all animal studies).

Summary of evidence

Evidence Supporting Clinical Question

<table>
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<tr>
<th>Good</th>
<th>Hypothermia After Cardiac Arrest Study Group, 2002 CD*</th>
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<td>Agnew, 2003 DE D'Cruz, 2002 E Horn, 1991 E</td>
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Level of evidence
A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival Italic = Animal studies
* = overlapping patients
### Evidence Neutral to Clinical Question

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|      |      |      | **Hachimi-Idrissi, 2001 (2) DE**  
      |      |      | **Katz, 2004 (1) E**  
      |      |      | **Sterz, 1991 E**  |
|      | Zeiner, 2004 E  
      | Callaway, 2002 E |      | **Katz, 2004 (2) E**  
      |      |      | **Mullan, 1961B**  
      |      |      | **Wolfe, 1960 B**  
      |      |      | **Xiao, 1998 E**  |
|      | Yanagawa, 1998 CDE |      | **Al-Senani, 2004**  
      |      |      | **CDE**  
      |      |      | **Felberg, 2001**  
      |      |      | **Nagao, 2000**  
      |      |      | **Sanada, 1998**  
      |      |      | **Silfvast, 2003**  
      |      |      | **Zeiner, 2000**  |

#### Level of evidence

A = Return of spontaneous circulation  
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### Evidence Opposing Clinical Question

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DISCUSSION: Initial human case series and human studies were promising but not continued. Subsequent animal studies involved complex combinations of induction of arrest models, and attempts to resuscitate, followed by a variety of techniques to induce hypothermia for a variable period of time.

- Animal models were not uniform in their outcomes and almost invariably did not provide a consistently high level of care (e.g., sedation/paralysis/ventilation/ICU care) which would be necessary in a human study. Human studies were initially feasibility in nature, followed by some controlled studies, and finally two landmark prospective multicentre studies.

- The definitive study to date is that performed by the Hypothermia After Cardiac Arrest Study Group which performed a methodologically good prospective randomized study, and confirmed that the induction of hypothermia in comatose survivors of out-of-hospital cardiac arrest due to ventricular fibrillation 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 due to ventricular fibrillation, was statistically underpowered to confirm the measured benefit. 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.

There seems good evidence supporting the use of induced hypothermia in the comatose survivors of out-of-hospital cardiac arrest due to ventricular fibrillation. Cooling should probably be initiated as soon as possible after return of spontaneous circulation, but appears successful even if it is delayed (e.g., 4-6 hours). Cooling should be to 32-34°C for 12 to 24 hours, and rewarming should be passive over at least 6 hours. These techniques should be readily achievable in all Intensive Care Units, where patients are already likely to be ventilated for at least the first 24 to 48 hours unless severely compromised (e.g., brain death, intractable cardiogenic shock). Simple techniques for cooling are being developed and should allow widespread implementation without additional costs. 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:

For other initial rhythms in out of hospital cardiac arrests: Bernard 1997, Level 3 (historical controls)

Statistical summary of critical studies: HACASG 2002; Bernard 2002

Summary of HCASG 2002:
- 3551 assessed 275 enrolled
- Good neurological outcome at 6 months 75/136 [55% in hypothermia 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%]
- (unadjusted Yates corrected P = 0.08) (RR 1.85; 95% CI 0.97-3.49, NNT = 4)
- Mortality 22/43 [51% in hypothermia group] vs 23/34 [68%]
- (unadjusted Yates corrected P = 0.22) (RR 0.7563; 95% CI 0.52-1.10, NNT = 6)

One study (Yanagawa, 1998) reported more pneumonia in a 48-hour hypothermia group.

Continued cooling can be achieved with external or internal methods. Shivering will necessitate intermittent or continuous neuromuscular blockade. Intravascular cooling enables tighter control of core temperature but the impact on neurological outcome of improved temperature control is unknown. Complications of mild therapeutic hypothermia may include increased infection, cardiovascular instability, coagulopathy and hyperglycaemia. Blood glucose concentration requires close monitoring and insulin is likely to be necessary to maintain normoglycaemia. Rewarming should be undertaken slowly (0.25-0.5°C h⁻¹) and hyperthermia should be strictly avoided. The optimum target temperature, rate of cooling, duration of hypothermia, and rate of rewarming have yet to be determined; further studies are essential.

Conclusion
CONSENSUS ON SCIENCE:
Evidence from one good randomized trial (LOE 1) and supportive evidence from four other human studies (LOE 2 to 4) demonstrate improvement in neurological outcome after discharge from hospital in patients who had experienced an out-of-hospital cardiac arrest. The supportive data from the higher level studies (LOE 1 and 2) came from out-of-hospital cardiac arrests where the initial rhythm was ventricular fibrillation, patients were still comatose, and who were cooled within minutes to hours after return of spontaneous circulation to 32-34°C for 12-24 hours. A number of different cooling techniques have been shown to effectively decrease the core body temperature.

TREATMENT RECOMMENDATION:
Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hrs when the initial rhythm was ventricular fibrillation (VF).
Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest as a result of any other rhythm, or cardiac arrest in hospital, cooling to 32-34°C for 12-24 hrs may also be beneficial.
Cooling should be started as soon as possible.
Rapid infusion of 30 ml kg⁻¹ of 4°C saline is a simple method of achieving a decrease in core temperature of approximately 1.5°C.

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, several original publications in the field of anaesthesia, trauma and resuscitation. Cochair ILCOR, Chair ALS Committee RC (UK) and member of the Executive committee of the ERC. No other conflicts.

Acknowledgements:
Nil
Citation List

Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard trade mark System and Icy trade mark catheter following cardiac arrest. Resuscitation 2004; 62: 143-50. Background: Cardiac arrest causes devastating neurological morbidity and mortality. Mild/moderate hypothermia is neuroprotective after global cerebral ischemia. More rapid controlled attainment of the target temperature may increase efficacy. Methods: We assessed the safety and feasibility of endovascular cooling in a single arm study of comatose patients who had been successfully resuscitated after cardiac arrest. Core temperature was reduced to a target of 33 degrees C for 24h using a closed loop endovascular system placed in the inferior vena cava, followed by controlled rewarming. Primary outcomes were speed and accuracy of cooling, survival and GOS after 30 days. Results: Thirteen patients were enrolled, six male, age [Formula: see text] years. Time from cardiac arrest to return of spontaneous circulation was 14.3min (range 5-32.5). It took 3h and 39min (median 210min, IQ 80-315) to reach 33 degrees C; cooling averaged [Formula: see text] degrees C/h (range 0.22-1.12 degrees C/h). Temperature was tightly maintained for all patients averaging [Formula: see text] degrees C. Rewarming lasted [Formula: see text] h. Five patients (38%) had 30-day Glasgow Outcome Scores of 1-2. Four patients died, none related to the hypothermia procedure. No unanticipated or procedure-related adverse events occurred. Conclusion: In comatose survivors of cardiac arrest, hypothermia via endovascular methods is safe and feasible, and target temperatures can be achieved and controlled rapidly and precisely. More studies are needed to assess the efficacy of rapid endovascular hypothermia after cardiac arrest. Level 4 study, neutral. Intravascular cooling with this device resulted in very tight control of body temperature.

Agnew DM, Koehler RC, Guerguerian AM, et al. Hypothermia for 24 hours after asphyxial cardiac arrest in piglets provides striatal neuroprotection that is sustained 10 days after rewarming. Pediatr Res 2003; 54:253-62. The neuroprotective effect of hypothermia instituted after resuscitation from asphyxial cardiac arrest has not been studied in immature brain, particularly in a large animal model with recovery periods greater than 4 d. Moreover, protection from severe hypoxia seen with 3h of hypothermia was reported to be lost when hypothermic duration was extended to 24 h in unsedated piglets, in contrast to the neuroprotection reported by 72 h of intrauterine cooling in fetal sheep. Piglets (5-7 postnatal days) were subjected to asphyxial cardiac arrest followed by 24 h of either hypothermia (34 degrees C) or normothermia (38.5-39 degrees C). Comparisons were made with normothermic and hypothermic surgical sham animals without asphyxia. All of these groups were sedated, paralyzed, and mechanically ventilated for the first 24 h to prevent shivering and possible depletion of glucose stores. Hypothermia per se did not cause remarkable structural abnormalities. Ischemic damage was evaluated in putamen at 1 d of recovery without rewarming and at 11 d (10 d +/- SD after rewarming). Ischemic cytopathology affected 60 +/- 12% of neurons in putamen of normothermic animals compared with 9 +/- 6% in hypothermic animals at 1 d of recovery without rewarming. At 11 d of recovery from hypoxia-ischemia, the density of viable neurons (neuron profiles/mm2) in putamen was markedly reduced in normothermic animals (81 +/- 40) compared with hypothermic animals (287 +/- 46), which was the same as in sham normothermic (271 +/- 21), sham hypothermic (288 +/- 46) and naive animals (307 +/- 51). These data demonstrate that 24 h of hypothermia at 34 degrees C with sedation and muscle relaxation after asphyxial cardiac arrest prevents necrotic striatal neuronal cell death in immature brain before rewarming, and that the effect is sustained at 11 d after injury without deleterious side effects. Level 5 (animals), supportive. Fair (not randomized).


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%], FE P=0.06). No increased bleeding, sepsis, coagulopathy, thrombocytopenia.

BACKGROUND: Cardiac arrest outside the hospital is common and has a poor outcome. Studies in laboratory animals suggest that hypothermia induced shortly after the restoration of spontaneous circulation may improve neurologic outcome, but there have been no conclusive studies in humans. In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest. METHODS: The study subjects were 77 patients who were randomly assigned to treatment with hypothermia (with the core body temperature reduced to 33 degrees C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility. RESULTS: The demographic characteristics of the patients were similar in the hypothermia and normothermia groups. Twenty-one of the 43 patients treated with hypothermia (49 percent) survived and had a good outcome—that is, they were discharged home or to a rehabilitation facility—as compared with 9 of the 34 treated with normothermia (26 percent, P=0.046). After adjustment for baseline differences in age and time from collapse to the return of spontaneous circulation, the odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011). Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia. There was no difference in the frequency of adverse events. CONCLUSIONS: Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest.

Level 2, supportive. 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 < 30 (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], Rel Risk and Rel Risk Red overlap 0; NNT 4.5 [2.3 - 76]; Chi square P=0.046; FE, P=0.061. Not adjusted from repeat/multiple looks.) Power calculations on 26% and 49% give 70 in each group!!! Adjusted for baseline differences (in age and time from 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.


STUDY HYPOTHESIS: Recent studies have shown that induced hypothermia for twelve to twenty four hours improves outcome in patients who are resuscitated from out-of-hospital cardiac arrest. These studies used surface cooling, but this technique provided for relatively slow decreases in core temperature. Results from animal models suggest that further improvements in outcome may be possible if hypothermia is induced earlier after resuscitation from cardiac arrest. We hypothesized that a rapid infusion of large volume (30 ml/kg), ice-cold (4 degrees C) intravenous fluid would be a safe, rapid and inexpensive technique to induce mild hypothermia in comatose survivors of out-of-hospital cardiac arrest. METHODS: We enrolled 22 patients who were comatose following resuscitation from out-of-hospital cardiac arrest. After initial evaluation in the Emergency Department (ED), a large volume (30 ml/kg) of ice-cold (4 degrees C) lactated Ringers solution was infused intravenously over 30 min. Data on vital signs, arterial blood gas, electrolyte and hematological was collected immediately before and after the infusion. RESULTS: The rapid infusion of large volume, ice-cold crystalloid fluid resulted in a significant decrease in median core temperature from 35.5 to 33.8 degrees C. There were also significant improvements in mean arterial blood pressure, renal function and acid-base analysis. No patient developed pulmonary edema. CONCLUSION: A rapid infusion of large volume, ice-cold crystalloid fluid is an inexpensive and effective method of inducing mild hypothermia in comatose survivors of out-of-hospital cardiac arrest, and is associated with beneficial haemodynamic, renal and acid-base effects. Further studies of this technique are warranted.

Level 5, supportive. Fair. Used 30 mL/kg cold fluids (4C) to decrease core temperature.


Hypothermia during brain ischemia can improve neurological outcome. This study tested whether local cranial cooling during the low-flow state of cardiopulmonary resuscitation (CPR) could produce clinically significant cerebral cooling. Ice was applied...
to the heads and necks of subjects (hypothermia group) with out-of-hospital cardiac arrest (OOHCA) during CPR. Nasopharyngeal and tympanic temperatures were measured as surrogates for cerebral temperature. The rate of cranial cooling in the hypothermia group (-0.06 0.06 °C/min) was not significantly increased compared with a control group without ice (-0.04 0.07 °C/min), although older age was associated with more rapid cranial cooling. Of note, many subjects with OOHCA are already mildly hypothermic (mean cranial temperature=35.0 1.2 °C) when they are first encountered in the field. This study suggests that brief cranial cooling is ineffective for rapidly lowering brain temperature. However, most cardiac arrest victims are spontaneously mildly hypothermic and preventing rewarming may provide some of the desired benefits of cerebral hypothermia. 

Level 1. Fair. Neutral (for temperature change).

Small study from Pittsburgh. 2 convenience samples: 17 observed temperatures (started at 35°C), 27 randomised (with 5 exclusions) to ice bags (0°C) to head/neck or usual care. Many differences between groups but no evidence of increased cooling in ice bag group (able to exclude cranial cooling >0.089°C/min).


Induction of mild hypothermia improves neurologic outcome after global cerebral ischemia. This study measured levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in hippocampal tissue of rats after resuscitation from 8 minutes of normothermic, asphyxial cardiac arrest. After resuscitation, rats were maintained either at normal temperature (37 degrees C) or cooled to mild hypothermia (33 degrees C, beginning 60 minutes after resuscitation). After 12 or 24 hours, neurotrophin levels in hippocampus were measured by immunoblotting. Ischemia and reperfusion increased hippocampal levels of BDNF. Induction of hypothermia during reperfusion potentiated the increase in BDNF after 24 hours, but not after 12 hours. Levels of NGF were not increased by postresuscitation hypothermia. Hypothermia also increased tissue levels and tyrosine phosphorylation of TrkB, the receptor for BDNF. Increased BDNF levels were correlated with activation of the extracellularly regulated kinase (ERK), a downstream element in the signal transduction cascade induced by BDNF. In contrast to the many deleterious processes during ischemia and reperfusion that are inhibited by induced hypothermia, increasing BDNF levels is a potentially restorative process that is augmented. Increased activation of BDNF signaling is a possible mechanism by which mild hypothermia is able to reduce the neuronal damage typically occurring after cardiac arrest.

Level 5 (animals). Fair (not all randomized). Supportive for biochemical markers.

Pittsburgh study in anesthetised then paralysed instrumented (incl. cerebral temperature probe) rats who had ETT disconnected (arrest within 180 sec). After 8 min reventilated (60/min, previously 40/min * 9 mL/kg), intravenous epinephrine (5 mcg/kg) and bicarbonate (1mEq/kg), chest compressions 200/min. All had ROSC in 2 minutes, stabilised for 60 min then extubated (not ventilated) and weaned to room air! Hypothermia group cooled (with cooling fan) to 33°C beginning at 50 min after reperfusion (held at 37°C until this), and maintained until sacrifice (up to 24 hours). Normothermia group maintained at 37°C (computer controlled heating lamp). Hypothermia group had significantly higher uncorrected CO2 (57±4 vs 44±5 mmHg at 60 min; repeated measures ANOVA, P<0.05). Hypothermia group had higher (better) levels of neurotrophic factors at 24 hours (not 12): Brain-Derived Neurotrophic Factor, Tyrosine receptor kinase (TrkB, receptor for BDNF) and Extracellularly Regulated Kinase (ERK, downstream to BDNF cascade).


BACKGROUND: No proven neuroprotective treatment exists for ischemic brain injury after cardiac arrest. Mild-to-moderate induced hypothermia (MIH) is effective in animal models. METHODS AND RESULTS: A safety and feasibility trial was designed to evaluate mild-to-moderate induced hypothermia by use of external cooling blankets after cardiac arrest. Inclusion criteria were return of spontaneous circulation within 60 minutes of advanced cardiac life support, hypothermia initiated within 90 minutes, persistent coma, and lack of acute myocardial infarction or unstable dysrhythmia. Hypothermia to 33 degrees C was maintained for 24 hours followed by passive rewarming. Nine patients were prospectively enrolled. Mean time from advanced cardiac life support to return of spontaneous circulation was 11 minutes (range 3 to 30); advanced cardiac life support to initiation of hypothermia was 78 minutes (range 40 to 109); achieving 33 degrees C took 301 minutes (range 90 to 690). Three patients completely recovered, and 1 had partial neurological recovery. One patient developed unstable cardiac dysrhythmia. No other unexpected complications occurred. CONCLUSIONS: Mild-to-moderate induced hypothermia after cardiac arrest is feasible and safe. However, external cooling is slow and imprecise. Efforts to speed the start of cooling and to improve the cooling process are needed.

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).
Abstract: STUDY OBJECTIVE: To test the feasibility and the speed of a helmet device to achieve the target temperature of 34 degrees C in unconscious after out of hospital cardiac arrest (CA). METHODS: Patients with cardiac arrest due to asystole or pulseless electrical activity (PEA) who remained unconscious after restoration of spontaneous circulation (ROSC) were enrolled in the study and randomised into two groups: a normothermic group (NG) and a hypothermic group (HG). Bladder and tympanic temperature were monitored every 15 min. A helmet device was used to induce mild hypothermia in the HG. Later on, the effect of mild hypothermia on the haemodynamics, electrolytes, lactate, arterial pH, CaO2, CvO2 and O2 extraction ratio were analysed and compared to the values obtained from the NG. RESULTS: Thirty patients were eligible for the study, 16 were randomised into the HG and 14 were randomised into the NG. The median tympanic temperature at admission in both groups was 35.5 degrees C (range: 33.3-38.5 degrees C) and the median tympanic temperature after haemodynamic stabilisation was 35.7 degrees C (range: 33.6-38.2 degrees C). In the HG, the core and the central target temperature of 34 degrees C were achieved after a median time of 180 and 60 min, respectively after ROSC. At the start of the study, no significant differences between the NG and HG were seen. At the end of the study, lactate concentration and O2 extraction ratio were significantly lower in the HG; however the CvO2 was significantly lower in the NG. CONCLUSIONS: Mild hypothermia induced by a helmet device was feasible, easy to perform, inexpensive and effective, with no increase in complications.

Level 1 (small study). Good, supportive. Temperature lowering and physiologic improvements.

"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.

Study objective: we studied the long-term effect of a combined treatment with resuscitative mild hypothermia and induced hypertension on survival rate and neurological outcome after asphyxial cardiac arrest (CA) in rats. Methods: 36 male Wistar rats, were randomised into three groups: Group I (n=10): anaesthetised with halothane and N2O/O2 (70/30%) had vessel cannulation but no asphyxial CA; mechanical ventilation was continued to 1 h. Group II (n=13): under the same anaesthetic conditions and vessel cannulation, was subjected to asphyxial CA of 8 min, reversed by brief external heart massage and followed by mechanical ventilation to 1 h post restoration of spontaneous circulation (ROSC). Group III (n=13): received the same insult and resuscitation as described in group II, but in contrast to the previous group, a combination treatment of hypothermia (34°C) and induced hypertension was started immediately after ROSC and maintained for 60 min ROSC. Survival rate and neurological deficit (ND) scores were determined before arrest, at 2 and 24 h, and each 24 h up to 4 weeks after ROSC. Results: Baseline variables were the same in the three groups. Comparison of the asphyxial CA groups (groups II and III), showed an increased, although not statistically significant, survival rate at 72 h after ROSC in group III, and it became highly significant at 4 weeks after ROSC. The ND scores were the same in both asphyxial CA groups (groups II and III). Conclusions: Resuscitative mild hypothermia and induced hypertension after asphyxial CA in rats is associated with a better survival rate. This beneficial effect persisted for 4 weeks after ROSC.

Level 5 (animals), good (randomized), neutral. No difference in survival (type II) or neurological outcome. Fair study.

Anaesthetised, paralysed, intubated rats had arrest induced by clamping of ETT. Arrest in 3 min, asphyxia for 8 min total. Randomised: Sham asphyxia vs standard CPR and mechanical ventilation for 1 hour vs mild hypothermia (34°C) and induced hypertension (MAP 140 with NaCl and Norad.). Then weaned, extubated and hydrated with bolus subcut. injections saline. Lower glucose, lactate, PaO2 and hematocrit in Group III (hyper/hypot). Higher survival in hypo/hyper at 4 weeks post ROSC (5/13 [38.4%] vs 1/13 [7.6%] "P<0.001" but FE P=0.16 !!). Neurological outcome same in arrest groups.

Abstract: This study examined whether prolonged hypothermia induced 1 hour after resuscitation from asphyxial cardiac arrest would improve neurologic outcome and alter levels of stress-related proteins in rats. Rats were resuscitated from 8 minutes of asphyxia resulting in cardiac arrest. Brain temperature was regulated after resuscitation in three groups: normothermia (36.8 degrees C x 24 hours), immediate hypothermia (33 degrees C x 24 hours, beginning immediately after resuscitation), and delayed hypothermia (33 degrees C x 24 hours, beginning 60 minutes after resuscitation). Mortality and neurobehavioral deficits were improved in immediate and delayed hypothermia rats relative to normothermia rats. Furthermore, both immediate and delayed hypothermia improved neuronal survival in the CA1 region of the hippocampus assessed at 14 days. In normothermia rats, the 70-kDa heat shock protein (Hsp70) and 40-kDa heat shock protein (Hsp40) were increased within 12 hours after resuscitation in the hippocampus. Delayed hypothermia attenuated the increase in Hsp70 levels in the hippocampus but did not affect Hsp70 induction in
the cerebellum. Hippocampal expression of Hsp40 was not affected by hypothermia. These data indicate that prolonged hypothermia during later reperfusion improves neurologic outcome after experimental global ischemia and is associated with selective changes in the pattern of stress-induced protein expression.

Level 5 (animals), good (randomized, in part), supportive. Not ventilated/paralysed/ICU. Positive study (mortality, NDScore, biochemical marker).

Pittsburgh rat arrest model. Paralysed, intubated, instrumented rats disconnected from ventilator for 8 minutes (all had circulatory arrest within 200 seconds). Then re-ventilated (100%, 60/min), epinephrine (5mcg/kg) and bicarbonate (1mEq/kg) and external compressions (200/min). All who ROSC in 2 minutes included, and weaned to extubation.

Experiment 1: Randomly assigned to normothermia (12, maintained at 36.8°C for 24 hrs), immediate hypothermia (8, immediately after resuscitation cooled to 33°C for 24 hours), and delayed hypothermia group (8, kept at 36.8°C for 45 minutes after resuscitation then cooled to 33°C for 24 hours). Both hypothermia groups then rewarmed over 2 hours to 36.8°C. Mortality less in hypothermia groups (0/8 and 0/8 vs 4/12; Mantel-Cox, P<0.05). Neurological Deficit Score measured by blinded observer were improved in hypothermia groups compared to normothermia groups on all 14 days (Kruskall Wallis, P<0.05). Both hypothermia groups had significantly more neurons in the CA1 region of the hippocampus than the normothermia group (at 14 days on histology).

Experiment 2: Same arrest model but 3 rats per group (? non-randomised) normothermia or delayed hypothermia (33°C, 60 min after resuscitation), and assessed at 6, 12, or 24 hours after reperfusion. Delayed hypothermia attenuated the increaese of Heat Shock Protein 70 (Hsp70) in hippocampus (multiple factor ANOVA, P<0.05).

Histological damage after cardiac arrest is less than that observed after vessel occlusion models.

Department of Emergency Medicine, University of Pittsburgh, Pennsylvania, USA.


No abstract available.

Level 5. Fair (not randomized), supportive. German study. 23 supine, tracheotomised, anaesthetised, instrumented adult cats (2-4.25kg). Induced VF, no treatment for 15 min, cpr (incl. bilat thoracic compression) with drugs and defibrillation. With commencement CPR cats stayed normothermic or received external brain cooling (for 30 min, cortex to 20C, eosoph to 30C in cooling device regulated at -25C). NON-RANDOMISED. After ROSC for 20 min, 15 still alive, hyperventilated to CO2 30±5. These animals sacrificed (Gludtardialdehyde) after 4 hrs. Significantly better morphological outcome in 2 of 3 evaluated regions. Impossible to compare groups.


Abstract: BACKGROUND: Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation. METHODS: In this multicenter trial with blinded assessment of the outcome, patients who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32-34°C for 40 hours). As compared with 54 of 137 patients; risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81). Mortality at six months was 41 percent in the hypothermia group (56 of 137 patients died), as compared with 55 percent in the normothermia group (76 of 138 patients; risk ratio, 0.74; 95 percent confidence interval, 0.58 to 0.95). The complication rate did not differ significantly between the two groups. CONCLUSIONS: In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality.

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 hypotherm 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 "normotherma" 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).
OBJECTIVE: External cooling is commonly used to force induction of mild hypothermia but requires equipment, has a slow onset of action, and must be prolonged to provide permanent neurologic benefits after hypoxic-ischemia. It is unknown whether the method for inducing mild hypothermia affects neurologic outcome after near-drowning. The objective of the study was to induce mild hypothermia with neurotensin analog NT77 or external cooling in a rat model of near-drowning. We hypothesize that NT77 would be more effective for improving neurologic outcome than external cooling of the same duration. DESIGN: Rats were randomized to a normothermia control, neurotensin-induced hypothermia, brief external cooling, or prolonged external cooling group after asphyxial cardiac arrest. SETTING: Laboratory investigation. SUBJECTS: Forty-eight rats. INTERVENTIONS: Mild hypothermia was induced by external cooling for 4 hrs (brief external cooling) or 24 hrs (prolonged external cooling) or by neurotensin-induced hypothermia administration 30 mins after asphyxial cardiac arrest in rats. MEASUREMENTS: Outcome was assessed by a neurologic deficit score, the Morris water maze, and CA1 hippocampus histology 15 days after resuscitation. MAIN RESULTS: Neurologic deficit score at 72 hrs after asphyxial cardiac arrest was lower with neurotensin-induced hypothermia (score, 0) and prolonged external cooling (score, 0) vs. normothermic control (score, 20) and brief external cooling (score, 18; p <.05). Latency time in the Morris water maze 15 days after asphyxial cardiac arrest was decreased with neurotensin-induced hypothermia (14+/9 secs) and prolonged external cooling (18+/9 secs) vs. normothermic control (74+/17 secs) and brief external cooling (78+/18 secs, p <.05). There was less ischemic neuronal damage with neurotensin-induced hypothermia (28+/24%) and prolonged external cooling (21+/14%) vs. normothermic control (61+/32%) and brief external cooling (51+/32%). CONCLUSIONS: Neurotensin-induced hypothermia improved neurologic outcome after asphyxial cardiac arrest in rats vs. brief external cooling but was comparable to prolonged external cooling.

Level 5 (animals), good (randomized), neutral. Study of neurotensin analog NT77 but included standard hypothermic group. Hypothermia induced 30 minutes after ROSC. Malondialdehyde levels in the brain were used to assess oxidative stress in each group.

Regulated hypothermia produces a decrease in core temperature by lowering the brain's temperature set-point while maintaining thermoregulation at that lower set point. In contrast, forced hypothermia lowers core temperature by overwhelming the body's capacity to thermoregulate, but does not change the set-point. Regulated hypothermia has been shown to be cerebral protective in hibernating mammals. The effect of regulated hypothermia on the brain during reperfusion from hypoxic-ischemia has not been well studied. We induced regulated hypothermia with a neurotensin analogue (NT77) to determine whether it could reduce oxidative stress in the brain during reperfusion from asphyxial cardiac arrest (ACA) in rats. Mild hypothermia (32-34 degrees C) was induced by brief (4 h) external cooling (BC), NT77 or prolonged external cooling (24 h) (PC) 30 min after resuscitation from 8 min of ACA in rats. Malondialdehyde (MDA) levels in the brain were measured during reperfusion to quantitate oxidative stress. Results: MDA levels in the hippocampus were elevated at 16 h of normothermic reperfusion versus 48 h with BC reperfusion. There was no increase in hippocampal MDA levels in the NT77 and PC groups at 24-72 h of reperfusion. Regulated hypothermia induced by NT77 reduced oxidative stress in the hippocampus during reperfusion from hypoxic-ischemia in comparison to forced brief external cooling of the same duration. In addition, the duration of external cooling after resuscitation also alters oxidative stress in the brain during reperfusion.

Level 5 (animals), fair (not randomized?), neutral. Study of neurotensin analog NT77 but included standard hypothermic group. Hypothermia induced 30 minutes after ROSC.

No abstract available.
Level 5 (animals), fair (not randomized), neutral. Not blinded/treatment protocols??.
"20 anaesthetised dogs were subjected to 6 minutes of acute asphyxia. There was no significant difference between the mortality in the normothermic and hypothermic groups (28-30 C)." Occluded cuffed ETT, apparent cardiac arrest in 100%, open chest cardiac massage. After closure of chest (approx 15 min), either normothermic; or cooled to 28°C by immersion in bath of cold water (for ? duration, and ? allowed to warm over 6-12 hours). No discussion of airway. 7/10 died with normothermia vs 6/10 with hypothermia.

Abstract: OBJECTIVES: The purpose of this study was to evaluate the efficacy of an alternative cardiopulmonary cerebral resuscitation (CPCR) using emergency cardiopulmonary bypass (CPB), coronary reperfusion therapy and mild hypothermia.

BACKGROUND: Good recovery of patients with out-of-hospital cardiac arrest is still inadequate. An alternative therapeutic method for patients who do not respond to conventional CPCR is required. METHODS: A prospective preliminary study was performed in 50 patients with out-of-hospital cardiac arrest meeting the inclusion criteria. Patients were treated with standard CPCR and, if there was no response, by emergency CPB plus intra-aortic balloon pumping. Immediate coronary angiography for coronary reperfusion therapy was performed in patients with suspected acute coronary syndrome. Subsequently, in patients with systolic blood pressure above 90 mm Hg and Glasgow coma scale score of 3 to 5, mild hypothermia (34 °C for at least two days) was induced by coil cooling. Neurologic outcome was assessed by cerebral performance categories at hospital discharge. RESULTS: Thirty-six of the 50 patients were treated with emergency CPB, and 30 of 39 patients who underwent angiography suffered acute coronary artery occlusion. Return of spontaneous circulation and successful coronary reperfusion were achieved in 92% and 87%, respectively. Mild hypothermia could be induced in 23 patients, and 12 (52%) of them showed good recovery. Factors related to a good recovery were cardiac index in hypothermia and the presence of serious complications with hypothermia or CPB. CONCLUSIONS: The alternative CPCR demonstrated an improvement in the incidence of good recovery. Based upon these findings, randomized studies of this hypothermia are needed.

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%).

Department of Emergency and Critical Care Medicine, Nihon University School of Medicine, Tokyo, Japan.


Abstract: We report two patients with out-of-hospital cardiac arrest who recovered after hypothermia therapy. A 25-year-old man and a 16-year-old boy were transferred to our hospital after cardiopulmonary arrest due to idiopathic ventricular fibrillation and hypertrophic cardiomyopathy, respectively. We carried out hypothermia therapy using cooling blankets, and the patients were maintained at 32-33 degrees C for 96 and 36 h, respectively. After slow re-warming, they regained consciousness and recovered. During hypothermia, hypokalemia and arrhythmia occurred. Their arrest times (no spontaneous circulation and no CPR) were 10 min and 8 min, and CPR times (no spontaneous circulation while CPR was being performed) were 24 min and 20 min, respectively. In cases where the duration of ischemia is prolonged, the prognosis is expected to be poor. Therefore, we believe that hypothermia therapy is beneficial for such patients.


Mild resuscitative hypothermia has been shown to improve neurological outcome after cardiac arrest presenting with ventricular fibrillation (VF) due to cardiac causes. We describe the experience of inducing mild hypothermia in three patients with non-cardiac causes of arrest and long delays before a return of spontaneous circulation (ROSC). In one patient, extreme metabolic acidosis due to inadvertent oesophageal intubation complicated therapy, and the role of point-of-care diagnostics in the prehospital setting is briefly discussed. All patients survived to discharge from hospital, and neuropsychological examinations revealed good recovery. It is concluded that mild resuscitative hypothermia may be beneficial also in patients with obvious non-coronary causes for cardiac arrest.

Level 5, fair, neutral.


BACKGROUND AND METHODS: This study was designed to explore the effect of mild cerebral and systemic hypothermia (34 degrees C) on outcome after prolonged cardiac arrest in dogs. After ventricular fibrillation with no flow of 10 min, and standard external CPR with epinephrine (low flow) from ventricular fibrillation time of 10 to 15 min, defibrillation and restoration of spontaneous normotension were between ventricular fibrillation time of 16 and 20 min. This procedure was followed by controlled ventilation to 20 h postarrest and intensive care to 72 h postarrest. In control group 1 (n = 10), core temperature was 37.5 degrees C;
in control group 2 (n = 10), cooling was started immediately after restoration of spontaneous normotension; and in group 3 (n = 10), cooling was initiated with start of CPR. Cooling was by clinically feasible methods. RESULTS: Best overall performance categories achieved (1 = normal; 5 = brain death) were better in group 2 (p = .012) and group 3 (p = .005) than in group 1. Best neurologic deficit scores were 36 +/- 14% in group 1, 22 +/- 15% in group 2 (p = .02), and 19 +/- 18% in group 3 (p = .01). Brain histopathologic damage scores were also lower (better) in groups 2 (p = .05) and 3 (p = .03). Myocardial damage was the same in all three groups. CONCLUSION: Mild cerebral hypothermia started during or immediately after external CPR improves neurologic recovery.


Pittsburgh dog study. 37*8 month old coonhounds (21 kg), anaesthetised, intubated, instrumented, induced VF, waited 10 min, CPR and drugs for 5 min, then defibrillation and ALS as necessary. Received 50 mcg/kg epinephrine (surprisingly all hypertensive after ROSC (MAP>200 in normo and delayed hypo groups)) and 2 mmol/kg bicarbonate! Randomised (presumably not concealed as 10/10/10 in final groups) to 3 groups: maintained at 37.5°C, maintained at 37.5 until ROSC then cooled to core 34°C, cooled to 34°C with start of CPR. Aggressive cooling with head in ice water (4°C), IV saline (4°C) nasal and gastric irrigation (4°C saline). Excluded if took > 5 min to ROSC (6) and prolonged ventilation (1). Sedated (protocol plus PRN by unblinded) and paralysed (weaned over 24 hours, no mention of CO2 control or target in ICU, 18 hours of neurotoxic 50% N2O). Assessed neurological status every 8 hrs (by 3 unblinded assessors) from 24 to 72 hours (one blinded observer added at 72 hours only). Pathology of brain by blinded observer (at 72 hours). No difference in good cerebral outcome (best OPC 1 or 2: 1/10 normo, 5/10 delayed hypo; FE P=0.14). Better "best Overall Performance Categories", better neurologic deficit scores and better histopathological damage scores in either of hypothermic groups (vs control). Many limitations = fair study only methodologically.


BACKGROUND AND PURPOSE: High serum levels of neuron-specific enolase (NSE) and S-100B protein are known to be associated with ischemic brain injury and poor outcome after cardiac arrest. Therapeutic hypothermia has been shown to improve neurological outcome after cardiac arrest. The aim of this study was to evaluate the effect of therapeutic hypothermia on levels of serum NSE and S-100B protein, their time course, and their prognostic value in predicting unfavorable outcome after out-of-hospital cardiac arrest. METHODS: Seventy patients resuscitated from ventricular fibrillation were randomly assigned to hypothermia of 34°C with start of CPR. Aggressive cooling with head in ice water (4°C), IV saline (4°C) nasal and gastric irrigation (4°C saline). Excluded if took > 5 min to ROSC (6) and prolonged ventilation (1). Sedated (protocol plus PRN by unblinded) and paralysed (weaned over 24 hours, no mention of CO2 control or target in ICU, 18 hours of neurotoxic 50% N2O). Assessed neurological status every 8 hrs (by 3 unblinded assessors) from 24 to 72 hours (one blinded observer added at 72 hours only). Pathology of brain by blinded observer (at 72 hours). No difference in good cerebral outcome (best OPC 1 or 2: 1/10 normo, 5/10 delayed hypo; FE P=0.14). Better "best Overall Performance Categories", better neurologic deficit scores and better histopathological damage scores in either of hypothermic groups (vs control). Many limitations = fair study only methodologically.


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.


Dog model from Cleveland Ohio. Induced VF in anaesthetised, intubated, VF for 5 min, then open-chest CPR with ventilation, then defibrillated ± pressors. Once ROSC, either left in room temperature environment, or cooled with cooling blanket to 31°C (took approx. 2 hours), and kept for 24 hours before gradually warmed to 38°C. Neither group ventilated. Sedation as required for shivering and movements. Not randomised, not blinded. 3/10 survived in hypothermia group vs 0/10 (FE, P=0.21).


Abstract: It has been shown in dogs that mild hypothermia (34 degrees C) during or immediately after ventricular fibrillation cardiac arrest can improve cerebral outcome. The effect of mild hypothermia on outcome after 8 minutes of asphyxiation (5 minutes' cardiac

Abstract: The effects of mild hypothermia (MH) were investigated. From 1995 to 1996, 28 adult patients with out-of-hospital cardiopulmonary arrest (CPA) had return of spontaneous circulation and survived for more than two days. Thirteen patients were in the MH group. In the MH group, core temperature was maintained between 33 and 34 degrees C for 48 h, and then re-warmed to a temperature of 37 degrees C, at a rate of no greater than 1 degrees C per day. Fifteen patients, admitted before the MH protocol was instituted, were in the control group. Despite the fact that the number of witnessed arrests in the control group were greater than in the MH group, there were both more survivors (7/13 vs. 5/15) and more fully recovered patients (3/13 vs. 1/15) in the MH vs Control group. Eleven of 13 MH patients, as compared to 6/15 controls developed pneumonia. Our study, although preliminary, suggests that MH might confer improved outcome, as has been shown in animal models, after CPA. This treatment is associated with an increase in pneumonic complications.

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).


Abstract: BACKGROUND AND PURPOSE: Recent animal studies showed that mild resuscitative hypothermia improves neurological outcome when applied after cardiac arrest. In a 3-year randomized, prospective, multicenter clinical trial, we hypothesized that mild resuscitative cerebral hypothermia (32 degrees C to 34 degrees C core temperature) would improve neurological outcome after cardiac arrest. METHODS: We lowered patients' temperature after admission to the emergency department and continued cooling for at least 24 hours after arrest in conjunction with advanced cardiac life support. The cooling technique chosen was external head and total body cooling with a cooling device in conjunction with a blanket and a mattress. Infrared tympanic thermometry was monitored before a central pulmonary artery thermistor probe was inserted. RESULTS: In 27 patients (age 58 [interquartile range [IQR] 52 to 64] years; 7 women; estimated "no-flow" duration 6 [IQR 1 to 11] minutes and "low-flow" duration 15 [IQR 9 to 23] minutes; admitted to the emergency department 36 [IQR 24 to 43] minutes after return of spontaneous circulation), we could initiate cooling within 62 (IQR 41 to 75) minutes and achieve a pulmonary artery temperature of 33+/1 degrees C 287 (IQR 42 to 401) minutes after cardiac arrest. During 24 hours of mild resuscitative hypothermia, no major complications occurred. Passive re-warming >35 degrees C was accomplished within 7 hours. CONCLUSIONS: Mild resuscitative hypothermia in patients is feasible and safe. A clinical multicenter trial might prove that mild hypothermia is a useful method of cerebral resuscitation after global ischemic states.

Level 4, fair, neutral. Safe and feasible.

Case series (piilot 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 133 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).


BACKGROUND: Mild therapeutic hypothermia (MTH) improves neurological outcome in patients after cardiac arrest. From animal and human studies it appears that hypothermia impairs renal function. The aim of this study was to examine the effects of MTH on renal function in humans. METHODS: Patients were participants recruited in one of the centres of the hypothermia after cardiac arrest-multicenter trial. We measured serum creatinine and creatinine clearance (C(Cr)) within 24 h of MTH, at 4 hourly intervals. Patients were followed for acute renal failure and need for renal supportive therapy for 28 days. RESULTS: We included 60 patients (32 hypothermic, 28 normothermic). Median serum creatinine on admission was [[119 micromol/l (IQR 108-133)] [1.35 mg/dl (IQR 1.22-1.50)]] in hypothermic and [[114 micromol/l (IQR 99-131)] [1.29 mg/dl (IQR 1.12-1.48)]] in normothermic patients, and decreased to [[69 micromol/l (IQR 62-84)] [0.78 mg/dl (IQR 0.70-0.95)]] in the hypothermic group and to [[88 micromol/l (IQR 71-123)] [1.00 mg/dl (IQR 0.80-1.39)]] in the normothermic group within 24h. C(Cr) was decreased on admission. Within 24 h C(Cr) improved to normal values in normothermic patients [1.53 ml/s (IQR 1.15-2.35) [92 ml/min (IQR 69-141)]] and remained low in hypothermic patients [0.88 ml/s (IQR 0.63-1.38) [53 ml/min (IQR 38-83)]] (P = 0.0006). No difference was found between the groups in the development of acute renal failure or the need for renal supportive therapy. CONCLUSION: Twenty four hours of MTH was associated with a delayed improvement in renal function. This was not reflected in the serum creatinine values, which were low in the hypothermic group. This transient impaired renal function appeared to be completely reversible within 4 weeks.

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