

WORKSHEET for Evidence-Based Review of Science for Veterinary CPR

1. Basic Demographics

Worksheet author(s)

Jane Quandt	Date Submitted for review:

2. Clinical question:

In dogs and cats that remain comatose after resuscitation from cardiac arrest (P) does a specific onset, level, and duration of therapeutic hypothermia (I) compared to normothermia (C) improve outcome (O) (neurological intact survival)?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

4. Search strategy (including electronic databases searched):

4a. Databases

- Pub Med (1978 to 2011)
1. comatose after cardiac arrest
 2. treatment with hypothermia
 3. dog
 4. cat

There were a total of 218 hits.

4b. Other sources

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria

Comatose after cardiac arrest with treatment via hypothermia.
There were no specific articles on the use of hypothermia as a clinical treatment in dogs or cats that suffered cardiac arrest.

Exclusion criteria

Abstracts only. Editorials. Letters to the editor. Reports on human patients that suffered cardiac arrest following suicide attempts by hanging.

4d. Number of articles/sources meeting criteria for further review: 9

-Reviewed articles on human studies for the protocol of hypothermia treatment in comatose cardiac arrest victims, no clinical papers on dogs or cats.

- Reviewed articles on rats as a research model for hypothermia treatment.
- Reviewed articles on dogs as a research model for hypothermia treatment.

5. Summary of evidence

Evidence Supporting Clinical Question

Good			<i>Nozari 2004 dog study A,B,D</i>			<i>Che 2011A,B,D rat study</i>
Fair			<i>Nozari 2011 dog study comparing early or delayed hypothermia A,B,D</i>			<i>Bro-Jeppesen 2009 B,C,D Human study on quality of life after CA</i>
Poor						<i>Thenayan 2008 human retrospective study D Gillies 2010 human retrospective study on cooling techniques B,E Vanston 2010 human retrospective study on predictors of neurologic outcome B,D Cheung 2006 Review of human RCT found through data search C,D</i>
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation

C = Survival to hospital discharge

E = Other endpoint

B = Survival of event

D = Intact neurological survival

Italics = Non-target species studies

DRAFT

Evidence Neutral to Clinical question

Good						
Fair						
Poor						
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Non-target species studies

Evidence Opposing Clinical Question

Good						
Fair						
Poor						
	1	2	3	4	5	6
Level of evidence (P)						

A = Return of spontaneous circulation
 B = Survival of event

C = Survival to hospital discharge
 D = Intact neurological survival

E = Other endpoint
Italics = Non-target species studies

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Mild hypothermia as a treatment following cardiac arrest has been shown to be beneficial in human arrest patients. It has been shown to improve neurologic outcome. There are no papers I could find that discuss this treatment modality in clinical application for dogs or cats.

A prospective randomized study in rats gave good information on the onset and duration of hypothermia as relates to survival and neurologic function. Adult male rats that had ROSC after 10 minutes of asphyxia CA were randomized to two groups, a normothermic group of 37 degrees C and a hypothermic group of 33 degrees C. Therapeutic hypothermia, TH, was initiated at 0, 1, 4, or 8 hours after ROSC and maintained for 24 or 48 hours. The survival was 45%, 36%, 36%, and 14% respectively. Normothermic controls had a 17% survival rate. The TH group had good neurologic function rates of 24%, 24%, 19%, and 0% respectively compared to 2% for the normothermic group. The results were not different when TH was 24 or 48 hours. But, surviving neuron counts were greater when TH was maintained for 48 hours. To the authors knowledge this is the first animal paper to look at different TH onset times beyond 1 hour after ROSC and compared different durations of TH. There were a total of 8 groups with 21 animals in each group. There was a neurologic scoring system to assess neurologic outcome, a score of 450 out of 500 was required for it to be defined as a good neurologic outcome. This paper tells us that TH that is initiated between 0 and 4 hours after ROSC will result in the best neurologic outcome. The TH was achieved with a fan, hand-held spray bottle, and thermopad.

A 4 year prospective human study looked at comatose patients with out of hospital CA. The last 2 years of the study patients were treated with TH compared to controls of the previous 2 years. Cerebral performance was significantly improved after TH in comatose patients resuscitated with from VF/VT. Significant improvement in survival, cognitive status, or quality of life could not be detected long term. They defined TH as a core temperature of 32 to 34 degrees C for 12 to 24 hours after ROSC. A standardized algorithm for monitoring included; continuous ECG, CVP, arterial catheter, central temperature measurements from a Foley catheter, treatment goals of MAP of 65-100 mmHg by use of dopamine 2-10 ug/kg/min if needed, HR of 40-90 BPM, CVP of 2-10 mmHg, blood glucose of 4.5 – 6.1 mmol/L and diuresis > 1 ml/kg/hr. Cooling was achieved by rapid infusion of 30 ml/kg of 4 degrees C Ringers solution, and surface cooling. The core target temperature was 32.5 to 34 degrees C maintained for 24 hours. Rewarming was by 0.5 degrees C per hour until a normothermia of 37 degrees C. Patients were sedated with propofol, fentanyl, and the muscle paralytic cisatracurium to control shivering. TH conferred an improved cerebral outcome at discharge but not with survival. Improvement in cognitive status or quality of life was not detected on long-term follow up. While this paper dealt with human patients it did provide an algorithm for monitoring and supporting the TH patient. It also described how cooling was achieved and how fast rewarming occurred. Sedation was also mentioned. These are all area that will need to be addressed in the animal patient.

A retrospective review was done of human patients undergoing TH and assessed the validity of predictors of post CA neurologic outcome. The prognostic indicators of poor neurologic outcome were: the presence of myoclonus status epilepticus, absent pupillary and corneal reflexes, and motor responses no better than extension on day 3, bilaterally absent N20 responses of somatosensory evoked potentials on day 1 to 3, and elevated serum neuron-specific enolase > 33 g/L at days 1 to 3 after CA. Again while this was a human paper it introduced the indicators of poor neurologic outcome.

A human retrospective study was done looking at clinical markers to help predict neurological recovery in patients treated with TH. Again this paper acts as a reference for the TH protocol. TH was initiated within 4 hours with a goal temperature of 32 to 34 degrees C achieved within 8 hours and then maintained for 8 hours. All patients were mechanically ventilated, sedated with propofol, and

paralyzed with vecuronium. Patients were passively rewarmed and sedation and paralysis was discontinued when the patient's temperature was 36.5 degrees C. Hyperthermia that occurred after warming was treated with cooling blankets and antipyretics. A Glasgow Coma Score was done 12 hours after rewarming and after discontinuation of sedation and paralysis. A Cerebral Performance Scale (CPS) of 1, discharge with no cerebral functional disability or 2 moderate cerebral disability was done to determine neurologic outcome. A first rhythm that was non-ventricular tachycardia/fibrillation, acute kidney injury (acute renal failure in the first 72 hours in ICU), and any treated cardiac arrhythmia were significant risk factors for poor neurologic recovery. This paper also found that the longer it took to reach the hypothermic goal temperature the better the neurologic outcome. They postulated that this may be due to more preserved hypothalamic thermoregulatory function in those patients compared to those with poorer outcomes.

A human retrospective cohort study was done comparing cooling techniques. There were 2 groups, those cooled via surface cooling, n of 41 or endovascular cooling, n of 42. The groups were decided based on if the endovascular cooling device was available. All groups had cooling initiated by IV iced Hartmann's solution given at 15 to 30 ml/kg. Body temperature was monitored by a bladder thermistor. A temperature of 32 to 34 degrees C was targeted for 12 to 24 hours. Surface cooling was done by bag filled with an ice slurry that were applied to both sides of the neck, axillae, groins, and under the knees. In the endovascular group with the device inserted into the femoral artery. This paper list the potential complications of cooling; symptomatic bradycardia, required treatment with atropine, sympathomimetics, or pacing, target temperature not reached, pancreatitis, new diagnosis of pneumonia in first 7 days, bleeding or platelet transfusion and requirement for renal replacement therapy. The surface cooled group had a higher incidence of overcooling and failure to reach target temperature. There were 2 factors associated with mortality, high APACHE II score and CA other than ventricular fibrillation or pulseless ventricular tachycardia. They found endovascular cooling to be superior to surface cooling with better control during rewarming. Rapid rewarming may negate the potential benefits of TH. But endovascular cooling is not without potential complications either, such as catheter related blood stream infections and higher rates of endovascular nosocomial pneumonia and bleeding. There was no difference in outcome with either technique, a randomized controlled trial is needed.

A randomized, controlled study was done using a clinically relevant CA outcome model in dogs. Anesthetized dogs were subject to CA no flow of 3 minutes duration, followed by 7 minutes of basic life support and 10 minutes of stimulated unsuccessful advanced life support. The times were chosen to mimic an out of hospital CA in a human and the CPR time. The dogs were assigned to 4 treatment groups with 20 minutes of advanced life support; group 1 control n=7, CPR with normothermia, group 2 n=6, with moderate hypothermia via a venovenous extracorporeal shunt cooling to a tympanic temperature of 27 degrees C, group 3 n=6, same as group 2 but with mild hypothermia, tympanic temperature of 34 degrees C, group 4 n=5, normothermic venovenous shunt. Cooling was induced with a bolus of 20 ml/kg of 2 degrees C normal saline into the superior vena cava followed by the extracorporeal pumping. It must be taken into consideration that the group numbers were small and the use of a venovenous extracorporeal shunt is not practical in a small animal hospital setting. After 40 minutes of v. fib reperfusion was with cardiopulmonary bypass for 4 hours which included defibrillation to achieve spontaneous circulation. The use of cardiopulmonary bypass was to simulate a possible clinical scenario for cases of refractory v. fib. All dogs were maintained at mild hypothermia, 34 degrees C to 12 hours with mechanical ventilation, muscle paralysis to 48 hours, and ICU care to 96 hours then euthanized. The hypothermic dogs came off the bypass pump and ventilation and survived to 96 hours. Again the use of cardiopulmonary bypass is not practical for small animal care as the hospitals do not have a pump or the skilled personal to use it. The normothermia group dogs died within 58 hours with

multiple organ failure. In the hypothermia groups all 12 dogs survived to 96 hours without gross extracerebral organ damage. The hypothermia dogs had good functional neurologic outcome with normal or near normal brain histology. This study did demonstrate that organ preservative occurs at the safe limit of 34 degrees C and there is no need to go lower. Myocardial damage scores were worse in the normothermic groups compared to the hypothermic groups. The mechanism of the protection may include decreased heart rate, decreased oxygen demands, decreased apoptosis, and increased production of heat shock proteins. The goal of the study was to show that moderate hypothermia can be used as a bridge to prolonged cardiopulmonary bypass and result in survival with full neurologic recovery.

A second study in dogs by the same author was done to determine the time window for intra-arrest cooling. Dogs were anesthetized and breathing spontaneously when v. fib was induced. CA with no flow was allowed for 3 minutes, then 7 minutes of CPR basic life support and 50 minutes of advanced life support. There were 2 randomized groups, an early hypothermic group, n=9, in which mild hypothermia, 34 degrees C, was induced with IV fluid bolus flush and venous blood shunt cooling after 10 minutes of v. fib. In group 2, n=8, hypothermia was induced at v. fib at 20 minutes. After 60 minutes of v. fib restoration of spontaneous circulation was achieved via cardiopulmonary bypass for 4 hours and intensive care for 96 hours. Dogs were mechanically ventilated for 48 hours, anesthesia and analgesia was provided by N2O/O2 and boluses of morphine and diazepam as needed. In the early hypothermia group 7 of 9 dogs survived to 96 hours, 5 with good neurologic outcome. In the delayed hypothermia group 7 of 8 dogs died within 37 hours of multiple organ failure. If mild hypothermia is to be used in CPR it should be instituted as soon as possible. Importantly, a 20 minute versus a 10 minute delay in cooling negates the beneficial effects of hypothermia in this model of prolonged v. fib CA. As with the previous paper this model does not transfer to clinical small animal practice due to the use of cardiopulmonary bypass. There were some interesting points; mild to moderate hypothermia would be expected to facilitate rather than reduce defibrillation success, the 20 ml/kg cold fluid bolus may affect the chance of survival by altering the blood rheology and improving myocardial and cerebral blood flow. A fluid bolus of 30 ml/kg ice-cold, 4 degrees C, LRS given to comatose survivors of CA had a decrease in core temperature of 1.6 degrees C over 25 minutes and improved blood pressure, this same effect was also seen in pigs. There could be a synergistic effect of the hypothermia and the volume administration.

A systemic review of the human literature of RCT using therapeutic hypothermia as a neuroprotectant in post CA patients was done. Their inclusion criteria were; adult patients, > than 18 years of age, with primary CA who remained comatose after ROSC. Patients were randomized to mild hypothermia, 32-34 degrees C or normothermia within 24 hours of presentation. The studies had to include pre-determined outcomes of discharge neurologic outcome, mortality or significant treatment-related adverse events. Four studies met their criteria. The pooled data indicated that mild hypothermia decreased in hospital mortality and reduced the incidence of poor neurologic outcome. The numbers needed to treat were 7 patients to save 1 life and 5 patients to improve neurologic outcome.

7. Conclusion

Anoxic brain injury is an ongoing process after ROSC. Hypothermia is thought to have a neuroprotective role after ROSC by decreasing metabolic demand, decreasing the release of excitatory neurotransmitters, and decreasing inflammation. The potential adverse effects associated with hypothermia include increased rates of

hemodynamic instability, coagulopathy, and immune deficiency which can lead to increased rates of sepsis and pneumonia.

It is difficult to see a clinical utilization of hypothermia post CA as practiced on human patients for use in small animals. The use of cardiopulmonary bypass is not an option. In those cases where bypass is not used the hypothermia protocol requires mechanical ventilation for 12 to 24 hours with sedation and muscle paralysis. While it is possible to ventilate animals for this duration muscle paralysis is not frequently used and would require extensive monitoring. Cooling dogs and cats with cold IV fluids could be easily accomplished but maintaining the appropriate temperature and not overcooling may prove difficult. Slow re-warming to prevent rebound hyperthermia and weaning from mechanical ventilation could also prove challenging in smaller patients. In human medicine hypothermia is predominantly utilized in out-of hospital CA patients that are brought to the hospital for further care, this may not represent the most commonly seen animal patient as there are no ambulance services as with human medicine to help in stabilization and CPR before the patient arrives at the hospital. The majority of CA in the human population present with an arrhythmia of v.fib. Most animals do not die with this arrhythmia, rather it is more commonly PEA or asystole. The use of hypothermia in small animal patients may best be used by not actively warming the CA patient.

8. Acknowledgement

none

9. Citation list

Level 6 Poor

[Neurology](#). 2008 Nov 4;71(19):1535-7.

Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest.

[Al Thenayan E](#), [Savard M](#), [Sharpe M](#), [Norton L](#), [Young B](#).

Source Department of Clinical Neurological Sciences, London Health Sciences Centre-University Hospital, London, Ontario, Canada.

Abstract

BACKGROUND: Several predictors of poor neurologic outcome after cardiac arrest (CA) were proven to be valid. However, these studies preceded the advent of therapeutic induced mild hypothermia (TIMH), which may alter their validity. The objective of this study is to reassess the validity of these predictors in post-CA patients treated with TIMH.

METHODS: Retrospective chart review of 37 consecutive adults who were comatose after resuscitation from CA and treated with TIMH.

RESULTS: None of six patients without pupillary reactivity, six without corneal reflexes on day 3, or eight with myoclonus status epilepticus recovered awareness. Two of 14 patients with motor responses no better than extension at day 3 recovered motor responses only after 6 days post-arrest (one at 5 and one at 6 days post-rewarming) and regained awareness.

CONCLUSIONS: Loss of motor responses better than extension on day 3 was not prognostically reliable after therapeutic induced mild hypothermia for comatose cardiac arrest survivors. None of the patients who lost pupillary or corneal reflexes on day 3 or developed myoclonus status epilepticus recovered awareness.

Level 6 Fair

[Resuscitation](#). 2009 Feb;80(2):171-6. Epub 2008 Dec 25.

The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest.

[Bro-Jeppesen J](#), [Kjaergaard J](#), [Horsted TI](#), [Wanscher MC](#), [Nielsen SL](#), [Rasmussen LS](#), [Hassager C](#).

Source Department of Cardiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, DK-2100 Copenhagen, Denmark.

Abstract

AIMS: To assess the impact of therapeutic hypothermia on cognitive function and quality of life in comatose survivors of out of Hospital Cardiac arrest (OHCA).

METHODS: We prospectively studied comatose survivors of OHCA consecutively admitted in a 4-year period. Therapeutic hypothermia was implemented in the last 2-year period, intervention period (n=79), and this group was compared to patients admitted the 2 previous years, control period (n=77). We assessed Cerebral Performance Category (CPC), survival, Mini Mental State Examination (MMSE) and self-rated quality of life (SF-36) 6 months after OHCA in the subgroup with VF/VT as initial rhythm.

RESULTS: CPC in patients alive at hospital discharge was significantly better in the intervention period with a CPC of 1-2 in 97% vs. 71% in the control period, p=0.003, corresponding to an adjusted odds ratio of a favourable cerebral outcome of 17, p=0.01. No significant differences were found in long-term survival (57% vs. 56% alive at 30 months), MMSE, or SF-36. Therapeutic hypothermia (hazard ratio: 0.15, p=0.007) and bystander CPR (hazard ratio 0.19, p=0.002) were significantly related to survival in the intervention period.

CONCLUSION: CPC at discharge from hospital was significantly improved following implementation of therapeutic hypothermia in comatose patients resuscitated from OHCA with VF/VT. However, significant improvement in survival, cognitive status or quality of life could not be detected at long-term follow-up.

Level 6 Poor

[CJEM](#). 2006 Sep;8(5):329-37.

Systematic review of randomized controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients.

[Cheung KW](#), [Green RS](#), [Magee KD](#).

Source Department of Emergency Medicine, Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada.

Abstract

OBJECTIVE: Several randomized controlled trials have suggested that mild induced hypothermia may improve neurologic outcome in comatose cardiac arrest survivors. This systematic review of randomized controlled trials was designed to determine if mild induced hypothermia improves neurologic outcome, decreases mortality, or is associated with an increased incidence of adverse events.

DATA SOURCES: The following databases were reviewed: Cochrane Controlled Trials Register (Issue 4, 2005), MEDLINE (January 1966 to November 2005), EMBASE (1980 to November 2005), CINAHL (1982 to November 2005) and Web of Science (1989 to November 2005). For each included study, references were reviewed and the primary author contacted to identify any additional studies.

STUDY SELECTION: Studies that met inclusion criteria were randomized controlled trials of adult patients (>18 years of age) with primary cardiac arrest who remained comatose after return of spontaneous circulation. Patients had to be randomized to mild induced hypothermia (32 degrees C-34 degrees C) or normothermia within 24 hours of presentation. Only studies reporting pre-determined outcomes including discharge neurologic outcome, mortality or significant treatment-related adverse events were included. There were no language or publication restrictions.

DATA SYNTHESIS: Four studies involving 436 patients, with 232 cooled to a core temperature of 32 degrees C-34 degrees C met inclusion criteria. Pooled data demonstrated that mild hypothermia decreased in-hospital mortality (relative ratio [RR] 0.75; 95% confidence interval [CI], 0.62-0.92) and reduced the incidence of poor neurologic outcome (RR 0.74; 95% CI, 0.62-0.84). Numbers needed to treat were 7 patients to save 1 life, and 5 patients to improve neurologic outcome. There was no evidence of treatment-limiting side effects.

CONCLUSIONS: Therapeutically induced mild hypothermia decreases in-hospital mortality and improves neurologic outcome in comatose cardiac arrest survivors. The possibility of treatment-limiting side effects cannot be excluded.

Level 6 Good

[Crit Care Med](#). 2011 Jun;39(6):1423-30.

Impact of therapeutic hypothermia onset and duration on survival, neurologic function, and neurodegeneration after cardiac arrest.

[Che D](#), [Li L](#), [Kopil CM](#), [Liu Z](#), [Guo W](#), [Neumar RW](#).

Source Center for Resuscitation Science, Department of Emergency Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA.

Abstract

OBJECTIVE: Post-cardiac-arrest therapeutic hypothermia improves outcomes in comatose cardiac arrest survivors. This study tests the hypothesis that the efficacy of post-cardiac-arrest therapeutic hypothermia is dependent on the onset and duration of therapy.

DESIGN: Prospective randomized laboratory investigation.

SETTING: University research laboratory.

SUBJECTS: A total of 268 male Long Evans rats.

INTERVENTIONS: Post-cardiac-arrest therapeutic hypothermia.

MEASUREMENTS AND MAIN RESULTS: Adult male Long Evans rats that achieved return of spontaneous circulation after a 10-min asphyxial cardiac arrest were block randomized to normothermia ($37^{\circ}\text{C} \pm 1^{\circ}\text{C}$) or therapeutic hypothermia ($33^{\circ}\text{C} \pm 1^{\circ}\text{C}$) initiated 0, 1, 4, or 8 hrs after return of spontaneous circulation and maintained for 24 or 48 hrs. Therapeutic hypothermia initiated 0, 1, 4, and 8 hrs after return of spontaneous circulation resulted in 7-day survival rates of 45%*, 36%*, 36%*, and 14%, respectively, compared to 17% for normothermic controls and survival with good neurologic function rates of 24%*, 24%*, 19%*, and 0%, respectively, compared to 2% for normothermic controls (* $p < .05$ vs. normothermia). These outcomes were not different when therapeutic hypothermia was maintained for 24 vs. 48 hrs. In contrast, hippocampal CA1 pyramidal neuron counts were $53\% \pm 27\%^*$, $53\% \pm 19\%^*$, $51\% \pm 24\%^*$, and $65\% \pm 16\%^*$ of normal, respectively, when therapeutic hypothermia was initiated 0, 1, 4, or 8 hrs after return of spontaneous circulation compared to 9% in normothermic controls (* $p < .01$ vs. normothermia). Furthermore, surviving neuron counts were greater when therapeutic hypothermia was maintained for 48 hrs compared to 24 hrs ($68\% \pm 15\%^*$ vs. $42\% \pm 22\%^*$, * $p < .0001$).

CONCLUSIONS: In this study, post-cardiac-arrest therapeutic hypothermia resulted in comparable improvement of survival and survival with good neurologic function when initiated within 4 hrs after return of spontaneous circulation. However, histologic assessment of neuronal survival revealed a potentially broader therapeutic window and greater neuroprotection when therapeutic hypothermia was maintained for 48 vs. 24 hrs.

Level 6 Poor

[Resuscitation](#). 2010 Sep;81(9):1117-22. Epub 2010 Jul 4.

Therapeutic hypothermia after cardiac arrest: a retrospective comparison of surface and endovascular cooling techniques.

[Gillies MA](#), [Pratt R](#), [Whiteley C](#), [Borg J](#), [Beale RJ](#), [Tibby SM](#).

Source Department of Intensive Care, Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, United Kingdom. michael.gillies@nhs.net

Abstract

OBJECTIVES: Therapeutic hypothermia (32-34 degrees C) is recommended for comatose survivors of cardiac arrest; however, the optimal technique for cooling is unknown. We aimed to compare therapeutic hypothermia using either surface or endovascular techniques in terms of efficacy, complications and outcome.

DESIGN: Retrospective cohort study.

SETTING: Thirty-bed teaching hospital intensive care unit (ICU).

PATIENTS: All patients (n=83) undergoing therapeutic hypothermia following cardiac arrest over a 2.5-year period. The mean age was 61 ± 16 years; 88% of arrests occurred out of hospital, and 64% were ventricular fibrillation/tachycardia.

INTERVENTIONS: Therapeutic hypothermia was initiated in the ICU using iced Hartmann's solution, followed by either surface (n=41) or endovascular (n=42) cooling; choice of technique was based upon endovascular device availability. The target temperature was 32-34 degrees C for 12-24 h, followed by rewarming at a rate of 0.25 degrees C/h(-1).

MEASUREMENTS AND MAIN RESULTS: Endovascular cooling provided a longer time within the target temperature range ($p=0.02$), less temperature fluctuation ($p=0.003$), better control during rewarming (0.04), and a lower 48-h temperature load ($p=0.008$). Endovascular cooling also produced less cooling-associated complications in terms of both overcooling ($p=0.05$) and failure to reach the target temperature ($p=0.04$). After adjustment for known confounders, there were no differences in outcome between the groups in terms of ICU or hospital mortality, ventilator free days and neurological outcome.

CONCLUSION: Endovascular cooling provides better temperature management than surface cooling, as well as a more favorable complication profile. The equivalence in outcome suggested by this small study requires confirmation in a randomized trial.

Level 3 Fair

[Circulation](#). 2006 Jun 13;113(23):2690-6.

Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation.

[Nozari A](#), [Safar P](#), [Stezoski SW](#), [Wu X](#), [Kostelnik S](#), [Radovsky A](#), [Tisherman S](#), [Kochanek PM](#).

Source Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114-2696. anozari@partners.org.

Abstract

BACKGROUND: Mild hypothermia improves outcome when induced after cardiac arrest in humans. Recent studies in both dogs and mice suggest that induction of mild hypothermia during cardiopulmonary resuscitation (CPR) greatly enhances its efficacy. In this study, we evaluate the time window for the beneficial effect of intra-arrest cooling in the setting of prolonged CPR in a clinically relevant large-animal model.

METHODS AND RESULTS: Seventeen dogs had ventricular fibrillation cardiac arrest no flow of 3 minutes, followed by 7 minutes of CPR basic life support and 50 minutes of advanced life support. In the early hypothermia group (n=9), mild hypothermia (34 degrees C) was induced with an intravenous fluid bolus flush and venovenous blood shunt cooling after 10 minutes of ventricular fibrillation. In the delayed hypothermia group (n=8), hypothermia was induced at ventricular fibrillation 20 minutes. After 60 minutes of ventricular fibrillation, restoration of spontaneous circulation was achieved with cardiopulmonary bypass for 4 hours, and intensive care was given for 96 hours. In the early hypothermia group, 7 of 9 dogs survived to 96 hours, 5 with good neurological outcome. In contrast, 7 of 8 dogs in the delayed hypothermia group died within 37 hours with multiple organ failure (P=0.012).

CONCLUSIONS: Early application of mild hypothermia with cold saline during prolonged CPR enables intact survival. Delay in the induction of mild hypothermia in this setting markedly reduces its efficacy. Our data suggest that if mild hypothermia is used during CPR, it should be applied as early as possible.

Level 3 Good

[Crit Care Med](#). 2004 Oct;32(10):2110-6.

Mild hypothermia during prolonged cardiopulmonary cerebral resuscitation increases conscious survival in dogs.

[Nozari A](#), [Safar P](#), [Stezoski SW](#), [Wu X](#), [Henchir J](#), [Radovsky A](#), [Hanson K](#), [Klein E](#), [Kochanek PM](#), [Tisherman SA](#).

Source Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA, USA.

Abstract

OBJECTIVE: Therapeutic hypothermia during cardiac arrest and after restoration of spontaneous circulation enables intact survival after prolonged cardiopulmonary cerebral resuscitation (CPCR). The effect of cooling during CPCR is not known. We hypothesized that mild to moderate hypothermia during CPCR would increase the rate of neurologically intact survival after prolonged cardiac arrest in dogs.

DESIGN: Randomized, controlled study using a clinically relevant cardiac arrest outcome model in dogs.

SETTING: University research laboratory.

SUBJECTS: Twenty-seven custom-bred hunting dogs (19-29 kg; three were excluded from outcome evaluation).

INTERVENTIONS: Dogs were subjected to cardiac arrest no-flow of 3 mins, followed by 7 mins of basic life support and 10 mins of simulated unsuccessful advanced life support attempts. Another 20 mins of advanced life support continued with four treatments: In control group 1 (n = 7), CPCR was with normothermia; in group 2 (n = 6, 1 of 7 excluded), with moderate hypothermia via venovenous extracorporeal shunt cooling to tympanic temperature 27 degrees C; in group 3 (n = 6, 2 of 8 excluded), the same as group 2 but with mild hypothermia, that is, tympanic temperature 34 degrees C; and in group 4 (n = 5), with normothermic venovenous shunt. After 40 mins of ventricular fibrillation, reperfusion was with cardiopulmonary bypass for 4 hrs, including defibrillation to achieve spontaneous circulation. All dogs were maintained at mild hypothermia (tympanic temperature 34 degrees C) to 12 hrs. Intensive care was to 96 hrs.

MEASUREMENTS AND MAIN RESULTS: Overall performance categories and neurologic deficit scores were assessed from 24 to 96 hrs. Regional and total brain histologic damage scores and extracerebral organ damage were assessed at 96 hrs. In normothermic groups 1 and 4, all 12 dogs achieved spontaneous circulation but remained comatose and (except one) died within 58 hrs with multiple organ failure. In hypothermia groups 2 and 3, all 12 dogs survived to 96 hrs without gross extracerebral organ damage (p < .0001). In group 2, all but one dog achieved overall performance category 1 (normal); four of six dogs had no neurologic deficit and normal brain histology. In group 3, all dogs achieved good functional outcome with normal or near-normal brain histology. Myocardial damage scores were worse in the normothermic groups compared with both hypothermic groups (p < .01).

CONCLUSION: Mild or moderate hypothermia during prolonged CPCR in dogs preserves viability of extracerebral organs and improves outcome.

Level 6 Poor

[South Med J](#). 2010 Apr;103(4):301-6.

Predictors of poor neurologic outcome in patients undergoing therapeutic hypothermia after cardiac arrest.

[Vanston VJ](#), [Lawhon-Triano M](#), [Getts R](#), [Prior J](#), [Smego RA Jr](#).

Department of Palliative Medicine, Scranton Temple Residency Training Program, Mercy Hospital, The Commonwealth Medical College, Scranton, PA 18510, USA.

Abstract

BACKGROUND: Therapeutic hypothermia (TH) has been shown to reduce the degree of anoxic brain injury, decrease mortality, and improve neurologic recovery in patients surviving cardiac arrest. However, there is a paucity of data on potential markers of neurologic outcome that physicians can use in this setting.

METHODS: A retrospective medical records review of 41 consecutive survivors of cardiac arrest treated with TH (2004-08) was examined.

RESULTS: Mean patient age was 66 years old. Most subjects had an out-of-hospital, witnessed cardiac arrest, and two-thirds had received bystander cardiopulmonary resuscitation (CPR). About half of the patients had nonventricular tachycardia/fibrillation (VT/VF) arrests. Fifty-nine percent (24 of 41 subjects) died or experienced severe neurologic impairment. By bivariate analysis, factors associated with a poor neurologic prognosis included: 1) a first rhythm at cardiac arrest other than VT/VF ($P = 0.01$); 2) the presence of acute kidney injury (AKI) in the intensive care unit (ICU) ($P < 0.001$); 3) any treated cardiac arrhythmia after admission ($P = 0.05$); and 4) a Glasgow Coma Score ≤ 8 determined 12 hours after rewarming ($P < 0.001$). Using multiple regression analysis, non-VT/VF arrest, AKI, and cardiac arrhythmia remained significant risk factors for poor neurologic recovery. The cumulative risk of death or poor neurologic outcome increased with the presence of two or more risk factors.

CONCLUSION: Several simple, reproducible clinical markers can help predict neurologic recovery, during and after treatment, in patients managed with TH for cardiac arrest.