

WORKSHEET for Evidence-Based Review of Science for Veterinary CPR

1. Basic Demographics

Worksheet author(s)

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Date Submitted for review:

5/3/11

2. Clinical question:

In dogs and cats with ROSC after cardiac arrest (P), does rewarming at a certain rate (C/hour) (I) compared to fast rewarming to normal temperature (C) improve outcome (O) (neurological intact survival)?

3. Conflict of interest specific to this question:

No conflicts of interest.

4. Search strategy (including electronic databases searched):

4a. Databases

We plan to use Pubmed with keywords:

- “rewarming post cardiac arrest”
- “rewarming AND cardiac arrest” limit years 2000-2011
- “rewarming rate AND cardiac arrest” limit English language and years 2000-2011
- “rewarming rate” limit English language and years 2000-2011
- “rewarming dog CPR” limit English language
- “hypothermia dog CPR” limit English language
- “hypothermia dog rewarming” limit English language
- “rewarming cat CPR” limit English language
- “hypothermia cat CPR” limit English language
- “hypothermia cat rewarming” limit English language

Search in CAB for “rewarming,” “cardiac arrest and warming,” and “post-resuscitation” yielded zero results for each keyword attempted, so we will not be using CAB.

4b. Other sources

We will also be reviewing and selecting additional applicable articles in the bibliographies of articles yielded by the above keyword search.

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

Inclusion criteria

Articles in English language; experimental hypothermia in humans, dogs, and cats; articles dealing with resuscitation and body temperature monitoring in humans, dogs, and cats.

Exclusion criteria

Those articles not in English language; articles dealing with therapeutic hypothermia.

4d. Number of articles/sources meeting criteria for further review: 91 articles

- “rewarming post cardiac arrest”- **5 articles**
- “rewarming AND cardiac arrest” limit years 2000-2011-**6 articles**
- “rewarming rate AND cardiac arrest” limit English language and years 2000-2011-**1 article**
- “rewarming rate” limit English language and years 2000-2011- **11 articles**
- “rewarming dog CPR” limit English language- **3 articles**
- “hypothermia dog CPR” limit English language – **29 articles**
- “hypothermia dog rewarming” limit English language – **28 articles**
- “rewarming cat CPR” limit English language – **0 articles**
- “hypothermia cat CPR” limit English language – **4 articles**
- “hypothermia cat rewarming” limit English language – **3 articles**

5. Summary of evidence

Evidence Supporting Clinical Question

Good			<p>Bigelow WG 1950; ABE=hemodynamic monitoring</p> <p>Wu X 2006; ABD</p> <p>Wu X 2008; ABDE=evaluation of oxygen and glucose supplement during hypothermia</p>			<p>Jo YH 2011; B and E= until tissue samples obtained</p> <p>Gordan ML 2010; B, E= tissue samples</p> <p>Eshel G 2002; B Grigore AM 2002; D</p> <p>Thompson HJ, 2010; D</p> <p>Ueda Y 2004; E=cerebral vascular responses</p> <p>Suehiro E 2003; E= cerebrovascular reactivity</p> <p>Kawahara F 2003; E= jugular venous oxygen</p>
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						saturation
Fair						Saleh M 2005; E=inotropy, afterdrop magnitude, ICU stay, blood lactate Piktel JS 2011; E=heart rhythm
Poor					Savvas I 2006; ABCD	
	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

DRAFT

Evidence Neutral to Clinical question

Good			<p>Fischer UW 2005; E=diastolic, systolic function</p> <p>Zhou Y 1998; D</p> <p>Moss JF 1986; ABE=methods of rewarming</p> <p>Leonov Y 1990; ABDE=brain and myocardial histopathology</p> <p>Safar P 1996; ABDE=brain histopathology</p> <p>Murray JP 1990; BE=oxygen extraction</p> <p>Tanimoto H 2007; ABDE=extracorporeal lung and heart assist</p> <p>Ao H 2001; ABDE= extracorporeal lung and heart assist</p> <p>Kuboyama K 1993; ABDE=delay in cooling</p> <p>Ebmeyer U 1998; BDE=epidural brain compression injury</p> <p>Behringer W 2000; ABDE=cold aortic flush</p> <p>Jeung KW 2008; ABDE=cold carotid flush</p> <p>Behringer W 2003; DE=suspended animation</p> <p>Aoki A 2002; E= cerebral metabolism</p>			<p>Kim K 2010; B and E=tissue samples obtained</p> <p>Tortorici MA 2009; E=tissue samples</p> <p>Mizushima Y 2000; E=cardiac function, hepatic blood flow</p> <p>Nakane M 2001; E=biopsy</p> <p>Pokela M 2003; B</p>
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Fair			Haughn, C 2003; BE=veno-veno circuit for rewarming			Kim WG 2005; B Undar A 2000; E= viscoelasticity blood
Poor			Majsce DJ 1993; D		Kaplan MI 2011; ABCD	Morita S 2011; C Brunette D 2000; C Delaney K 2006; E=normothermia Silfvast T 2005; C Lavinio A 2007; E= cerebrovascular reactivity Diao C 2002; E=brain perfusion model
	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)						
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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

DRAFT

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

Patients who have undergone cardiopulmonary arrest commonly suffer from hypothermia as a result of the arrest event or the disease that has led to the arrest event. In the past two decades, there is compelling evidence that permitting hypothermia and even inducing hypothermia in post-cardiopulmonary arrest may help preserve neurologic function. Few data exist, however, demonstrating the optimal temperature or duration of hypothermia, nor the rate or time interval over which rewarming should occur. While no studies have directly looked at rewarming these patients after unplanned cardiopulmonary arrest (CPA), a variety of studies in different species evaluating rewarming after hypothermic cardiopulmonary arrest exist. In each study that compared slow versus faster rewarming rates in post-arrest patients, the patients warmed more slowly had improved outcomes. A variety of other studies exist which evaluate rewarming hypothermic patients who have not arrested. In each of these studies that compared fast versus slow rewarming rates, the patients who were rewarmed more slowly had better outcomes. A portion of the studies examined rewarming in patients specifically with regards to cerebral recovery and of those, a few studies exist that compare rewarming rates. Outcomes from these studies included clinical patient behaviors as well as examining preservation of microcirculatory reactivity and cerebral blood flow, NF κ B expression, and oxygen saturation of the brain; no matter the parameter, slow rewarming was beneficial to the patient versus faster rewarming.

Case reports of successful return of spontaneous circulation (ROSC) after CPA in veterinary medicine minimally discuss rewarming or rewarming rates. Wu et al. report successful ROSC after CPA in a cat inadvertently administered penicillin G benzathine who was mildly but persistently hypothermic after presentation to the university veterinary medical center. No information was given about rewarming and success of rewarming. Savvas reported successful ROSC after CPA in a dog associated with a 5.33 mg/kg extradural lidocaine injection. After ROSC, the dog was hypothermic and required seven hours to reach normal body temperature despite active surface rewarming.

There are many studies examining methods and rates of cooling in experimental hypothermic canine cardiac arrest models, but far fewer examining rewarming and rewarming rates. One canine study of hypothermic arrest (Zhou, Wang, et al) looked at brain pathologic changes after rewarming and showed that there were more severe changes in the cerebellum and the hippocampus in the fast rewarming group versus the slow rewarming group. A second canine study (Majsee, Towfighi, et al) revealed that there were indications of cerebral ischemia in dogs who underwent hypothermic cardiopulmonary arrest greater than 1.5 hrs in duration prior to rewarming to repair congenital defects in the heart. This study did not specifically address rewarming rates. Wu et al. recognized neurological deterioration (generalized seizures and histological evidence of neuronal degeneration and necrosis) in five of six dogs surviving rapid rewarming (1° C/hour) after profound hypothermia. The post-hoc creation of another group undergoing profound hypothermia for an additional 24 hours with a slower rewarming rate (0.3° C/hour) demonstrated that five of six dogs in this group regained normal function and no dogs had generalized seizures. Histopathological brain lesions were reported to be mild in this group. An experimental canine study from the 1950s (Bigelow et al.) examined rapid rewarming after profound hypothermia under vinyl ether anesthesia by submersion to the neck in a hot water bath at 40-42° C. Four of five dogs died during the rewarming process and had severe hepatic congestion at necropsy. The fifth dog died after 4 days with clinical jaundice.

A single study in a feline model (Aoki, Mori et al) revealed ischemic damage in the cerebral cortex when cerebral perfusion pressure was lower (experimental head injury with increased intracranial pressure model). These cats did not arrest but were cooled and later rewarmed; there was no comparison of rewarming rates.

In conclusion, although studies of rewarming in dogs who have arrested for natural causes rather than experimental hypothermic arrest are few, it appears that slow rewarming should be conducted in all hypothermic patients. Slow rewarming appears to be neuroprotective in all species regardless of the cause of the hypothermia. At this time there is no data to support the optimal rate of slow rewarming in any species.

7. Conclusion

No data exist examining rewarming rates in dogs and cats experiencing ROSC post-CPA. Experimental data in dogs exists which indicates that slower rewarming results in improved survival and improved neurologic function (LOE 3, Wu et al.). Since the data that we do have is from experimental models of hypothermia-induced cardiac arrest in dogs and cats, and it is not clear how applicable this data will be in the clinical setting of ROSC where hypothermia is usually a result of the CPA and not the reverse as in research models. There is also a great deal of overlap in the rewarming rates in these experimental models in different studies; rewarming rates described as slow or gradual range from 0.004 to 0.49° C per minute, and rewarming rates described as fast or rapid range from 0.01 to 0.56 °C per minute. It is also unclear from the literature whether hypothermia should be maintained for a period of time after ROSC for preservation of neurologic function or if rewarming should be initiated immediately after ROSC.

We cannot make a recommendation as to the most favorable rate of rewarming in canine or feline patients nor is it apparent from the data if the optimal rate of rewarming is variable and dependent on the degree of hypothermia.

8. Acknowledgement

None.

9. Citation list

Ao H, Tanimoto H, Yoshitake A, et al. Long-term mild hypothermia with extracorporeal lung and heart assist improves survival from prolonged cardiac arrest in dogs. Resuscitation 48(2):163-74, 2001.

BACKGROUND AND PURPOSE:

although normothermic extracorporeal lung and heart assist (ECLHA) improves cardiac outcomes, patients can not benefit from hypothermia-mediated brain protection. The present study evaluated the effects of long-term ECLHA with mild to moderate hypothermia (33 degrees C) in a canine model of prolonged cardiac arrest.

METHODS:

15 dogs were assigned to either the hypothermic (seven dogs, 33 degrees C) or normothermic group (eight dogs, 37.5 degrees C). All dogs were induced to normothermic ventricular fibrillation (VF) for 15 min, followed by 24 h of ECLHA and 72 h of intensive care. The hypothermia group maintained core (pulmonary artery) temperature at 33 degrees C for 20 h starting from resuscitation, then were rewarmed by 28 h. Outcome evaluations included: (1) mortality; (2) catecholamine dose; (3) time to extubation; (4) necrotic myocardial mass (g); and (5) neurological deficits score (NDS).

RESULTS:

in the normothermic group five dogs died of cardiogenic shock and one dog succumbed to poor oxygenation. The two surviving dogs remained comatose (NDS 60.5 +/- 4.9%) with necrotic myocardial mass of 14.5 +/- 3.5 g. In the hypothermic group, one dog died from pulmonary dysfunction, the other six dogs survived. The surviving dogs showed brain damage (29.8 +/- 2.5%), but there was evidence of some brain-protective effect. The mass of necrotic myocardium was 4.2 +/- 1.3 g in the hypothermic group or 3.4 times smaller than in the normothermic group. The survival rate was significantly higher in the hypothermic than in the normothermic

group ($P < 0.05$). The catecholamine requirement was also lower in the hypothermic than in the normothermic dogs ($P < 0.05$).

CONCLUSIONS:

Long-term mild to moderate hypothermia with ECLHA induced immediately after cardiac arrest improved survival as well as cerebral and cardiac outcomes.

Level 3, good, neutral, funding: not reported

Key points: extracorporeal lung and heart assist improves survival, evaluated catecholamine levels, neurological deficit scores

Aoki A, Mori K, Maeda M. Adequate cerebral perfusion pressure during rewarming to prevent ischemic deterioration after therapeutic hypothermia. *Neurol Res* 24:271-280, 2002.

Ischemic deterioration during rewarming is one of the most notable clinical complications after successful therapeutic cerebral hypothermia, but the mechanism is not completely understood. Hypothermia may cause vasoconstriction and relative ischemia, especially with insufficient cerebral perfusion pressure (CPP). Various parameters were evaluated to determine the critical CPP threshold to avoid ischemia during rewarming. Cat experimental head injury was induced by inflating an epidural rubber balloon, and intracranial pressure was maintained at 30 mmHg. During rewarming after cerebral hypothermia, CPP was maintained at >120 mmHg ($n = 16$), 90 mmHg ($n = 11$), 60 mmHg ($n = 11$), and 40 mmHg ($n=4$) by controlling the blood pressure. Cerebral blood flow, cerebral metabolic rate for oxygen, arteriovenous difference of oxygen (AVDO₂), cerebral venous oxygen saturation (ScvO₂), and extracellular glutamate concentrations were monitored by glutamate oxidase electrode. After rewarming, the cerebral metabolic parameters were almost restored to the pre-injury level in animals with CPP of more than 90mmHg. However, in the animals with CPP= 60 mmHg, all parameters significantly deteriorated and indicated misery perfusion; ScvO₂ was low ($29.5\pm 1.1\%$), AVDO₂ was significantly high (9.9 ± 0.8 ml 100 g(-1) min(-1)) (one-way analysis of variance, $p<0.05$), and electron microscopic features showed subcellular ischemic change. Extracellular glutamate significantly increased during the rewarming period only in the CPP= 40 mmHg group. CPP less than 60 mmHg during rewarming causes secondary ischemic insult, which might indicate continuation of cerebral vasoconstriction in hypothermia. CPP higher than 90 mmHg is required to avoid the potential risk of relative ischemia after hypothermia.

Level 6, neutral, funding: partial Japan Ministry of Education, Science, and Culture

Key points: elevated intracranial pressure model in cats without arrest (simulating head trauma), no comparison rewarming rates

Behringer W, Prueckner S, Safar P, et al. Rapid induction of mild cerebral hypothermia by cold aortic flush achieves normal recovery in a dog outcome model with 20-minute exsanguination cardiac arrest. *Acad Emerg Med* 7(12):1341-8, 2000.

OBJECTIVES: Resuscitation attempts in trauma victims who suffer cardiac arrest (CA) from exsanguination almost always fail. The authors hypothesized that an aortic arch flush with cold normal saline solution (NSS) at the start of exsanguination CA can preserve cerebral viability during 20-minute no-flow.

METHODS: Twelve dogs were exsanguinated over 5 minutes to CA of 20-minute no-flow, resuscitated by cardiopulmonary bypass, followed by post-CA mild hypothermia (34 degrees C) continued to 12 hours, controlled ventilation to 20 hours, and intensive care to 72 hours. At CA 2 minutes, the dogs received a 500-mL flush of NSS at either 24 degrees C (group 1, $n = 6$) or 4 degrees C (group 2, $n = 6$), using a balloon-tipped catheter inserted via the femoral artery into the descending thoracic aorta.

RESULTS: The flush at 24 degrees C (group 1) decreased tympanic membrane temperature [mean (+/-SD)] from 37.5 degrees C (+/-0.1) to 35.7 degrees C (+/-0.2); the flush at 4 degrees C (group 2) to 34.0 degrees C (+/-1.1) ($p = 0.005$). In group 1, one dog achieved overall performance category (OPC) 2 (moderate disability), one OPC 3 (severe disability), and four OPC 4 (coma). In group 2, four dogs achieved OPC 1 (normal), one

OPC 2, and one OPC 3 ($p = 0.008$). Neurologic deficit scores (0-10% normal, 100% brain death) [median (25th-75th percentile)] were 62% (40-66) in group 1 and 5% (0-19) in group 2 ($p = 0.01$). Total brain histologic damage scores were 130 (62-137) in group 1 and 24 (10-55) in group 2 ($p = 0.008$).

CONCLUSIONS: Aortic arch flush of 4 degrees C at the start of CA of 20 minutes rapidly induces mild cerebral hypothermia and can lead to normal functional recovery with minimal histologic brain damage. The same model with aortic arch flush of 24 degrees C results in survival with brain damage in all dogs, which makes it suitable for testing other (e.g., pharmacologic) preservation potentials.

Level 3, good, neutral, funding: United States Navy grant

Key points: incremental rewarming for 12 hours, cold aortic flush after 20 minutes of cardiac arrest, brain histopathology

Behringer W, Safar P, Wu X et al. Survival without brain damage after clinical death of 60-120 mins in dogs using suspended animation by profound hypothermia. Crit Care Med 31(5):1523-31, 2003.

OBJECTIVES: This study explored the limits of good outcome of brain and organism achievable after cardiac arrest (no blood flow) of 60-120 mins, with preservation (suspended animation) induced immediately after the start of exsanguination cardiac arrest.

DESIGN: Prospective experimental comparison of three arrest times, without randomization.

SETTING: University research laboratory.

SUBJECTS: Twenty-seven custom-bred hunting dogs (17-25 kg).

INTERVENTIONS: Dogs were exsanguinated over 5 mins to cardiac arrest no-flow of 60 mins, 90 mins, or 120 mins. At 2 mins of cardiac arrest, the dogs received, via a balloon-tipped catheter, an aortic flush of isotonic saline at 2 degrees C (at a rate of 1 L/min), until tympanic temperature reached 20 degrees C (for 60 mins of cardiac arrest), 15 degrees C (for 60 mins of cardiac arrest), or 10 degrees C (for 60, 90, or 120 mins of cardiac arrest). Resuscitation was by closed-chest cardiopulmonary bypass, postcardiac arrest mild hypothermia (tympanic temperature 34 degrees C) to 12 hrs, controlled ventilation to 20 hrs, and intensive care to 72 hrs.

MEASUREMENTS AND MAIN RESULTS: We assessed overall performance categories (OPC 1, normal; 2, moderate disability; 3, severe disability; 4, coma; 5, death), neurologic deficit scores (NDS 0-10%, normal; 100%, brain death), regional and total brain histologic damage scores at 72 hrs (total HDS >0-40, mild; 40-100, moderate; >100, severe damage), and morphologic damage of extracerebral organs. For 60 mins of cardiac arrest ($n = 14$), tympanic temperature 20 degrees C ($n = 6$) was achieved after flush of 3 mins and resulted in two dogs with OPC 1 and four dogs with OPC 2: median NDS, 13% (range 0-27%); and median total HDS, 28 (range, 4-36). Tympanic temperature of 15 degrees C ($n = 5$) was achieved after flush of 7 mins and resulted in all five dogs with OPC 1, NDS 0% (0-3%), and HDS 8 (0-48). Tympanic temperature 10 degrees C ($n = 3$) was achieved after flush of 11 mins and resulted in all three dogs with OPC 1, NDS 0%, and HDS 16 (2-18). For 90 mins of cardiac arrest ($n = 6$), tympanic temperature 10 degrees C was achieved after flush of 15 mins and resulted in all six dogs with OPC 1, NDS 0%, and HDS 8 (0-37). For 120 mins of cardiac arrest ($n = 7$), three dogs had to be excluded. In the four dogs within protocol, tympanic temperature 10 degrees C was achieved after flush of 15 mins. This resulted in one dog with OPC 1, NDS 0%, and total HDS 14; one with OPC 1, NDS 6%, and total HDS 20; one with OPC 2, NDS 13%, and total HDS 10; and one with OPC 3, NDS 39%, and total HDS 22.

CONCLUSIONS: In a systematic series of studies in dogs, the rapid induction of profound cerebral hypothermia (tympanic temperature 10 degrees C) by aortic flush of cold saline immediately after the start of exsanguination cardiac arrest-which rarely can be resuscitated effectively with current methods-can achieve survival without functional or histologic brain damage, after cardiac arrest no-flow of 60 or 90 mins and possibly 120 mins. The use of additional preservation strategies should be pursued in the 120-min arrest model.

Level 3, good, neutral, funding: United States Department of Defense grant, United States Army MRM/C/TATRC grant, and Cardeon Corporation

Key points: suspended animation, neurological deficit scores, brain histopathology

Bigelow WG, Lindsay WK, and Greenwood WF. Hypothermia-Its Possible Role in Cardiac Surgery: An Investigation of Factors Governing Survival in Dogs at Low Body Temperatures. Ann Surg 132(5): 849-866, 1950.

The use of hypothermia as a form of anesthetic could conceivably extend the scope of surgery in many new directions. A state in which the body temperature is lowered and the oxygen requirements of tissues are reduced to a small fraction of normal would allow exclusion of organs from the circulation for prolonged periods. Such a technic might permit surgeons to operate on the "bloodless heart" without recourse to extracorporeal pumps, and perhaps allow transplantation of organs.

Level 3, neutral, funding: financed in part by a Defence Board of Canada grant

Key points: dogs cooled to 20° C, then rapid rewarming to 40-42 ° C (four of five died)

Brunette DD, McVaney K. Hypothermic cardiac arrest: an 11 year review of ED management and outcome. Am J of Emerg Med 18:418-22, 2000.

The purpose of this study was to examine the emergency department (ED) management of hypothermic cardiac arrest and its outcome. The medical records of all patients with hypothermic cardiac arrest treated in the ED from January 1, 1988 to January 31, 1999 were retrospectively reviewed. Data collected included initial body temperature, serum potassium, methods of rewarming, return of perfusing rhythm, and morbidity and mortality. Data were analyzed by descriptive methods. Eleven patients were treated in the ED resuscitation room for hypothermic cardiac arrest. Six patients were found in cardiac arrest in the field, one patient arrested during transport, and four patients arrested after ED arrival. The average initial temperature was 79.1 degrees F (range 69.0 degrees F to 86.7 degrees F). Seven patients received an ED thoracotomy with internal cardiac massage and warm mediastinal irrigation. Four patients had airway management in the ED and then direct transport to the operating room for cardiac bypass rewarming. Three of the seven patients who received an ED thoracotomy subsequently went to intraoperative cardiac bypass rewarming. Five of the seven (71.4%) patients who received an ED thoracotomy survived, versus none of the four patients (0%) who went directly to intraoperative cardiac bypass. A direct comparison of immediate ED thoracotomy versus intraoperative cardiac bypass without ED thoracotomy is cautiously made as this was an unmatched and nonrandomized study. Three of the surviving patients underwent intraoperative cardiac bypass rewarming after receiving an ED thoracotomy. In two of these patients a perfusing rhythm had been established after thoracotomy in the ED and before transport to the operating room for cardiac bypass. Only one of seven (14.3%) patients who arrested prehospital survived versus four of four (100%) who arrested in the ED. ED thoracotomy with internal cardiac massage and mediastinal irrigation rewarming is effective in the management of hypothermic cardiac arrest.

Level 6, neutral, funding none

Key points: retrospective study 11 patients with hypothermic arrest presenting to emergency department, no comparison of rewarming rates

Delaney KA, Vassallo SU, Larkin GL, et al. Rewarming rates in urban patients with hypothermia: prediction of underlying infection. Academic Emerg Med 13:913-921, 2006.

Background: In the urban setting, hypothermia is commonly associated with illness or intoxication, with death often secondary to infection.

Objectives: To evaluate factors that affect the rewarming rate (RWR) and the ability of the RWR and other clinical markers to predict the presence or absence of underlying infection in an adult urban population.

Methods: This was a prospective observational study of hypothermic patient visits to a large emergency department. Serial temperatures were obtained during rewarming to construct rewarming curves. Rewarming modalities selected by emergency physicians were correlated with admission temperatures. Univariate associates of RWR and infection were assessed.

Results: The authors identified 96 patient visits. The median temperature was 89.5°F (range 73.0-95°F). Thirteen patients had temperatures of <80.0°F. Seven died within 14 hours of presentation; six, of infection. No patient experienced ventricular fibrillation. Potential candidate predictors of infection from a multivariate analysis were a RWR of <1.8°F per hour and a serum albumin of .7 g/dL. Rapid rewarming was associated with the absence of infection and a temperature below 86.0°F. IN patients without significant underlying illness, rewarming rates appeared to be independent of the modality of rewarming.

Conclusions: Rewarming rates reflect intrinsic capacity for thermogenesis. Increased RWRs were associated with the absence of infection. The achievement of normothermia did not prevent death in infected patients. Initiation of invasive rewarming in urban patients with hypothermia who have not had hypothermic cardiac arrest may be unwarranted. Management of this population should emphasize support, detection, and treatment of underlying illness.

Level 6, neutral, funding: grant from Aaron Diamond Foundation

Key points: Evaluation of rewarming rate (prospective observational study) of patients visiting emergency department, linkage of rewarming rate to underlying disease, no patients with cardiac arrest

Diao C, Zhu L, Wang H. Cooling and rewarming for brain ischemia or injury: theoretical analysis. *Annals Biomed Engineering* 31:346-353, 2003.

Abstract—A three-dimensional model is developed in this study to examine the transient and steady state temperature distribution in the brain during selective brain cooling and subsequent rewarming. Selective brain cooling is induced through either wearing a cooling helmet or packing the head with ice. The ischemic region of the brain is simulated through reducing the blood perfusion rate to 20% of its normal value. The geometric and thermal properties and physiological characteristics for each layer, as well as the arterial blood temperature, are used as the input to the Pennes bioheat equation. Our data suggest that rapid cooling of the brain gray matter can be achieved by SBC on the head surface ~26 min for adults versus 15 min for infants. Suboptimal thermal contact between the head surface and the coolant in most commercially available cooling helmets is suspected to be the main reason for delayed cooling in SBC as compared to the ice packing. The study has also demonstrated that the simulated 3 °C/h passive rewarming rate by exposing the head to room temperature after removing the source of cooling may be too rapid.

Level 6, neutral, funding: AHA grant

Key points: experimental model that suggested that slower rewarming rates are better for the ischemic brain

Ebmeyer U, Safar P, Radovsky A, et al. Moderate hypothermia for 48 hours after temporary epidural brain compression injury in a canine outcome model. *J Neurotrauma* 15(5):323-36, 1998.

In a previous study with this dog model, post-insult hypothermia of 31 degrees C for 5 h prevented secondary intraventricular pressure (IVP) rise, but during 35 degrees C or 38 degrees C, one-half of the dogs developed delayed IVP rise to brain death. We hypothesized that 31 degrees C extended to 48 h would prevent brain herniation. Using epidural balloon inflation, we increased contralateral IVP to 62 mm Hg for 90 min. Controlled ventilation was to 72 h and intensive care to 96 h. Group 1 dogs (n = 10) were normothermic controls (37.5 degrees C). Group 2 dogs (n = 10) were surface-cooled from 15 to 45 min of balloon inflation and maintained at moderate hypothermia (31 degrees C) to 48 h. Rewarming was from 48 to 72 h. Four additional dogs of hypothermia Group 2 had to be excluded from analysis for pneumonia and/or bleeding diathesis. After balloon deflation, IVP increased to 20 mm Hg or greater at 154 +/- 215 (range 15-720) min following the insult in Group 1 and at 1394 +/- 1191 (range 210-3420) min in Group 2 (p = 0.004), still during 31 degrees C but without further increase during hypothermia. Further IVP rise led to brain death in Group 1 in 6 of 10 dogs at 44 +/- 18 (range 21-72) h (all during controlled ventilation); and in Group 2, in 6 of 10 dogs at 87 +/- 11 (range 72-96) h (p = 0.001), all after rewarming, during spontaneous breathing. Survival to 96 h was achieved by 4 of 10 dogs in Group 1, and by 7 of 10 dogs in Group 2 (NS). Three of the six brain deaths in Group 2 occurred at 96 h. The macroscopically damaged brain volume was only numerically smaller in Group

2. The vermis downward shift was 6.8 ± 3.5 mm in Group 1, versus 4.7 ± 2.2 mm in Group 2 ($p = 0.05$). In an adjunctive study, in 4 additional normothermic dogs, hemispheric cerebral blood flow showed post-insult hypoperfusion bilaterally but no evidence of hyperemia preceding IVP rise to brain death. In conclusion, in this model, moderate hypothermia during and for 48 h after temporary epidural brain compression can maintain a low IVP during hypothermia but cannot prevent lethal brain swelling after rewarming and may cause coagulopathy and pulmonary complications.

Level 3, good, neutral, funding: NIH grant, Asmund S. Laerdal Foundation

Key points: 48 hours of hypothermia at 31°C , rewarming of $0.5^\circ\text{C}/\text{hour}$

Eschel G, Reisler G, Berkovitch M, et al. Comparison of fast versus slow rewarming following acute moderate hypothermia in rats. Paediatric Anaesthesia 12:235-242, 2002.

Background: The aim of this study was to compare the biochemical and physiological responses of fast vs. slow rewarming from moderate hypothermia in anaesthetized rats.

Methods: Anaesthetized rats were surface cooled to 28°C , for 20 min, then rewarmed either quickly over 30 min or slowly over 120 min with monitoring of vital signs, systemic vascular resistance (SVR), cardiac output, biochemical changes and activity for 31 days.

Results: At hypothermia, cardiac output decreased to $77 \pm 38 \text{ ml}\cdot\text{min}^{-1}$ and lactate increased to $4.62 \pm 4.73 \text{ mmol}\cdot\text{l}^{-1}$. Fast rewarming caused an abrupt increase in cardiac output ($270 \pm 24 \text{ ml}\cdot\text{min}^{-1}$) and a sharp drop in SVR ($325.6 \pm 23.3 \text{ dyne}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$), compared with a smoother course with cardiac output ($142 \pm 18 \text{ ml}\cdot\text{min}^{-1}$, $P < 0.01$) and SVR ($662.8 \pm 41.0 \text{ dyne}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$, $P < 0.01$), measured during slow rewarming. Lactate failed to return to normal values (upon returning to normothermia) ($2.5 \pm 0.75 \text{ mmol}\cdot\text{l}^{-1}$) only in the fast rewarming group. In both groups, activity in the open field was not different from control rats.

Conclusions: In rats, moderate hypothermia for 20 min does not appear to cause lasting biochemical or behavioural consequences, whether rewarming lasted over 30 or 120 min. However, there was a greater early change in cardiac output and heart rate, due to systemic vasodilatation in the fast rewarming animals. These acute changes may have consequences in patients with compromised cardiovascular reserves.

Level 6, good, funding: none reported

Key points: cooled rats rewarmed at various rates with improvement in slow rewarming group, no arrest induced in the rats

Fischer U, Cox CS, Laine GA, et al. Mild hypothermia impairs left ventricular diastolic but not systolic function. J Investigative Surg 18:291-96, 2005.

Hypothermia is a component of myocardial protection during cardiopulmonary bypass (CPB) and cardioplegic arrest (CA). Patients in the early post CPB period often show mild hypothermia and cardiac dysfunction. We sought to investigate the impact of hypothermia on left ventricular (LV) function. Anesthetized dogs ($n = 12$) were instrumented with myocardial ultrasonic crystals and LV micromanometer. Systolic function was measured by preload recruitable stroke work (PRSW). Diastolic function was measured by $-dP/dt(\text{max})$ and tau. In six dogs (Norm group), body temperature was maintained at baseline levels. In another six dogs (Hypo group), body temperature dropped gradually over the time course of the experiment. The body temperature in the Hypo group decreased from 37.0 ± 0.3 degrees C to 35.2 ± 1.0 degrees C. $-dP/dt(\text{max})$ decreased and tau increased significantly with hypothermia but were stable in the Norm group. Both tau and $-dP/dt(\text{max})$ showed a linear relationship to the body temperature ($r = .91$ and $r = .93$, respectively). PRSW did not change and cardiac output decreased with hypothermia. Thus, even mild hypothermia impairs LV diastolic but not systolic function. Cardiac output is temperature sensitive and therefore rewarming of patients post-CPB has priority.

Level 3, neutral, funding: none reported in paper

Key points: Anesthetized dog model with temperature drop gradually in hypothermic model, no patients arrested, did not rewarm dogs

Gordon ML, Kellerman K, Blobner M, et al. Fast rewarming after deep hypothermic circulatory arrest in rats impairs histologic outcome and increases NFκβ expression in the brain. *Perfusion* 25:349-354, 2010.

Objective: Deep hypothermia is used as a neuroprotectant during cardiac surgery utilizing deep hypothermic circulatory arrest (DHCA), although the ideal rewarming strategy is not known yet. Some of the neuroprotective properties of hypothermia seem to be mediated by Nuclear Factor Kappa B (NFκB) as an important transcription factor. The current study was designed to investigate the effect of the rewarming rate on histologic outcome and cerebral NFκB expression one day following DHCA in rats. Methods: With IRB approval, 20 rats were cannulated for cardiopulmonary bypass (CPB), cooled to a rectal temperature of 15-18°C, subjected to 45min of DHCA and randomly assigned to either a slow (40 min) or a fast (20 min) rewarming protocol. At 24 hours post DHCA, the number of eosinophilic neurons was analyzed with hematoxylin and eosin (HE) staining, and NFκB expression immunohistochemically. The two experimental groups were compared with untreated control rats. Results: HE staining showed more eosinophilic neurons in the motor cortex following fast rewarming (60 [15-388]) compared to slow rewarming (15 [10-21]) (p<0.05). Neuronal expression of NFκB was increased in the fast rewarming group in both brain areas, the motor cortex (fast: 258 [135-393]; slow: 165 [80-212]; control: 73 [44-111]) as well as the hippocampus (fast: 243 [209-314]; slow: 202 [187-239]; control: 86 [68-108]) (p<0.05). Hyperthermic episodes were strictly avoided. Conclusions: Fast rewarming with strict avoidance of hyperthermia after DHCA in rats was accompanied by pronounced histologic damage and accentuated cerebral NFκB expression.

Level 6, good, funding: Deutsche Forschungsgemeinschaft

Key points: rats undergoing cardiopulmonary bypass and warmed slowly or more quickly showed much worse histologic damage than faster rewarming

Grigore AM, Grocott HP, Mathew JP, et al. The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesth Analg* 94:4-10, 2002.

Neurocognitive dysfunction is a common complication after cardiac surgery. We evaluated in this prospective study the effect of rewarming rate on neurocognitive outcome after hypothermic cardiopulmonary bypass (CPB). After IRB approval and informed consent, 165 coronary artery bypass graft surgery patients were studied. Patients received similar surgical and anesthetic management until rewarming from hypothermic (28 degrees -32 degrees C) CPB. Group 1 (control; n = 100) was warmed in a conventional manner (4 degrees -6 degrees C gradient between nasopharyngeal and CPB perfusate temperature) whereas Group 2 (slow rewarm; n = 65) was warmed at a slower rate, maintaining no more than 2 degrees C difference between nasopharyngeal and CPB perfusate temperature. Neurocognitive function was assessed at baseline and 6 wk after coronary artery bypass graft surgery. Univariable analysis revealed no significant differences between the Control and Slow Rewarming groups in the stroke rate. Multivariable linear regression analysis, examining treatment group, diabetes, baseline cognitive function, and cross-clamp time revealed a significant association between change in cognitive function and rate of rewarming (P = 0.05). IMPLICATIONS: Slower rewarming during cardiopulmonary bypass (CPB) was associated with better cognitive performance at 6 wk. These results suggest that a slower rewarming rate with lower peak temperatures during CPB may be an important factor in the prevention of neurocognitive decline after hypothermic CPB.

Level 6, good, funding: NIH grant USA

Key points: patients undergoing artery bypass graft surgery, comparison of rewarming rates and post-surgical outcome

Haughn C, Gallo U, Raimonde AJ, et al. Feasibility of a novel veno-veno circuit as a central rewarming method in a severely hypothermic canine model. *Curr Surg* 60(4):442-8, 2003.

PURPOSE: Many victims of accidental hypothermia are successfully resuscitated, but questions remain regarding the optimum rewarming techniques. Most of the invasive warming techniques such as closed thoracic lavage, hemodialysis, peritoneal dialysis, and cardiopulmonary bypass require specialized personnel, equipment, and procedures that are not readily available in all facilities. The objective of this study was to investigate the technical feasibility of utilizing a novel veno-veno rewarming circuit to resuscitate severely hypothermic subjects. If this alternative invasive warming technique is successful, it could be available to treat hypothermic patients in virtually any emergency department setting.

METHODS: The rewarming system consisted of a Baxter ThermoCyl warmer (Baxter Co., McGaw Park, IL), a roller pump, hemodialysis tubing, connectors, and 2 venous catheters. Blood was pumped from the body via the femoral vein, through the roller pump, into the warmer, and then returned to the body via the right jugular vein. Seven adult mongrel hounds of similar weights (20 to 25 kg) were anesthetized and instrumented for data collection. Temperature probes were placed in the rectum, the peritoneal cavity, and the esophagus to record core temperatures. Each animal was cooled by ice packing to a central core temperature of 29 degrees C and then rewarmed using the described veno-veno circuit. Vital signs, pulse oximetry, cardiac rhythm, and laboratory values were obtained prior to cooling the animals, and were repeated for every degree Celsius change once warming began. Christopher Haughn, MD, was the second place winner in the Basic Sciences Resident Competition at the Ohio American College of Surgeons meeting.

RESULTS: Because of technical difficulties, data from 1 dog were not included in the results. Of the remaining 6 dogs, all were rewarmed from 29 degrees C to 37 degrees C. Adverse side effects included gross hematuria, acidemia (median pH decrease was 0.088), and decreases in haptoglobin (median decrease 13.5 g/dl), hemoglobin (median decrease 1.35 g/dl), and arterial pO₂ level (median decrease 167 mm Hg). Decreases in blood pressure and heart rate were also noted during the cooling process, but reversed upon rewarming.

CONCLUSIONS: From this pilot study, we conclude that our novel veno-veno circuit rewarming is a feasible method of rewarming hypothermic subjects and warrants further investigation and comparison with other active warming methods.

Level 3, fair, neutral, funding: The Summa Health System Foundation

Key points: non-survival study, evaluation of veno-veno central rewarming circuit

Jeung KW, Min Y, Heo T. Rapidly induced selective cerebral hypothermia using a cold carotid arterial flush during cardiac arrest in a dog model. Resuscitation 77(2):235-41, 2008.

PURPOSE: The present study was undertaken to determine whether flushing the carotid artery with normal saline at 4 degrees C (hypothermic carotid arterial flush, HCAF) during cardiac arrest can achieve selective cerebral hypothermia rapidly during cardiac arrest and improve cerebral outcome.

METHODS: Ventricular fibrillation (VF) was induced in fourteen dogs and circulatory arrest was maintained for 9 min. Dogs were then resuscitated by cardiopulmonary resuscitation. The dogs were divided into two groups; a control group (n=7), which underwent precisely the same procedure as the experimental group but not HCAF, and an experimental group (HCAF group; n=7), which received HCAF from 8 min after the onset of VF.

RESULTS: Two dogs in the control group and in the HCAF group died within 72 h after the recovery of spontaneous circulation (ROSC) due to extracerebral complications. The remaining 10 dogs survived to final evaluation at 72 h post-ROSC. In the HCAF group, tympanic temperature decreased from 37.7 degrees C (37.5-37.8) to 34 degrees C in 1 min (1-1.5) from the start of HCAF and was maintained below 34 degrees C until 6.5 min (3-12) after the start of HCAF, whereas oesophageal and rectal temperatures were maintained above 35 degrees C. Neurological deficit scores (0-100%) at 72 h post-ROSC were 42.4% (27.0-80.6) in the control group and 18.4% (14.0-36.0) in the HCAF group (p<0.05).

CONCLUSION: HCAF induced selective cerebral hypothermia rapidly during cardiac arrest and improved neurological deficit scores after 9 min of no blood flow in the described canine cardiac arrest model.

Level 3, good, neutral, funding: not reported

Key points: incremental rewarming, 0.25° C/hour until 37° C, cold aortic flush, neurological deficit scores

Kaplan MI, Lee JA, Hovda LR, Brutlag A. Adverse effects associated with inadvertent intravenous penicillin G procaine-penicillin G benzathine administration in two dogs and a cat. JAVMA 238 (4): 507-510, 2011.

CASE DESCRIPTION: 2 dogs and a cat were inadvertently given penicillin G procaine-penicillin G benzathine IV instead of propofol during induction of anesthesia for routine dental prophylaxis. One dog and the cat required hospitalization because of severe neurologic impairment and cardiopulmonary arrest (cat); the remaining dog did not develop any clinical signs.

CLINICAL FINDINGS: In the 2 animals that developed signs consistent with an immediate adverse reaction, clinical signs included muscle tremors, seizures, blindness, vocalization, agitation, and transient loss of vision. Hypothermia, pruritus, hypotension, and cardiac arrest were also documented.

TREATMENT AND OUTCOME: The 2 affected patients responded to treatment with anticonvulsant medications, centrally acting muscle relaxants, sedation, and intensive supportive care including IV fluid administration and oxygen supplementation as needed. Cardiopulmonary cerebral resuscitation was performed successfully in the cat. The dog that did not develop any clinical signs was not treated. The 2 affected patients recovered fully and were discharged from the hospital after 3 to 4 days with no apparent sequelae.

CLINICAL RELEVANCE: Penicillin G procaine-penicillin G benzathine and propofol are common drugs in veterinary practice and may both be administered to patients undergoing elective procedures. Because of their similar milky white appearance, veterinarians should label syringes and take care to avoid this medication error. There is no specific antidote for penicillin or procaine toxicosis. Aggressive and immediate treatment is required in patients that develop an adverse reaction to ensure a successful outcome.

Level 5, good, neutral, funding not reported

Key points: no temperature change in 5 hours in the ROSC cat after CPA

Kawahara F, Kadoi Y, et al. Slow rewarming improves jugular venous oxygen saturation during rewarming. Acta Anaesthesiol Scand 47:419-424, 2003.

Background: There have been many studies regarding the etiology of postoperative cognitive dysfunction after coronary artery bypass graft (CABG) surgery. Although its etiology remains unresolved, one possible factor related to postoperative cognitive dysfunction is a reduced internal jugular venous oxygen hemoglobin saturation (SjvO₂) during the rewarming period. The purpose of this study was to examine the effect of rewarming rates on SjvO₂ during rewarming.

Methods: One-hundred patients scheduled for elective CABG surgery were randomly divided into two groups; control group (0.48 ± 0.09°C, n = 50), slow rewarming group (0.24 ± 0.09°C, n = 50). After the induction of anesthesia, a fiberoptic oximetry oxygen saturation catheter was inserted into the right jugular bulb to monitor SjvO₂ continuously. Hemodynamic parameters, arterial and jugular venous blood gases were measured at nine time-points.

Results: Cerebral desaturation (defined as a SjvO₂ value below 50%) during rewarming was more frequent in the control group than in the slow group. Cerebral desaturation time (duration when SjvO₂ was less than 50%) and the ratio of the cerebral desaturation time to the total CPB time in the control group differed significantly from those in the slow group (control group: 17 ± 11 min, 12 ± 4%, slow group: 10 ± 8 min, 7 ± 4%, respectively, P < 0.05). There was no significant difference in mini-mental state examination on the day before the operation nor at 1 month after the surgery among four values (the day before the operation: control group; 48 ± 8, slow group; 48 ± 7, at one month after the surgery: control group; 46 ± 7, slow group; 45 ± 9).

Conclusions: A slow rewarming rate could reduce the chance of a decrease in SjvO₂ during rewarming.

Level 6, good, funding: grant Japanese Ministry of Science and Education

Key points: evaluated central venous oxygen saturation during rewarming at slow versus faster rate (although the actual rates of rewarming were not clearly stated); cardiopulmonary bypass grant human patients

Kim K, Jo YH, Rhee JE, et al. Effect of speed of rewarming and administration of anti-inflammatory or anti-oxidant agents on acute lung injury in an intestinal ischemia model treated with therapeutic hypothermia. Resuscitation 81: 100-105, 2010.

Aim of the study: Acute lung injury (ALI) develops in various clinical situations and is associated with high morbidity and mortality and therapeutic hypothermia (HT) has been studied to attenuate the ALI. However, the optimal method of rewarming has not been determined. We determined the effect of speed of rewarming and the administration of anti-inflammatory or anti-oxidant agents on ALI in an intestinal ischemia and reperfusion (I/R) model treated with HT.

Materials and methods: A Sprague–Dawley rat model of intestine ischemia and reperfusion was used. Two parallel animal experiments were conducted. In the survival study, rats (n = 5 per group) underwent normothermic intestinal ischemia (60 min, 36–38 °C) and then randomized into 7 groups with reperfusion: normothermia (NT), HT without rewarming (30–32 °C, HT), 2 h HT + rewarming for 1 h (RW1), 2 h HT + rewarming for 2 h (RW2), RW1 + N-acetyl cysteine (RW-NAC), RW1 + ethylpyruvate (RW-EP), and RW1 + dexamethasone (RW + Dexa). In the second experiment, we investigated the histological and biochemical effects on the lung 4 h after reperfusion (n = 8 per group).

Results: The survival rate was lowest after NT. The HT, RW2, and RW-Dexa groups survived longer than the RW1, RW-NAC, and RW-EP groups. ALI scores were lower in the HT, RW2, and RW-Dexa groups than RW1. Lung malondialdehyde content was also lower in these groups. Interleukin (IL)-6 was significantly higher in the RW1 group. Inducible NO synthase gene expression in lung was lower in the HT, RW2, and RW-Dexa than RW1, and serum NO was lower in the RW2 and RW-Dexa than RW1.

Conclusion: Gradual rewarming and administration of dexamethasone improved survival and attenuated ALI after intestinal I/R injury treated with HT in rats.

Level 6, good, funding: grant Korea Healthcare Technology R&D Project

Key points: non-arrest model in rats, slower rewarming had positive effect on reducing ALI changes in lungs

Kim WG and Yang H. End-point temperature of rewarming and hypothermic cardiopulmonary bypass in pediatric patients. Artificial Organs 29:876-879, 2005.

In an attempt to find an adequate end-point rewarming temperature after hypothermic cardiopulmonary bypass (CPB), 50 pediatric patients who underwent cardiac surgery were randomly assigned for the end-point rectal rewarming temperature at either 35.5 (Group 1) or 37.0 degrees C (Group 2). The patients' rectal temperature, with heart rate and blood pressure, was measured 0.5, 1.0, 4.0, 8.0, and 16.0 h after the arrival in the intensive care unit. For all patients, nonpulsatile perfusion with a roller pump and a membrane or bubble oxygenator was used for oxygenation. Age, sex, body surface area, total bypass time, and rewarming time were comparable in both groups. No afterdrop and no statistical differences in the rectal temperatures between the two groups were observed. Also, no statistical differences were observed between the two groups with respect to the heart rate and blood pressure. No shivering was noted in all patients. In conclusion, with the restoration of rectal temperature above 35.5 degrees C at the end of CPB in pediatric patients, the present study found no afterdrop.

Level 6, neutral, funding: grant Seoul National University Hospital research fund

Key points: pediatric human patients undergoing cardiac surgery, no patient arrest, minimal difference in rewarming rates but slower rewarming better outcome

Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. Crit Care Med 21(9):1348-58, 1993.

OBJECTIVE: Previously, we documented that mild hypothermia (34 degrees C) induced immediately with reperfusion after ventricular fibrillation cardiac arrest in dogs improves functional and morphologic cerebral outcome. This study was designed to test the hypothesis that a 15-min delay in the initiation of cooling after reperfusion would offset this beneficial effect.

DESIGN: Prospective, randomized, controlled study.

SETTING: Animal intensive care unit.

SUBJECTS: A total of 22 custom-bred coonhounds.

INTERVENTIONS: Eighteen dogs underwent normothermic ventricular fibrillation arrest (no blood flow) of 12.5 mins, reperfusion with brief cardiopulmonary bypass, defibrillation within 5 mins, intermittent positive-pressure ventilation to 20 hrs, and intensive care to 96 hrs. Three groups of six dogs each were studied: group 1, normothermic controls; group 2, core temperature 34 degrees C from reperfusion to 1 hr; and group 3, delayed initiation of cooling until 15 mins after normothermic reperfusion, and 34 degrees C from 15 mins to 1 hr 15 mins after cardiac arrest.

MEASUREMENTS AND MAIN RESULTS: Tympanic membrane temperature (which represented brain temperature) in group 2 reached 34 degrees C at 6 +/- 3 (SD) mins after reperfusion; and in group 3 at 29 +/- 1 mins after reperfusion. Best overall performance categories achieved (1, normal; 5, brain death) compared with group 1, were better in group 2 ($p < 0.5$) but not in group 3 (NS). Similar results were found with best neurologic deficit scores (0%, normal; 100%, brain death), i.e., 44 +/- 4% in group 1, 19 +/- 15% in group 2 ($p < .01$), and 38 +/- 9% in group 3 (NS). Total brain histologic damage scores (< 30 minimal damage; > 100 severe damage), however, were 150 +/- 32 in group 1, 81 +/- 13 in group 2 ($p < .001$ vs. group 1), and 107 +/- 17 in group 3 ($p < .05$ vs. group 1).

CONCLUSIONS: Mild, resuscitative cerebral hypothermia induced immediately with reperfusion after cardiac arrest improves cerebral functional and morphologic outcome, whereas a delay of 15 mins in initiation of cooling after reperfusion may not improve functional outcome, although it may slightly decrease tissue damage.

Level 3, good, neutral, funding: Asmund S. Laerdal Foundation

Key points: external rewarming over 3-5 hours, delay of cooling by 15 minutes does not improve function outcome but may slightly decrease tissue damage

Lavinio A, Timofeev I, Nortje J, et al. Cerebrovascular reactivity during hypothermia and rewarming. *Brit J Anaesthesia* 99:237-44, 2007.

BACKGROUND: Experimental evidence from a murine model of traumatic brain injury (TBI) suggests that hypothermia followed by fast rewarming may damage cerebral microcirculation. The effects of hypothermia and subsequent rewarming on cerebral vasoreactivity in human TBI are unknown. **METHODS:** This is a retrospective analysis of data acquired during a prospective, observational neuromonitoring and imaging data collection project. Brain temperature, intracranial pressure (ICP), and cerebrovascular pressure reactivity index (PRx) were continuously monitored. **RESULTS:** Twenty-four TBI patients with refractory intracranial hypertension were cooled from 36.0 (0.9) to 34.2 (0.5) degrees C [mean (sd), $P < 0.0001$] in 3.9 (3.7) h. Induction of hypothermia [average duration 40 (45) h] significantly reduced ICP from 23.1 (3.6) to 18.3 (4.8) mm Hg ($P < 0.05$). Hypothermia did not impair cerebral vasoreactivity as average PRx changed non-significantly from 0.00 (0.21) to -0.01 (0.21). Slow rewarming up to 37.0 degrees C [rate of rewarming, 0.2 (0.2) degrees C h(-1)] did not increase ICP [18.6 (6.2) mm Hg] or PRx [0.06 (0.18)]. However, in 17 (70.1%) out of 24 patients, rewarming exceeded the brain temperature threshold of 37 degrees C. In these patients, the average brain temperature was allowed to increase to 37.8 (0.3) degrees C ($P < 0.0001$), ICP remained stable at 18.3 (8.0) mm Hg ($P = 0.74$), but average PRx increased to 0.32 (0.24) ($P < 0.0001$), indicating significant derangement in cerebrovascular reactivity. After rewarming, PRx correlated independently with brain temperature ($R = 0.53$; $P < 0.05$) and brain tissue O₂ ($R = 0.66$; $P < 0.01$). **CONCLUSIONS:** After moderate

hypothermia, rewarming exceeding the 37 degrees C threshold is associated with a significant increase in average PRx, indicating temperature-dependent hyperaemic derangement of cerebrovascular reactivity.

Level 6, neutral, funding: UK Government Technology Foresight Initiative and Medical Research Council, British Journal of Anesthesia/Royal College of Anaesthetists Fellowship, Academy of Medical Sciences Health Foundation, Senior Surgical Scientist Fellowship

Key points: retrospective study with human patients, intracranial hypertension severe head trauma, focus of study rewarming above 37 degrees Celsius negatively affects cerebrovascular reactivity

Leonov Y, Stertz F, Safar P et al. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 10(1):57-70, 1990.

We previously found mild hypothermia (34-36 degrees C), induced before cardiac arrest, to improve neurologic outcome. In this study we used a reproducible dog model to evaluate mild hypothermia by head cooling during arrest, continued with systemic cooling (34 degrees C) during recirculation and for 1 h after arrest. In four groups of dogs, ventricular fibrillation (no flow) of 12.5 min at 37.5 degrees C was reversed with cardiopulmonary bypass and defibrillation in less than or equal to 5 min, and followed by controlled ventilation to 20 h and intensive care to 96 h. In Study A we resuscitated with normotension and normal hematocrit; Control Group A-I (n = 12) was maintained normothermic, while Treatment Group A-II (n = 10) was treated with hypothermia. In Study B we resuscitated with hypertension and hemodilution. Control Group B-I (n = 12) was maintained normothermic (6 of 12 were not hemodiluted), while Treatment Group B-II (n = 10) was treated with hypothermia. Best overall performance categories (OPCs) achieved between 24 and 96 h postarrest were in Group A-I: OPC 1 (normal) in 0 of 12 dogs, OPC 2 (moderate disability) in 2, OPC 3 (severe disability) in 7, and OPC 4 (coma) in 3 dogs. In Group A-II, OPC 1 was achieved in 5 of 10 dogs (p less than 0.01), OPC 2 in 4 (p less than 0.001), OPC 3 in 1, and OPC 4 in 0 dogs. In Group B-I, OPC 1 was achieved in 0 of 12 dogs, OPC 2 in 6, OPC 3 in 5, and OPC 4 in 1 dog. In Group B-II, OPC 1 was achieved in 6 of 10 dogs (p less than 0.01), OPC 2 in 4 (p less than 0.05), and OPC 3 or 4 in 0 dogs. Mean neurologic deficit and brain histopathologic damage scores showed similar significant group differences. Morphologic myocardial damage scores were the same in all four groups. We conclude that mild brain cooling during and after insult improves neurologic outcome after cardiac arrest.

Level 3, good, neutral, funding: NIH grant

Key points: brain and myocardial histopathology after 34° C for 1 hour, then rewarming to 37.5 ° C over 1 hour

Majsce DJ, Towfighi J, Vannucci RC. Neuropathologic aspects of hypothermic circulatory arrest in newborn dogs. Acta Neuropathol 85:190-198, 1993.

A model of hypothermic circulatory arrest with recovery has been developed in the newborn dog. Eleven puppies were anesthetized with halothane, paralyzed and artificially ventilated with 70% nitrous oxide – 30% oxygen to paO₂ >60mmHg, paCO₂= 33-42 mmHg and pHa= 7.35-7.42.

Level 3, poor, funding: no funding reported

Key points: arrest model in dogs but no information on rate of rewarming, focused more on duration of hypothermia and effects thereafter

Mizushima Y, Wang P, Cioffi WG, et al. Should normothermia be restored and maintained during resuscitation after trauma and hemorrhage? J Trauma 48:58-65, 2000.

Background: Although hypothermia often occurs after trauma and has protective effects during ischemia and organ preservation, it remains unknown whether maintenance of hypothermia or restoring the body temperature to normothermia during resuscitation has any deleterious or beneficial effects on heart performance and organ blood flow after trauma-hemorrhage.

Methods: Male rats underwent laparotomy (i.e., induced trauma) and were exsanguinated to and maintained at a mean arterial pressure of 40 mm Hg until 40% of the maximum shed volume was returned in the form of

Ringer's lactate. Body temperature decreased from approximately 36.5°C to below 32°C. The animals were then resuscitated with four times the volume of maximal bleedout with Ringer's lactate. In one group, body temperature was rewarmed to 37°C during resuscitation. In another group, body temperature was maintained at hypothermia (32°C) for 4 hours after resuscitation. In an additional group, the body temperature was kept at 37°C during hemorrhage as well as during resuscitation. Left ventricle performance parameters such as maximal rate of left ventricular pressure increase and decrease (\pm dp/dtmax) were measured up to 4 hours. Cardiac output and regional blood flow were determined by radioactive microspheres at 4 hours after the completion of resuscitation.

Results: The maintenance of normothermia during hemorrhage or prolonged hypothermia after resuscitation depressed the left ventricular performance parameters, cardiac output, and regional blood flow in various organs. Rewarming the body to normothermia during resuscitation, however, significantly increased heart performance, cardiac output (from hypothermia 16.2 ± 1.4 to 22.3 ± 1.4 mL/min per 100 g body weight, $p < 0.05$) and total hepatic blood flow (from hypothermia 117.5 ± 5.3 to 166.0 ± 9.3 mL/min per 100 g tissue, $p < .05$).

Conclusion: Our data indicate that restoration of normothermia during resuscitation improves cardiac function and hepatic blood flow compared with hypothermia.

Level 6, good, funding: NIH grant

Key points: rat model; exsanguinated and later resuscitated with IV fluids and either rewarmed or not during fluid administration; rewarming improved condition but no rates rewarming

Morita W, Inokuchi S, Yamagiwa T, et al. Efficacy of portable and percutaneous cardiopulmonary bypass rewarming versus that of conventional internal rewarming for patients with accidental deep hypothermia. Crit Care Med 39:1064-1068, 2011.

OBJECTIVE:: Since 2001, at our institution, a portable and percutaneous cardiopulmonary bypass system has been used for rewarming of patients with accidental deep hypothermia. Before 2001, a conventional internal rewarming technique was used. The aim of this research is to examine the efficacy of portable and percutaneous cardiopulmonary bypass for rewarming of patients with accidental severe hypothermia and compare it with that of conventional rewarming methods. DESIGN:: Historical study. SETTING:: •••. PATIENTS: From April 1992 to March 2009, 70 patients with accidental deep hypothermia (core temperature $< 28^{\circ}\text{C}$) were transferred to our hospital. Two patients presented with intracranial hemorrhage on initial head computed tomography scans. These two patients were excluded because each required an emergency operation. Therefore, 68 patients were included in this study. We compared patients' clinical characteristics and outcomes. The parameters included the following: sex, age, vital signs on arrival to our hospital (Glasgow coma Scale scores, systolic blood pressure, heart rate, respiratory rate, core temperature), electrocardiogram on arrival to our hospital, rewarming speed, time of rewarming until 34°C was reached, ventricular fibrillation occurrence rate during rewarming, cause of cold environmental exposure, Glasgow Outcome Scale scores, and mortality. In addition, we divided the conventional and portable and percutaneous cardiopulmonary bypass rewarming groups into two categories depending on whether cardiopulmonary arrest occurred on arrival to our hospital. We also compared the survival rate and average Glasgow Outcome Scale scores for each group. INTERVENTIONS:: None. MEASUREMENTS AND MAIN RESULTS: Patients' clinical backgrounds did not differ significantly between the conventional and portable and percutaneous cardiopulmonary bypass rewarming groups. Glasgow Outcome Scale scores and survival rates of the portable and percutaneous cardiopulmonary bypass rewarming group patients, irrespective of whether cardiopulmonary arrest was experienced on arrival to our hospital, were significantly higher than those of the conventional rewarming group. CONCLUSIONS:: Portable and percutaneous cardiopulmonary bypass rewarming can improve the mortality rates and Glasgow Outcome Scale scores of accidental deep hypothermia patients.

Level 6, fair, funding: none

Key points: relevance very low to question, evaluation of function of cardiopulmonary bypass machine to rewarm human patients

Murray JP, Pavlin EG. Oxygen delivery and consumption during hypothermia and rewarming in the dog. *Anesthesiology* 72(3):510-6, 1990.

Changes in oxygen consumption (VO₂) and oxygen delivery (DO₂) were compared in three groups of paralyzed, sedated dogs: 1) a group (n = 5) cooled to 29 degrees C and immediately rewarmed to 37 degrees C; 2) a group (n = 5) cooled to and maintained at 29 degrees C for 24 h, and then rewarmed; and 3) a group (n = 5) maintained at 37 degrees C for 24 h. During the cooling phase, in both the acute and prolonged hypothermia animals, VO₂ and DO₂ decreased significantly from control values (P less than 0.05). The decrease in DO₂ occurred as a result of a similar decrease in cardiac index (CI; P less than 0.05) that was associated with a significant increase in systemic vascular resistance index (SVRI; P less than 0.05). Arteriovenous oxygen content difference (C(a-v)O₂), O₂ extraction ratio, mixed venous oxygen tension (PVO₂), pH, and base deficit (BD) were not different from control values even during prolonged hypothermia. Normothermic control dogs also demonstrated a significant decrease in CI (P less than 0.05) at 24 h. Surface rewarming increased VO₂ back to control values in the acute hypothermia group and to values above control (P less than 0.05) in the prolonged hypothermia group. DO₂ remained below control in both groups, resulting in a significant increase in O₂ extraction (P less than 0.05) and a decrease in PVO₂ (P less than 0.05) in the prolonged hypothermia animals. Following rewarming administration of sodium nitroprusside returned DO₂, CI, and SVRI to control values but did not increase VO₂. All animals survived the study without need for inotropic support.

Level 3, good, neutral, funding: not reported

Key points: rewarmed from 29° C to 37° C over a 4 hour period via surface rewarming, measured oxygen consumption and oxygen delivery

Moss JF, Haklin M, Southwick HW, Roseman DL. A Model for the Treatment of Accidental Severe Hypothermia. *J Trauma* 26(1): 68-74 1986.

Central to the controversy that surrounds the treatment of accidental severe hypothermia is the question of how the method of rewarming affects myocardial performance, and therefore survival. We induced severe hypothermia and cardiac arrest in 15 mongrel dogs. Each dog was rewarmed by one of three methods: partial cardiac bypass (Group I); peritoneal dialysis (Group II); or external rewarming with a fluid-circulated blanket (Group III). The cardiac arrest state was supported by partial cardiac bypass in Group I and by standard mechanical cardiopulmonary resuscitation (CPR) in Groups II and III. In all dogs, the hypothermically depressed myocardial performance returned to normal upon rewarming. Groups I and II had similar rewarming times and required similar volumes of crystalloid and bicarbonate solutions to maintain adequate cardiac filling pressures and arterial pH. However, Group III had a significantly slower rewarming time and required significantly greater volumes of crystalloid and bicarbonate solutions. The sole procedural death occurred in Group III. Our results show that partial cardiac bypass, peritoneal dialysis, and the fluid-circulated blanket are equally effective in rewarming severely hypothermic dogs with cardiac arrest, provided that the cardiac arrest is relieved by partial cardiac bypass or standard mechanical CPR and that physiologic levels of intravascular volume, oxygenation, and pH are maintained.

Level 3, good, support, funding: Raymond fund, Presbyterian-St. Luke's Hospital and by the Chris Hospital Medical Education Fund

Key points: surface rewarming took the longest, required most intravenous fluids

Mujscce DJ, Towfighi J, Yager JY, et al. Neuropathologic aspects of hypothermic circulatory arrest in newborn dogs. *Acta Neuropathologica* 85:190-198, 1993.

A model of hypothermic circulatory arrest with recovery has been developed in the newborn dog. Eleven puppies were anesthetized with halothane, paralyzed and artificially ventilated with 70% nitrous oxide-30%

oxygen to PaO₂ >60 mmHg, paCO₂= 33-42 mmHg and pHa= 7.35-7.42. Animals were surface cooled to 20°C, following which cardiac arrest was effected with i.v. KCl. Dogs remained asystolic without ventilation for 1.0, 1.5, or 1.75. Resuscitation was accomplished with closed chest compression, mechanical ventilation, i.v. epinephrine and NaHCO₃, and rewarming to 37°C. Thereafter, the puppies were maintained for either 18-22h (n=9) or 72 hr (n=2), at which time they underwent perfusion-fixation of their brains for pathologic analysis. Of the total, four out of four puppies arrested for 1.0 h exhibited no brain damage, including one recovered for 72 h; whereas one out of three and four out of four puppies arrested for 1.5 and 1.75 h, respectively, showed brain damage predominantly of the cerebral cortex but also of the basal ganglia and amygdaloid nucleus. The hippocampus was spared, even in a 1.75h-arrested animal which was maintained for 72h. No differences in pre- or post-arrest systemic blood pressure, heart rate, or acid-base balance were observed between the brain damaged and undamaged animals except for the single damaged animal arrested for 1.5 h, for which the blood pressure prior to cardiac arrest and during recovery as the lowest of all survivors. We conclude that newborn dogs undergoing hypothermic circulatory arrest for 1.0-1.5 h and which are fully recoverable without systemic hypotension exhibit no brain damage, whereas puppies arrested for 1.75 h exhibit brain damage entirely on the basis of global cerebral ischemia arising during the cardiac arrest. The experimental model has relevance to newborn human infants undergoing hypothermic circulatory arrest for the operative correction of congenital heart defects and should be useful for studying mechanisms of cellular injury in brain and other organs during prolonged ischemia.

Level 3, poor, funding: none reported

Key points: canine model of hypothermia focused more on duration of hypothermia and its effects; no information on rewarming times or rates for the dogs was reported

Nakane M, Kubota M, Nakagomi T, et al. Rewarming eliminates the protective effect of cooling against delayed neuronal death. Neuroreport 12:2439-2442, 2001.

Mild intra-ischemic hypothermia provides neuroprotection against delayed neuronal death in the hippocampal CA1. It has recently been reported that reduction in the metabolic rate of arachidonic acid (AA) liberated during ischemia might contribute to this neuroprotection. To examine whether rewarming during the early period of recirculation accelerates AA consumption and eliminates the neuroprotection, we measured the levels of AA in the hippocampus after various recirculation times under normothermia and hypothermia with or without rewarming. The tendency for AA to disappear was significantly different between each pair of groups. Histological examination 7 days after ischemia revealed no protection in the rewarmed group. These results suggest that neuronal injury during rewarming after hypothermia may be attributed to the rate of AA metabolism.

Level 6, good, funding: Research grant for cardiovascular disease from the Ministry of Health and Welfare, grant-in-aid for scientific research from the Ministry of Education, Science and Culture of Japan

Key points: rodent model comparing arachidonic acid levels in rewarming vs. non-rewarming groups after occlusion of carotid arteries

Piktel JS, Jeyaraj D, Said TH, et al. Enhanced dispersion of repolarization explains increased arrhythmogenesis in severe versus therapeutic hypothermia. Circ Arrhythm Electrophysiol 4:79-86, 2011.

Background: Hypothermia is proarrhythmic, and, as the use of therapeutic hypothermic (TH) increases, it is critically important to understand the electrophysiological effects of hypothermia on cardiac myocytes and arrhythmia substrates. We tested the hypothesis that hypothermia-enhanced transmural dispersion of repolarization (DOR) is a mechanism of arrhythmogenesis in hypothermia. In addition, we investigated whether the degree of hypothermia, the rate of temperature change, and cooling versus rewarming would alter hypothermia-induced arrhythmia substrates.

Methods and results: Optical action potentials were recorded from cells spanning the transmural wall of canine left ventricular wedge preparations at baseline (36°C), during cooling and during rewarming. Electrophysiological parameters were examined while varying the depth of hypothermia. On cooling to 26°C, DOR increased from 26±4 ms to 93±18 ms (P=0.021); conduction velocity decreased from 35±5 cm/s to 22±5 cm/s (P=0.010). On rewarming to 36°C, DOR remained prolonged, whereas conduction velocity returned to baseline. Conduction block and reentry was observed in all severe hypothermia preparations. Ventricular fibrillation/ventricular tachycardia was seen more during rewarming (4/5) versus cooling (2/6). In TH, (n=7), cooling to 32°C mildly increased DOR (31±6 to 50±9, P=0.012), with return to baseline on rewarming and was associated with decreased arrhythmia susceptibility. Increased rate of cooling did not further enhance DOR or arrhythmogenesis.

Conclusions: Hypothermia amplifies DOR and is a mechanism for arrhythmogenesis. DOR is directly dependent on the depth of cooling and rewarming. This provides insight into the clinical observation of a low incidence of arrhythmias in TH and has implications for protocols for the clinical application of TH.

Level 6, fair, funding: Departmental MetroHealth Foundation Grant, Emergency Medicine Foundation Career Development Grant, NIH Grant

Key points: benchtop evaluation of canine myocardial muscle, indicates that depth of hypothermia more important than the speed of rewarming as far as inducing arrhythmias

Pokela M, Heikkinen J, Biancari F, et al. Topical head cooling during rewarming after experimental hypothermic circulatory arrest. *Ann Thorac Surg* 75:1899-911, 2003.

Background: The aim of this study was to evaluate the potential neuroprotective effect of topical head cooling during the first 2 postoperative hours after experimental hypothermic circulatory arrest.

Methods: Twenty pigs underwent a 75-minute period of hypothermic circulatory arrest and were randomly assigned to rewarming to 37°C or to undergo topical cooling of the head for 2 hours from the start of rewarming followed by a period of external rewarming to 37°C.

Results: The 7-day survival rate was 70% in the control group and 60% in the topical head cooling group. Despite brain tissue oxygenation, intracranial pressures, mixed oxygen venous saturation, oxygen consumption, and extraction tended to be favorable in the topical head cooling group as a clear effect of mild hypothermia. The latter group had significantly higher postoperative brain lactate and pyruvate ratios, and lactate and glucose ratios. Furthermore, the topical head cooling group had worse fluid balance throughout the postoperative period. Brain histopathologic scores were comparable with the study groups, but among 7-days survivors these scores tended to be worse in the topical head cooling group.

Conclusions: Topical cooling of the head during the first 2 postoperative hours after experimental hypothermic circulatory arrest does not appear to provide any neuroprotective effect.

Level 6, good, funding: grant Oulu University Hospital, Finnish Foundation Cardiovascular Research and the Sigrid Juselius Foundation

Key points: pig model of hypothermic circulatory arrest; rewarming indirectly seems to be positive for these animals (not directly evaluated)

Safar, P, Xiao F, Radovsky A, et al. Improved cerebral resuscitation from cardiac arrest in dogs with mild hypothermia plus blood flow promotion. *Stroke* 27(1):105-13, 1996.

BACKGROUND AND PURPOSE:

In past studies, cerebral outcome after normothermic cardiac arrest of 10 or 12.5 minutes in dogs was improved but not normalized by resuscitative (postarrest) treatment with either mild hypothermia or hypertension plus hemodilution. We hypothesized that a multifaceted combination treatment would achieve complete cerebral recovery.

METHODS:

With our established dog outcome model, normothermic ventricular fibrillation of 11 minutes (without blood flow) was followed by controlled reperfusion (with brief normothermic cardiopulmonary bypass simulating low flow and low PaO₂ of external cardiopulmonary resuscitation) and defibrillation at < 2 minutes. Controlled ventilation was provided to 20 hours and intensive care to 96 hours. Control group 1 (n = 8) was kept normothermic (37.5 degrees C), normotensive, and hypocapnic throughout. Experimental group 2 (n = 8) received mild resuscitative hypothermia (34 degrees C) from about 10 minutes to 12 hours (by external and peritoneal cooling) plus cerebral blood flow promotion with induced moderate hypertension, mild hemodilution, and normocapnia.

RESULTS:

All 16 dogs in the protocol survived. At 96 hours, all 8 dogs in control group 1 achieved overall performance categories 3 (severe disability) or 4 (coma). In group 2, 6 of 8 dogs achieved overall performance category 1 (normal); 1 dog achieved category 2 (moderate disability), and 1 dog achieved category 3 (P < .001). Final neurological deficit scores (0% [normal] to 100% [brain death]) at 96 hours were 38 +/- 10% (22% to 45%) in group 1 versus 8 +/- 9% (0% to 27%) in group 2 (P < .001). Total brain histopathologic damage scores were 138 +/- 22 (110 to 176) in group 1 versus 43 +/- 9 (32 to 56) in group 2 (P < .001). Regional scores showed similar group differences.

CONCLUSIONS:

After normothermic cardiac arrest of 11 minutes in dogs, resuscitative mild hypothermia plus cerebral blood flow promotion can achieve functional recovery with the least histological brain damage yet observed with the same model and comparable insults.

Level 3, good, neutral, funding: NIH grant

Key points: rewarmed at 1° C/hour after 12 hours at 34° C for 12 hours post-ROSC

Saleh M, Barr A. The impact of slow rewarming on inotropy, tissue metabolism, and “after drop” of body temperature in pediatric patients. JECT 37: 173-179, 2005.

Pediatric patients undergoing surgical correction of congenital heart diseases using cardiopulmonary bypass (CPB) are subjected to hypothermia. Core temperature is cooled down to 26-28°C during CPB. Postoperative hypothermia in these patients remains a source of long-intensive care unit (ICU) stay. Therefore, this study was performed to build a rewarming strategy aiming to improve the cardiac performance, minimize the early after-drop in both core and foot temperatures, and to achieve early achievement of homeostasis. Thirty pediatric patients of acyanotic congenital heart diseases were randomly allocated into one of three equal groups of 10. Group I was kept at 3°C between nasopharyngeal and heater-cooler unit water temperatures during rewarming whereas group II and group III were kept at 5°C and 7°C respectively. The following parameters were measured: 1) cardiac performance (cardiac index and peak velocity); 2) cumulative amrinone consumption, blood lactate levels, and total body oxygen consumption; 3) intraoperative and postoperative peak and trough core and foot temperatures; and 4) time to extubation and ICU stay. Group I patients showed statistically significant increase in cardiac index and peak velocity compared with groups II and III, at p<0.05 and p<0.025, respectively. Statistically, the consumption of amrinone was significantly decreased in group I compared with groups II and III, with p<0.005 and p<0.0005, respectively, at 6 hours postoperatively. Group I showed an insignificant increase in blood lactate level, where groups II and III showed significant increases compared with controls (p<0.001 at 6 hours postoperatively). Intraoperatively, both trough core and peak foot temperatures on group I patients statistically were significantly higher than in group III patients at p<0.0005 and p<0.05, respectively. The same applies in the ICU as regards to the time to core temperature (p<0.0005) and the rate of foot rewarming (p<0.01). It was found that a difference of 3°C (group 1) between nasopharyngeal and heater-cooler unit water temperatures during rewarming demonstrated the best outcome compared with 5°C and 7°C differences (groups II and III respectively). This outcome was obvious in the following parameters: 1) the best cardiac performance (cardiac index and peak velocity); 2) the lowest values

of cumulative amrinone consumption and blood lactate level; 3) the least after-drop in both core and foot temperatures; and 4) achievement of early homeostasis, shortest ICU stays, and conservation of ICU resources. Level 6, good, funding: none reported
Key points: cardiopulmonary bypass patients, slow rewarming at 0.5°C/hr improved survival

Savvas I, Anagonstou T, Papazoglou LG, Raptopoulos D. Successful resuscitation from cardiac arrest associated with extradural lidocaine in a dog. *Vet Anaesth Analg* 33: 175-178, 2006

BACKGROUND:

Extradural lidocaine exerts several adverse effects which are seldom fatal. While cardiac arrest following extradural lidocaine injection has been reported in human beings, it has not hitherto been reported in dogs.

OBSERVATIONS:

The emergency management of a dog with complete urethral obstruction is described. We intended to perform vaginoscopy and cystostomy under extradural lidocaine anaesthesia, but cardiac asystole occurred a few minutes after injection. Resuscitation was successful. About 20 minutes later cardiac arrest recurred, and was treated successfully. The dog remained hypothermic for approximately 7 hours. Complete recovery without neurological deficit occurred the next day and the dog remained normal for at least 3 months. The probable cause of the problem was cranial lidocaine dispersion causing a drop in cardiac preload and cardiac arrest. The successful neurological outcome was attributed to early diagnosis and effective treatment. Hypothermia may have conferred cerebral protection during ischemia.

CONCLUSIONS:

Extradural local anaesthetic administration is not without risk and the technique should be tailored to individual animals. Constant monitoring is required to detect potentially fatal complications and increase the likelihood of successful outcome.

Level 5, poor, support, funding: not reported

Key points: surface rewarming, approximately 3° C increase in body temperature over 7 hours

Silfvast T, Pettila V. Outcome from severe accidental hypothermia in Southern Finland—a 10 yr review. *Resuscitation* 59:285-290, 2003.

The charts of all adult patients with accidental hypothermia who were admitted to a single academic hospital during a 10 year period were retrospectively retrieved. The aim was to identify factors associated with survival of those with hypothermic cardiac arrest. Of 75 admitted patients, 44 were found to be haemodynamically stable and not to require invasive rewarming measures. Of the remaining 31 patients, 23 were in refractory cardiac arrest due to primary hypothermia and rewarmed using cardiopulmonary bypass (CPB). The aetiology of hypothermia was immersion in cold water in 48%, exposure to cold environment in 39% and submersion in 13% of these patients. Their median age was 50 years, and 83% were males. The patients received a total of 70 min of conventional CPR before institution of CPB. Fourteen of these patients (61%) survived to discharge from hospital. Factors associated with survival were age ($P=0.015$), arterial pH ($P=0.011$), PaCO₂ ($P=0.003$), and serum potassium ($P=0.007$). Logistic regression analysis showed that of the 23 patients, 22 could be correctly classified as survivor or nonsurvivor based on the level of serum potassium and arterial pCO₂. It is concluded that patients with cardiac arrest due to primary hypothermia tolerate long periods of conventional CPR before institution of CPB. The possible predictive role of serum potassium and arterial pCO₂ needs further evaluation.

Level 6, poor, funding: none reported

Key points: retrospective study accidental hypothermia presented to human emergency room, no rewarming rates recorded but rewarming of patients indirectly appeared to be important for survival

Suehiro E, Ueda Y, Wei EP, et al. Posttraumatic hypothermia followed by slow rewarming protects the cerebral microcirculation. *J of Neurotrauma* 20:381-390, 2003.

In the clinical and laboratory setting, multiple reports have suggested the efficacy of hypothermia in blunting the damaging consequences of traumatic brain injury (TBI). With the use of posttraumatic hypothermia, it has been recognized that the time of initiation and duration of hypothermia are important variables in determining the degree of neuroprotection provided. Further, it has been recently recognized that the rate of posttraumatic rewarming is an important variable, with rapid rewarming exacerbating neuronal/axonal damage in contrast to slow rewarming which appears to provide enhanced neuroprotection. Although these findings have been confirmed in the brain parenchyma, no information exists for the cerebral microcirculation on the potential benefits of posttraumatic hypothermia followed by either slow or rapid rewarming. In the current communication we assess these issues in the pial circulation using a well-characterized model of TBI. Rats were prepared for the placement of cranial windows for direct assessment of the pial microcirculation prior to and after the induction of impact acceleration injury followed by moderate hypothermia with either subsequent slow or rapid rewarming strategies. The cranial windows allowed for the measurement of pial vessel diameter to assess ACh-dependent and CO₂ reactivity in the chosen paradigms. ACh was applied topically to assess ACh-dependent dilation, while CO₂ reactivity was assessed by changing the concentration of the inspired gas. Through this approach, it was found that posttraumatic hypothermia followed by slow rewarming maintained normal arteriolar vascular responses in terms of ACh-dependent dilation and CO₂ reactivity. In contrast, arterioles subjected to TBI followed by normothermia or hypothermia and rapid rewarming showed impaired vasoreactivity in terms of their ACh-dependent and CO₂ responses. This study provides additional evidence of the benefits of posttraumatic hypothermia followed by slow rewarming, demonstrating for the first time that the previously described neuroprotective effects extend to the cerebral microcirculation.

Level 6, good, funding: NIH grant USA

Key points: traumatic brain injury rat model, measuring cerebral vascular response, comparison of slow versus faster rewarming

Tanimoto H, Ichinose K, Okamoto T, et al. Rapidly induced hypothermia with extracorporeal lung and heart assist (ECLHA) improves the neurological outcome after prolonged cardiac arrest in dogs. Resuscitation 72(1):128-36, 2007.

PURPOSE:

We reported previously that therapeutic hypothermia with extracorporeal lung and heart assist (ECLHA) improved neurological outcome after 15 min cardiac arrest (CA) in dogs, although 45 min was needed to achieve hypothermia. We now investigate whether rapidly induced hypothermia with ECLHA (RHE) would result in a better outcome than slowly induced hypothermia with ECLHA (SHE) in dogs.

METHODS:

Fifteen mongrel female dogs were divided into two groups: an RHE (n = 7) and an SHE (n = 8) group. Normothermic ventricular fibrillation was induced for 15 min and the animals were resuscitated by ECLHA. Rapid hypothermia was induced with a heat exchanger added to the ECLHA circuit in the RHE group, and by immersing the drainage tube of the ECLHA circuit in an ice water bath in the SHE group. Hypothermia (33 degrees C) was maintained for 20 h. The dogs were weaned from ECLHA at 24 h after resuscitation and treated for 96 h; neurological deficit scores (NDS) were measured throughout this period.

RESULTS:

It took 1.6+/-0.8 min to reach 33 degrees C in the RHE group and 49.5+/-12.1 min to reach 33 degrees C in the SHE group. There was no difference in survival rate between the two groups. The NDS at 96 h in the RHE group was better than that in the SHE group (26% (range: 10-28%) versus 32% (26-37%); p < 0.05) although there was no significant difference in NDS between the two groups until 72 h.

CONCLUSION:

Rapid hypothermic induction might be an important factor to improve neurological outcomes in prolonged CA models.

Level 3, good, neutral, funding: not reported

Key points: 20 hours at 33° C post-ROSC, then rewarmed at 0.6° C/hour up to 37° C

Thompson HJ, Kirkness CJ, Mitchell PH. Hypothermia and rapid rewarming is associated with worse outcome following traumatic brain injury. J Trauma Nursing 17: 173-177, 2010.

Purpose: The purpose of the present study was to determine (1) the prevalence and degree of hypothermia in patients on emergency department admission and (2) the effect of hypothermia and rate of rewarming on patient outcomes.

Methods: Secondary data analysis was conducted on patients admitted to a level I trauma center following severe traumatic brain injury (n = 147). Patients were grouped according to temperature on admission according to hypothermia status and rate of rewarming (rapid or slow). Regression analyses were performed.

Findings: Hypothermic patients were more likely to have lower postresuscitation Glasgow Coma Scale scores and a higher initial injury severity score. Hypothermia on admission was correlated with longer intensive care unit stays, a lower Glasgow Coma Scale score at discharge, higher mortality rate, and lower Glasgow outcome score—extended scores up to 6 months postinjury (P < .05). When controlling for other factors, rewarming rates more than 0.25°C/h were associated with lower Glasgow Coma Scale scores at discharge, longer intensive care unit length of stay, and higher mortality rate than patients rewarmed more slowly although these did not reach statistical significance.

conclusion: Hypothermia on admission is correlated with worse outcomes in brain-injured patients. Patients with traumatic brain injury who are rapidly rewarmed may be more likely to have worse outcomes. Trauma protocols may need to be reexamined to include controlled rewarming at rates 0.25°C/h or less.

Level 6, good, funding: NIH grant

Key points: observational study on humans admitted to trauma centers with brain injury, rapid rewarming of hypothermic patients showed much worse outcomes than those warmed at less than 0.25°C/h

Tortorici MA, Mu Y, et al. Moderate hypothermia prevents cardiac arrest-mediated suppression of drug metabolism and induction of interleukin-6 in rats. Crit Care Med 37:263-9, 2009.

OBJECTIVE: Therapeutic hypothermia is being clinically used to reduce neurologic deficits after cardiac arrest (CA). Patients receiving hypothermia after CA receive a wide-array of medications. During hypothermia, drug metabolism is markedly reduced. Little, however, is known about the impact of hypothermia on drug metabolism after rewarming. The objective of this study was to examine the effect of CA and hypothermia on the functional regulation of two major drug metabolizing cytochrome P450 (CYP) isoforms. DESIGN: Laboratory investigation. SETTING: University pharmacy school and animal research facility. SUBJECTS: Thirty-six male Sprague-Dawley rats. INTERVENTIONS: Hypothermia was induced via surface cooling in a rat CA model and maintained for 3 hrs. Animals were killed at 5 or 24 hrs and liver was analyzed for hepatic activity and mRNA expression of CYP3A2 and CYP2E1. Plasma interleukin-6 (IL-6) concentrations were determined. The effect of IL-6 on pregnane X receptor-mediated transcription of the rat CYP3A2 promoter was evaluated via luciferase reporter in HepG2 cells. MEASUREMENTS AND MAIN RESULTS: At 24 hrs after CA a decrease in CYP3A2 and CYP2E1 activity was observed, 55.7% +/- 12.8% and 46.8% +/- 29.7% of control, respectively (p < 0.01). CA decreased CYP3A2 mRNA (p < 0.05), but not CYP2E1 mRNA. Expression of other pregnane X receptor target enzymes and transporter genes were similarly down-regulated. CA also produced an approximately ten-fold increase in plasma IL-6. CA-mediated inhibition of CYP3A2 and CYP2E1 was attenuated by hypothermia, as was the increase in IL-6. Furthermore, IL-6 attenuated pregnane X receptor-mediated transcription of the CYP3A2 promoter. CONCLUSIONS: CA produces CYP3A2 down-regulation at 24 hrs, potentially via IL-6 effects on pregnane X receptor-mediated transcription. Also, hypothermia attenuates the CA-mediated down-regulation, thereby normalizing drug metabolism after rewarming.

Level 6, good, neutral, funding: National Institute General Medical Sciences and National Institute of Neurological Disorders and Stroke

Key points: decreasing temperature decreases hepatic cytochrome P450 metabolism in a rodent model

Ueda Y, Suehiro E, et al. Uncomplicated rapid posthypothermic rewarming alters cerebrovascular responsiveness. *Stroke* 35:601-606, 2004.

Background and Purpose— Recently, we focused on the cerebrovascular protective effects of moderate hypothermia after traumatic brain injury, noting that the efficacy of posttraumatic hypothermia is related to the rate of posthypothermic rewarming. In the current communication, we revisit the use of hypothermia with varying degrees of rewarming to ascertain whether, in the normal cerebral vasculature, varying rates of rewarming can differentially affect cerebrovascular responsiveness.

Methods— Pentobarbital-anesthetized rats equipped with a cranial window were randomized to 3 groups. In 1 group, a 1-hour period of hypothermia (32°C) followed by slow rewarming (over 90 minutes) was used. In the remaining 2 groups, either a 1- or 2-hour period of hypothermia was followed by rapid rewarming (within 30 minutes). Vasoreactivity to hypercapnia and acetylcholine was assessed before, during, and after hypothermia. Additionally, the vascular responses to sodium nitroprusside (SNP) and pinacidil, a K_{ATP} channel opener, were also examined.

Results— Hypothermia itself generated modest vasodilation and reduced vasoreactivity to all utilized agents. The slow rewarming group showed restoration of normal vascular responsiveness. In contrast, hypothermia followed by rapid rewarming was associated with continued impaired responsiveness to acetylcholine and arterial hypercapnia. These abnormalities persisted even with the use of more prolonged (2-hour) hypothermia. Furthermore, posthypothermic rapid rewarming impaired the dilator responses of SNP and pinacidil.

Conclusions— Posthypothermic rapid rewarming caused cerebral vascular abnormalities, including a diminished response to acetylcholine, hypercapnia, pinacidil, and SNP. Our data with acetylcholine and SNP suggest that rapid rewarming most likely causes abnormality at both the vascular smooth muscle and endothelial levels.

Level 6, good, funding: NIH grant

Key points: Rodent study with evaluation of vascular responses to CO₂ and ACH after hypothermia and either slow or rapid rewarming indicating detriments of rapid rewarming.

Undar A, Vaughn WK, Calhoon JH. The effects of cardiopulmonary bypass and deep hypothermic circulatory arrest on blood viscoelasticity and cerebral blood flow in a neonatal piglet model. *Perfusion* 15:121-28, 2000.

The purpose of this study is to determine the effects of cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) on the viscoelasticity (viscosity and elasticity) of blood and global and regional cerebral blood flow (CBF) in a neonatal piglet model. After initiation of CPB, all animals (n = 3) were subjected to core cooling for 20 min to reduce the piglets' nasopharyngeal temperatures to 18 degrees C. This was followed by 60 min of DHCA, then 45 min of rewarming. During cooling and rewarming, the alpha-stat technique was used. Arterial blood samples were taken for viscoelasticity measurements and differently labeled microspheres were injected at pre-CPB, pre- and post-DHCA, 30 and 60 min after CPB for global and regional cerebral blood flow calculations. Viscosity and elasticity were measured at 2 Hz, 22 degrees C and at a strain of 0.2, 1, and 5 using a Vlastic-3 Viscoelasticity Analyzer. Elasticity of blood at a strain = 1 decreased to 32%, 83%, 57%, and 61% (p = 0.01, ANOVA) while the viscosity diminished 8.4%, 38%, 22%, 26% compared to the baseline values (p = 0.01, ANOVA) at pre-DHCA, post-DHCA, 30 and 60 min after CPB, respectively. The viscoelasticity of blood at a strain of 0.2 and 5 also had similar statistically significant drops (p < 0.05). Global and regional cerebral blood flow were also decreased 30%, 66%, 64% and 63% at the same experimental stages (p < 0.05, ANOVA). CPB procedure with 60 min of DHCA significantly alters the blood viscoelasticity, global and regional cerebral blood flow. These large changes in viscoelasticity may have a significant impact on organ blood flow, particularly in the brain.

Level 6, fair, neutral, funding: none reported

Key words: pig model, post-arrest cardiopulmonary hypothermic arrest, no comparison rewarming rates

Wu X, Drabek T, Kochanek PM, et al. Induction of profound hypothermia for emergency preservation and resuscitation allows intact survival after cardiac arrest resulting from prolonged lethal hemorrhage and trauma in dogs. *Circulation* 113: 1974-1982, 2006.

BACKGROUND:

Induction of profound hypothermia for emergency preservation and resuscitation (EPR) of trauma victims who experience exsanguination cardiac arrest may allow survival from otherwise-lethal injuries. Previously, we achieved intact survival of dogs from 2 hours of EPR after rapid hemorrhage. We tested the hypothesis that EPR would achieve good outcome if prolonged hemorrhage preceded cardiac arrest.

METHODS AND RESULTS:

Two minutes after cardiac arrest from prolonged hemorrhage and splenic transection, dogs were randomized into 3 groups (n=7 each): (1) the cardiopulmonary resuscitation (CPR) group, resuscitated with conventional CPR, and the (2) EPR-I and (3) EPR-II groups, both of which received 20 L of a 2 degrees C saline aortic flush to achieve a brain temperature of 10 degrees C to 15 degrees C. CPR or EPR lasted 60 minutes and was followed in all groups by a 2-hour resuscitation by cardiopulmonary bypass. Splenectomy was then performed. The CPR dogs were maintained at 38.0 degrees C. In the EPR groups, mild hypothermia (34 degrees C) was maintained for either 12 (EPR-I) or 36 (EPR-II) hours. Function and brain histology were evaluated 60 hours after rewarming in all dogs. Cardiac arrest occurred after 124+/-16 minutes of hemorrhage. In the CPR group, spontaneous circulation could not be restored without cardiopulmonary bypass; none survived. Twelve of 14 EPR dogs survived. Compared with the EPR-I group, the EPR-II group had better overall performance, final neurological deficit scores, and histological damage scores.

CONCLUSIONS:

EPR is superior to conventional CPR in facilitating normal recovery after cardiac arrest from trauma and prolonged hemorrhage. Prolonged mild hypothermia after EPR was critical for achieving intact neurological outcomes.

Level 3, good, support, funding: United States Army Medical Research and Materiel Command DAMD

Key points: rate of rewarming 0.3° C/hour

Wu X, Drabek T, Tisherman SA, et al. Emergency preservation and resuscitation with profound hypothermia, oxygen, and glucose allows reliable neurological recovery after 3 h of cardiac arrest from rapid exsanguination in dogs. *J Cereb Blood Flow Metab* 28(2):302-11, 2008.

We have used a rapid induction of profound hypothermia (<10 degrees C) with delayed resuscitation using cardiopulmonary bypass (CPB) as a novel approach for resuscitation from exsanguination cardiac arrest (ExCA). We have defined this approach as emergency preservation and resuscitation (EPR). We observed that 2 h but not 3 h of preservation could be achieved with favorable outcome using ice-cold normal saline flush to induce profound hypothermia. We tested the hypothesis that adding energy substrates to saline during induction of EPR would allow intact recovery after 3 h CA. Dogs underwent rapid ExCA. Two minutes after CA, EPR was induced with arterial ice-cold flush. Four treatments (n=6/group) were defined by a flush solution with or without 2.5% glucose (G+ or G-) and with either oxygen or nitrogen (O+ or O-) rapidly targeting tympanic temperature of 8 degrees C. At 3 h after CA onset, delayed resuscitation was initiated with CPB, followed by intensive care to 72 h. At 72 h, all dogs in the O+G+ group regained consciousness, and the group had better neurological deficit scores and overall performance categories than the O-groups (both P<0.05). In the O+G- group, four of the six dogs regained consciousness. All but one dog in the O-groups remained comatose. Brain histopathology in the O-G+ was worse than the other three groups (P<0.05). We conclude that EPR induced with a flush solution containing oxygen and glucose allowed satisfactory recovery of neurological function after a 3 h of CA, suggesting benefit from substrate delivery during induction or maintenance of a profound hypothermic CA.

Level 3, good, neutral, funding: United States Army Medical Research and Materiel Command DAMD
Key points: 34° C for 36 hours post-ROSC, then rewarmed at 0.3° C/hour to 36.5° C

Zhou Y, Wang D, Du M, et al. Lidocaine prolongs the safe duration of circulatory arrest during deep hypothermia in dogs. *Can J Anaesth* 45:692-698, 1998.

Purpose: To test the hypothesis that lidocaine prolongs the safe period of circulatory arrest during deep hypothermia.

Methods: Sixteen dogs were subjected to cooling, first surface cooling to 30°C and then core cooling to 20°C (rectal temperature). The circulation was then stopped for 90 min. In the lidocaine group, 4 mg·kg⁻¹ lidocaine was injected into the oxygenator two minutes before circulatory arrest and 2 mg·kg⁻¹ at the beginning of reperfusion and rewarming. The control group received equivalent volumes of normal saline. Post-operatively, using a neurological deficit scoring system (maximum deficit score — 100; minimum — zero indicating that no scored deficit could be detected). Neurological function was evaluated hourly for six hours and then daily for one week. The pharmacokinetic parameters were calculated using one compartment model.

Results: On the seventh day, the neurological deficit score and overall performance were better in the lidocaine (0.83 ± 2.04) than in the control group (8.33 ± 4.08, P < 0.05). During the experiment, the base excess values were also better in the lidocaine than in the control group (at 30 min reperfusion: -4.24 ± 1.30 vs -8.20 ± 2.82, P < 0.01, at 60 min reperfusion was -3.34 ± 1.87 vs -7.52 ± 2.40 (P < 0.01). On the eighth day the extent of pathological changes were milder in the lidocaine group than that in the control group. The elimination half life of lidocaine was 40.44 ± 7.99 during hypothermia and 2.01 ± 4.56 during rewarming.

Conclusions: In dogs lidocaine prolongs the safe duration of circulatory arrest during hypothermia.

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Key points: evaluation of lidocaine administration to dogs at time of circulatory arrest; all patients were cooled prior to arrest; improvement in neurologic function but unclear if temperature changes or lidocaine were most implicated.

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