Full Text

Wolters Kluwer Health | Lippincott Williams & Wilkins

Critical Care Medicine
OFFICIAL JOURNAL OF THE SOCIETY OF CRITICAL CARE MEDICINE

Resuscitative hypothermia

Author(s): Marion, Donald W. MD; Leonov, Yuval MD; Ginsberg, Myron MD PhD; Katz, Laurence M. MD; Kochanek, Patrick M. MD FCCM; Lechleuthner, Alex MD; Nemoto, Edwin M. PhD; Obrist, Walter PhD; Safar, Peter MD FCCM; Sterz, Fritz MD PhD; Tisherman, Samuel A. MD; White, Robert J. MD PhD; Xiao, Feng MD; Zar, Harvey MD

Issue: Volume 24(2S) Supplement, February 1996, pp 81S-89S

Publication Type: [Symposium Article]

From the International Resuscitation Research Conference of May 1994 at the University of Pittsburgh, PA.

Institution(s): Supported, in part, by grant DAMD 17-94-J-4013 from the United States Army Medical Research and Materiel Command (USAMRMC). the Laerdal Foundation for Acute Medicine, and Baxter Laboratories.

ISSN: 0090-3493

Accession: 00003246-199602001-00008

Email

Jumpstart

Find Citing Articles

≪ Table of Contents

About this Journal ≫

Table of Contents:

≪ Cerebral resuscitation from cardiac arrest: Treatment potentials.

≫ Funding resuscitation research.

Links

Abstract

Complete Reference

ExternalResolverBasic

Outline

- Abstract
- BRAIN TRAUMA
- CARDIAC ARREST
- COOLING METHODS
- FREE RADICAL REACTIONS
- CONCLUSIONS
- CONFERENCE ABSTRACTS*
- REFERENCES

Abstract

Resuscitative (postinsult) hypothermia is less well studied than protective-preservative (pre- and intra-arrest) hypothermia. The latter is in wide clinical use, particularly for protecting the brain during cardiac surgery. Resuscitative hypothermia was explored in the 1950s and then lay dormant until the 1980s when it was revived. This change occurred through the discoveries of brain damage mitigating effects after cardiac arrest in dogs, and after forebrain ischemia in rats, of mild (34 degrees C) hypothermia (which is safe), and of benefits derived from moderate hypothermia (30 degrees C) after traumatic brain injury or focal brain ischemia in various species. The idea that protection-preservation or resuscitation by hypothermia is mainly explained by its ability to reduce cerebral oxygen demand has been replaced by an increasingly documented synergism of many beneficial mechanisms. Deleterious chemical cascades during and after these insults are suppressed even by mild hypothermia. Prolonged moderate hypothermia carries some risks, e. g., arrhythmias, infection and coagulopathies. These side effects need further study. In global brain ischemia, protective-preservative mild hypothermia provides lasting mitigation of brain damage. Resuscitative mild hypothermia, however, may be beneficial in terms of long-

term outcome or may merely delay the inevitable loss of selectively vulnerable neurons. Even if the latter is true, mild hypothermia may extend the therapeutic window for other interventions. This extension of the therapeutic window requires further documentation. After normothermic cardiac arrest of 11 mins in dogs, mild resuscitative hypothermia from 15 mins to 12 hrs after reperfusion plus cerebral blood flow promotion normalized functional recovery with the least histologic damage seen thus far. Optimal duration of, and rewarming methods from, resuscitative hypothermia need clarification. The earliest possible induction of mild hypothermia after cardiac arrest seems desirable. Head-neck surface cooling alone is too slow. Among many clinically feasible rapid cooling methods, carotid cold flush and peritoneal cooling look promising. After traumatic brain injury or focal brain ischemia, which seem to still benefit from even later cooling, surface cooling methods may be adequate. Resuscitative hypothermia after cardiac arrest, traumatic brain injury, or focal brain ischemia should be considered for clinical trials.

(Crit Care Med 1996; 24(Suppl):S81-S89)

KEY WORDS: cardiac arrest; brain trauma; cardiopulmonary resuscitation; resuscitation; hypothermia; free radicals, cooling; cerebral resuscitation; cerebral ischemia; cerebral protection

BRAIN TRAUMA

Marion: This session concerns resuscitative (postinsult) therapeutic hypothermia, not protection (pretreatment) or preservation hypothermia (intrainsult treatment). Protection-preservation with moderate or deep therapeutic hypothermia is well established for preventing postischemic brain damage after total circulatory arrest for cardiothoracic [1] or neurologic surgery [2,3].

Dr. Safar defines therapeutic hypothermia levels as mild (34 degrees to 36 degrees C), moderate (28 degrees to 32 degrees C), deep (15 degrees to 25 degrees C), and profound (less than 15 degrees C); and differentiates between core temperatures, such as esophageal, central venous, pulmonary artery, urinary bladder, and rectal temperature; and brain temperatures, such as deep brain, cortical, epidural, tympanic membrane, nasopharyngeal, or intraventricular temperature.

My comments will concern hypothermia for traumatic brain injury (see also Rosomoff's comments in ``Resuscitation from severe brain trauma'' in this issue) [2]. During the past several years, neurotraumatology has become exciting, as a result of our improved understanding of mechanisms of secondary brain injury, i.e., injury that occurs after traumatic brain injury from mechanisms other than the direct injury. More than 20 yrs ago, many of us thought that all of the outcome following severe traumatic brain injury was determined at the time of impact. We now know that this concept is not true. In the past, when high-quality resuscitation efforts were not applied, outcomes were much worse than they are now. Rapid triage in the field, early tracheal intubation, the use of intracranial pressure (ICP) monitoring, and other techniques have improved outcome [4]. We are beginning to understand the molecular and cellular mechanisms that may be responsible for secondary brain injury. Areas of the brain around the physically (hopelessly) destroyed focus of a hemorrhagic brain contusion, i.e., in the ``penumbra zone,'' may be preserved with use of novel therapies designed to prevent or mitigate secondary damage. These therapies may mean the difference between a patient being able to speak or not. The ``penumbra zone'' needs definition.

Hypothermia has been proposed since the 1940s [3] as a potential way of reducing secondary brain injury in patients. There has been a great deal of animal work done in this area. In the 1950s, Rosomoff [2], using a dog model of brain contusion

(cold injury), showed that moderate hypothermia (28 degrees C) can reduce the damage, even when hypothermia was induced after the insult. In the early 1990s, Clifton et al. [5] showed in a rat model of brain contusion by fluid percussion that total body surface cooling to 30 degrees C early after the insult can improve behavior and weight loss. At the same time, Safar's group under Pomeranz et al. [6] and Ebmeyer et al. [7] showed, in their new dog outcome model of traumatic brain injury, that prolonged moderate therapeutic hypothermia can prevent or at least delay increases in intracranial pressure and reduce the lesion volume. Similarly, we used a pneumatic cortical percussion (contusion) injury model in rats and found that moderate therapeutic hypothermia can reduce the brain injured tissue volume by 50%, with cooling initiated before the insult [8]. We also found preservation of axons [9] using Povlishock's staining technique [10].

We also are conducting a prospective clinical study, enrolling patients with traumatic brain injury who are comatose on admission to the emergency department [11]. Eighty-two patients have been studied (updated by July 1995): 42 randomized to the normothermia group and 40 randomized to the hypothermia group. At 3 and 6 months after injury, there was no significant difference in the Glasgow Outcome Scale scores between the two groups. However, when those patients with admission Glasgow Coma Scale scores of 5 to 7 (26 in normothermia group; 22 in hypothermia group) were considered separately from those patients with lower admission coma scores, significant differences were apparent. At 6 months after injury, the mortality rate was 23% for the normothermia group and 9% for the hypothermia group, and the incidence of mild or no disability was 15% in the normothermia group and 41% in the hypothermia group. Other [12,13] clinical studies of hypothermia after traumatic brain injury showed benefit.

Ischemia is a major problem after traumatic brain injury [14]. Ischemia can increase extracellular excitatory amino acids, activate N-methyl-D-aspartate (NMDA) receptors [15], increase cytosolic calcium, and produce oxygen free radicals. The pathogenesis of the resulting increase in ICP from edema and/or hyperemia is still unclear. All of these changes are derangements potentially mitigated by hypothermia [15]. To improve outcome, we have learned to act early during the development of deleterious cascades following traumatic brain injury. Despite posttraumatic coma, there can be an increase in the cerebral metabolism [16]. Hypothermia in the normal brain reduces both active and basal cerebral metabolic rate for oxygen [17]. After traumatic brain injury in patients, we have seen in the ventricular cerebrospinal fluid increased cytokine concentrations, namely, interleukin-1 beta, which were reduced by moderate hypothermia [18].

In the laboratory, Katayama et al. [19] showed that in rats with fluid percussion injury, pharmacologic blocking of glutamate decreases brain swelling and behavioral deficits. In our studies in rats of traumatic brain injury by cortical contusion, glutamate in extracellular brain dialysis fluid was increased for several hours after the insult [8]. Moderate hypothermia (32 degrees C), however, did not seem to suppress the high concentrations of glutamate released after impact injury.

Hypothermia is beneficial when administered during brain ischemia or trauma, and probably beneficial when administered after these insults. Our knowledge is weaker on mechanisms. The importance of excitatory amino acid concentrations in traumatic brain injury is unclear. Inflammation is important after traumatic brain injury. In our traumatic brain injury patients treated with hypothermia, there has been a significant depression of cerebral metabolic rate for oxygen and ICP. Moderate hypothermia (30 degrees to 32 degrees C) for 24 hrs in traumatic brain injury patients seems relatively safe [11].

In the near future, we and others should learn whether there is an additional benefit from adding other neuroresuscitative agents to hypothermia. Some drugs, such as aminosteroids, are now undergoing clinical trials. Another issue which needs to be investigated is whether or not hypothermia truly causes a sustained beneficial effect or just delays the inevitable loss of neurons. How rapidly do we need to cool? How long should the therapeutic window be for hypothermia to be effective? The answers to these questions may be different for traumatic brain injury vs. cardiac arrest.

CARDIAC ARREST

Leonov: My comments relate to resuscitative hypothermia as part of cardiopulmonary-cerebral resuscitation from the temporary complete global brain ischemia of cardiac arrest. The mechanisms of secondary injury may be similar to traumatic brain injury, but the insult is global, and patients are unlikely to recover fully after more than 5 mins normothermic cardiac arrest without special therapy such as hypothermia. If there is no neurologic improvement 1 to 2 days after cardiac arrest, the prognosis is worse than after traumatic brain injury. There is no single resuscitative drug that can currently prevent postischemic-anoxic encephalopathy after more than equals 10 mins in normothermic arrest (no flow) [20].

Prearrest induction of moderate hypothermia (28 degrees C to 32 degrees C) has been used since the 1950s to protect and preserve the brain against global ischemia as it occurs during open-heart surgery [1]. Dr. Safar will review our road from moderate to mild resuscitative cerebral hypothermia after cardiac arrest (A5).

Safar: Moderate hypothermia for resuscitation from cardiac arrest was studied in uncontrolled trials in animals in the 1950s with unconvincing results, primarily because of a lack of reliable animal models at that time [20]. Despite occasionally encouraging results in patients [21,22], moderate resuscitative hypothermia was abandoned because of uncertain benefit and management problems. Nevertheless, we inserted in 1961 ``hypothermia'' for ``step H'' into the cardiopulmonary-cerebral resuscitation sequence (see ``On the history of modern resuscitation'' in this issue). It was then believed that hypothermia must be moderate in order to give benefit. Research into moderate resuscitative hypothermia early after cardiac arrest was revived in the 1980s by our group. We found barely significant benefit in reproducible outcome models in dogs [23,24]. In 1987, at the previous International Researchers Conference on clinical Death in Pittsburgh [25], Dr. Leonov et al. [24] presented their data on moderate hypothermia after cardiac arrest in dogs. More important, however, was the discovery at that time of potentially beneficial effects of protective-preservative mild cerebral hypothermia (34 degrees C to 36 degrees C), which is clinically safe [26,27]. This safety of mild hypothermia is in contrast to moderate hypothermia, which can cause arrhythmias, rearrest, infection, and clotting problems [1]. At that conference in 1987, Hossmann [26] presented acute experiments with global brain ischemia in cats, in which there was a correlation of mild (accidental) hypothermia at the start of global brain ischemia with improved electroencephalogram recovery early after the insult. Also in 1987, Safar [27] discovered in outcome data of experiments with ``normothermic'' ventricular fibrillation (VF) in dogs, that mild (accidental) hypothermia at the start of VF cardiac arrest of 7.5 to 15 mins correlated with achieving functional normality (overall performance category 1) 3 to 4 days later. Brader et al. [28] of our group demonstrated earlier, in large dogs, the feasibility of reducing brain temperature fairly rapidly during low-flow external cardiopulmonary resuscitation (CPR) using head surface cooling. This documentation of mild protective-preservative hypothermia prompted our group to embark on a series of five controlled outcome studies in dogs with resuscitative (immediately postarrest) mild hypothermia after normothermic VF

of 10, 11, or 12.5 mins no-flow, between 1988 and 1994 [29-33]. All of these studies, started with Drs. Leonov [29] and Sterz [30] as team leaders, documented significant mitigation of functional and histologic deficit at 96 hrs after reperfusion, by mild hypothermia induced within 15 mins of reperfusion [32] and sustained for 2 hrs [29-32] or 12 hrs [33]. Similar benefit was obtained with mild cooling in our outcome model of asphyxial cardiac arrest in rats [34].

Simultaneously and independently, three other groups, i.e., colleagues in Miami [35], Lund, Sweden [36], and Detroit [37], using incomplete forebrain ischemia models in rats, documented the beneficial effect of mild resuscitative hypothermia on histologic lesions in the hippocampus. These investigators also used their rat models for extensive biochemical studies. Although their models are clinically less relevant than the International Resuscitation Research Center's cardiac arrest models in dogs, the results of their rat studies and our dog studies support each other.

With prearrest induction of hypothermia, the lower the temperature the better the protection and preservation. Not so with induction after cardiac arrest. In dogs, mild resuscitative total body hypothermia [29,31] mitigated brain damage better than moderate [24,31] or deep hypothermia [31]. Deep cooling after cardiac arrest even worsened brain histologic damage [31]. This detrimental effect of deep hypothermia could be because of reduced microcirculation or other circulatory side effects of lower temperatures after cardiac arrest, which remain to be clarified. Also, the question of whether the 96-hr benefit lasts long-term or whether hypothermia merely delays the ultimate loss of neurons [38] remains to be answered in a reproducible cardiac arrest outcome model in dogs.

Marion: Clinical trials of therapeutic hypothermia, when appraised by Institutional Review Boards, may be attacked based on the different experiences of other specialists. For example, cardiac surgeons will question such trials' safety because cooling with bypass to moderate levels can often cause significant arrhythmias. These arrhythmias, however, should only occur with very rapid cooling in patients with sick hearts. We have not seen such difficulties in the traumatic brain injury cases mentioned above with relatively slow surface cooling in previously healthy traumatic brain injury patients.

Safar: In large dogs, mild cerebral hypothermia was induced by a variety of methods [28-33,39,40]. Core and directly measured deep brain temperatures quickly equilibrated during spontaneous circulation [39]. Immersion of the head in ice water caused tympanic membrane temperature (brain temperature) to decrease during CPR from 38 degrees C to 34 degrees C in about 20 mins [28], but much more slowly during normal circulation [39]. Preplaced cardiopulmonary bypass with heat exchanger (which is clinically not realistic) reduces tympanic membrane temperature to 34 degrees C within 2 mins [29,31,32]. In the dog, during and after external CPR, a clinically realistic (but cumbersome) combination of head-neck surface cooling plus intravenous, gastric, and nasopharyngeal cold infusions achieved 34 degrees C within 15 mins of restoration of spontaneous circulation [30]. When other cooling methods were explored in dogs [39], intracarotid flush with cold Ringer's solution was fastest, although continuous infusion possibly with cold oxygenated blood or blood substitute would be required to maintain the effect. Other blood cooling methods or external cooling methods were intermediate in speed. Head-neck or total body surface cooling alone was slowest. Nevertheless, we proposed to manufacturers a hood-like garment perfused by cold fluid, for head-neck surface cooling in patients. Xiao et al. (A1, [40]) introduced and documented the application of peritoneal cold lavage, which lowered tympanic membrane temperature to 34 degrees C in 10 to 15 mins in large dogs. Emergency physicians believe that peritoneal lavage would be more readily accepted by clinicians than carotid puncture.

The Pittsburgh group found less benefit when mild resuscitative cerebral hypothermia induction was delayed by 15 mins as compared with immediate cooling [32]. In 1994, we evaluated a clinically realistic resuscitation and cooling protocol with head-neck surface plus peritoneal cooling initiated immediately after normothermic reperfusion [33]. We achieved a tympanic membrane temperature of 34 degrees C at 10 to 20 mins of reperfusion and sustained mild hypothermia for 12 hrs. Cooling was combined with cerebral blood flow promotion (by hypertension, mild hemodilution, and normocapnia). With this combination treatment protocol, the best outcome of brain function and morphology was achieved so far.

We now recommend clinical trials, with induction of mild hypothermia during standard external CPR or as rapidly as possible after restoration of spontaneous circulation, using ice bags on head and neck or a still-to-be-developed molded head-neck cooler, plus physicians performing peritoneal cold lavage or intracarotid cold flush. To rapidly achieve mild postarrest hypothermia, clinical feasibility trials are needed. Occult shivering should be controlled by the postischemic coma itself or with a muscle relaxant and an anesthetic or narcotic. Shivering and other side effects of mild therapeutic hypothermia in various circumstances remain to be studied. The best duration of postcardiac arrest cooling also has not been determined.

In normal brain, hypothermia produces a 7% reduction in cerebral metabolic rate for oxygen with every 1 degree C reduction in brain temperature [41]. This reduction in cerebral metabolic rate for oxygen cannot explain the brain damage mitigating effect of mild hypothermia, which must be due to synergism of many physico-chemical mechanisms, which we have reviewed [20,29]. We hypothesize that even mild hypothermia mitigates the deleterious chemical cascades during and after ischemia (see Figure 4in ``Suspended animation for delayed resuscitation'' in this issue). We do not know, however, if hypothermia is merely postponing the inevitable. Reduction in metabolism was found to be minimal with mild hypothermia early [42], or prolonged [43] after cardiac arrest in dogs (A6). In the normal organism without cardiac arrest and without shivering, a progressive reduction in total body temperature is accompanied by a parallel reduction in overall oxygen up-take and blood flow values and cerebral metabolic rate for oxygen and cerebral blood flow [1,41]. These changes may not be the case after cardiac arrest and reperfusion, which, during normothermia, results in transient cerebral hyperemia followed by protracted delayed hypoperfusion [20,42].

Ginsberg: Let us consider brain temperature as a spectrum, ranging from the hypothermic to the hyperthermic. Hypothermia has the potential to be protective and resuscitative, while hyperthermia, even of mild degree, can be damaging to the ischemic or traumatized brain [44]. Preventing hyperthermia is more easily accomplished clinically. Experimental data in support of the deleterious nature of hyperthermia in the injured brain have been obtained from blood brain barrier studies [45] in the incomplete forebrain ischemia rat model. With normalization of the temperature by 2 degrees C, the barrier breakdown is prevented.

Our group considered the most valid neurologic outcome, in rats, to be histopathology. The goal is a structurally intact, functioning brain. In the incomplete forebrain ischemia model in rats, 10- or 20-min global ischemia is followed only by hippocampal and striatal lesions, but when the temperature is increased by 2 degrees C during ischemia of this duration. other structures that would normally not be susceptible are also injured. Brain tissue microdialysis has been used in this model to measure neurotrans-mitters and also hydroxyl radical formation with the salicylate technique [46,47]. A slight increase

in temperature during the insult causes an increase in hydroxyl radical production.

In clinical studies, Sternau et al. [48] found, with use of a thermoprobe in the cerebral ventricle, differences between brain and core (urinary bladder) temperatures of 0.5 degrees C to 1 degree C. This difference may be clinically significant since only core temperature is usually measured.

Focal ischemia (stroke), by middle cerebral artery occlusion for 2 hrs, in the rat, gives smaller infarct volume at 30 degrees C and larger infarct volume with mild hyperthermia [49]. Middle cerebral artery occlusion for 3 hrs and reperfusion for 24 hrs resulted in large infarcts when done at normothermia and small infarcts when done at 32 degrees C [50]. Reducing infarct volume in patients by 30%, as in this rat study, could be clinically significant. When cooling was delayed by 1.5 hrs and lasted 3 hrs, there was an intermediate benefit. Thus, the therapeutic window is not absolute. Animal models of stroke, however, have their limitations. For example, the dissolution of emboli is not duplicated. This dissolution is a common phenomenon, as we are learning now with transcranial Doppler studies in patients with stroke.

Does hypothermia protect (resuscitate) only transiently? We have shown that in the rat forebrain ischemia model, cooling the brain within 5 mins of insult and maintaining hypothermia during 3 hrs reduces hippocampal lesions at 3 days by 50% [51]. The 3-day end point was initially considered sufficient. Dietrich et al. [38] of our group had the idea that this protection might not be permanent. Dietrich et al. [38] looked at rat brains 2 months after ischemia and found no reduction of hippocampal damage, but rather the same degree as in normothermic controls. Thus, there is a diminution of the resuscitative effect over time. Neurons are dying with a delay in their death process. What would ordinarily take a day, may take more than 1 wk, if brief cooling is applied after the insult. On the other hand, protective-preservative (intra-ischemic) hypothermia resulted in permanent reduction of hippocampal damage even at 2 months [38]. Postischemic hypothermia would still be beneficial, since it could expand the therapeutic window to do something else to save neurons. This idea needs to be explored in greater detail.

Use of the excitatory amino acid receptor blocker (competitive N-methyl-D-aspartate antagonist) MK-801 appeared to reduce histologic damage after global brain ischemia [52]. This reduction, however, was due to inadvertent mild hypothermia. When examined with accurate temperature control in a dog model of cardiac arrest (by the Pittsburgh group) [53], and a rat model of forebrain ischemia [54], MK-801 was found to not improve postischemic cerebral outcome. When our group used MK-801 in addition to hypothermia postarrest, we achieved mitigation of brain damage even at 2 months [55].

We also found, in a fluid percussion model of traumatic brain injury [56], that the contused area is diminished by moderate hypothermia induced at 5 mins and maintained for 3 hrs, when we examined the pathology at 3 days. The therapeutic window for cooling after traumatic brain injury may be quite generous. Mild hypothermia induced at 4 to 6 hrs after traumatic brain injury might still be beneficial. Stroke patients who stay at home for a day before deciding to come to the hospital will probably not benefit, whereas trauma cases quickly airlifted for therapy will benefit.

A key question for future investigations is how to examine the many mechanisms and other variables, the many time points of initial therapy, drug doses, different drugs, etc. This question is not a trivial issue when using larger animals. How do we extrapolate from animals to human data in terms of therapeutic window of opportunity?

Obrist: In middle cerebral artery occlusion or cardiac arrest, the circulation is cut off almost instantly, focally or globally. But

in head trauma. this process may go on for days. It is a very unstable pathophysiologic situation, with secondary injury possibly occurring on the second and third day perhaps. Mild cooling initiated at 4 to 6 hrs after injury might still be beneficial because of this dynamically evolving process [11].

Ginsberg: Dr. Obrist's point is a very important point, which also applies in stroke. The critics of animal models of stroke would say that animal models do not model the secondary events that might occur. For example, the dissolution of emboli and sporadic return of circulation is a common phenomenon, as we are learning now with transcranial Doppler studies after clinical stroke. This dissolution can occur early, or after several days, sometimes after the tissue has really died. Such an event complicates the situation. But if anything, it may allow for a more generous window of opportunity.

Nemoto: We hypothesize that mild hypothermia is more efficacious in ameliorating ischemic brain damage than barbiturates, because hypothermia preferentially reduces basal cerebral metabolic rate for oxygen, i.e., cerebral metabolic rate for oxygen associated with the maintenance of neuronal viability, whereas barbiturates preferentially attenuate active cerebral metabolic rate for oxygen associated with neuronal function, which is not essential for neuronal viability. We have shown ([17], A4) in the normal rat brain that mild hypothermia does indeed preferentially reduce basal cerebral metabolic rate for oxygen from approximate 50% of total cerebral metabolic rate for oxygen at 38 degrees C to 35% of total cerebral metabolic rate for oxygen at 34 degrees C.

Safar: An unidentified speaker expressed the view that there are no important differences between rodents and primates in the biochemical molecular response to brain trauma or ischemia. The only differences are thickness of skull, convolution of brain, density of neurons, and handling of pharmaceutical agents. If the laboratory data indicate that there is a positive effect when applied early, hypothermia should be tried clinically, induced as early as possible. How long hypothermia should be continued after the insult remains uncertain. Evaluating prolonged therapy requires an animal intensive care unit setting similar to the one we have used in Pittsburgh for 20 yrs, which most groups do not have. It must include titrated life support, or at least, continuous observation from insult to end points [20]. Observation, after cardiac arrest, must be for at least 72 hrs. Cooling for 6, 12, or 24 hrs may be more effective than the 2 to 3 hr mild hypothermia tried thus far in the laboratory.

Another unidentified speaker warned about problems with sepsis, which he found even after 2 to 3 hrs of cooling in dogs, certainly after profound hypothermia (7 degrees C), but also after 28 degrees C; and problems with the gut in dogs at 33 degrees C. We suspect that complications in large animals with prolonged cooling [57] can be avoided with modern intensive care life support. Our observations in dogs with up to 12 hrs of mild hypothermia after cardiac arrest [33], or with 2 hrs of profound hypothermic circulatory arrest for ``suspended animation'' [58], or with moderate hypothermia of 48 hrs after traumatic brain injury [6,7]-all with at least 20 hrs of intensive care life support--have resulted in no significant extracerebral complications. But, if you cool a dog and put him back into a cage and leave him on his own, the end result is unpredictable. Fine details of anesthesia (pharmacologic poikilothermia), cooling and rewarming rates, and overall life support are crucial and deserve to be studied.

Kochanek: The whole issue of hypothermia delaying or permanently mitigating brain injury is an important one. It may very well turn out that when applied in a resuscitative fashion, hypothermia may delay some events, but totally shut down or

prevent others. Our traumatic brain injury group has been interested in this issue from the perspective of the effects of hypothermia on the inflammatory response to traumatic brain injury in the brain itself. Our group [59] has demonstrated that in humans, 48 hrs after traumatic brain injury, hypothermia appears to totally shut off interleukin-1 production. In contrast, in rats treated with 4 hrs of hypothermia in preliminary studies in our laboratory, neutrophil infiltration and edema formation are delayed rather than prevented [60]. Pomeranz et al. [6] and Ebmeyer et al. [7] showed in a new dog model of traumatic brain injury (temporary epidural compression) that posttraumatic brain injury intracranial hypertension was prevented with moderate, but not mild hypothermia; however, herniation still occurred during rewarming. Factors such as the type of insult and the depth and duration of hypothermia may influence the effectiveness of hypothermia. Alternatively, some end points may respond differently. It may also be very interesting to determine if therapies added just before rewarming could provide a synergistic effect, thus possibly shortening the necessary duration of hypothermia.

Obrist: Can you comment on the distinction botween the deleterious effects of inflammation vs. excitatory amino acids? Both of them are important; however, in terms of delay in initiating therapy and the duration of therapeutic hypothermia, is there a distinction between these two types of processes?

Kochanek: There may be very major differences. In cerebral focal ischemia, there seems to be a reduction in lesion size with leukocyte depletion. Normally, there are white cells sticking to vascular endothelium after traumatic brain injury, less so after leukocyte depletion or with use of an adhesion antagonist. We have not observed that in trauma. After traumatic brain injury in rats, we are looking at the early low flow. Low flow has been totally unaffected by leukocyte depletion. The only thing that we have been able to attenuate from an inflammation standpoint is a very different type of paradigm, and that is in the delayed development of cerebral swelling (hyperemia) 24 hrs after injury. There are different potential mechanisms that could operate at this stage after traumatic brain injury, and inflammation may play a key role in this delayed phase posttrauma.

COOLING METHODS

Katz: The clinical feasibility studies needed to find a simple, practical way of reducing brain temperature to 34 degrees C within 15 mins, is a challenge (A2). Our group [39] found in human cadavers with 37 degrees C core temperature, ice water surface cooling of head and neck lowered deep brain temperature to 34 degrees C only after 30 to 60 mins. In anesthetized patients, body surface cooling requires 30 to 60 mins to achieve esophageal temperature of 32 degrees C [1,21,22].

Let us return to clinical rapid cooling methods needed for cardiac arrest victims. In an exploratory study of 50 prehospital cardiac arrest patients [61], our paramedics monitored tympanic membrane and esophageal temperatures. We found that during standard external CPR of 5 to 60 mins, 50% of the patients developed spontaneous mild hypothermia with tympanic membrane temperature of less than equals 35 degrees C, without any cooling efforts. Tympanic membrane and esophageal temperatures were similar and ranged between 31 degrees C and 37.4 degrees C. Cardiac arrest (no flow) plus CPR times ranged between 5 and 60 mins. With spontaneous cooling during external CPR, it may be easier than assumed to lower brain temperature to 34 degrees C quite rapidly by variously combining cooling methods which could be applied by paramedics in the field.

Lechleuthner: For the rapid induction of mild cerebral hypothermia, as apparently required after cardiac arrest [32], I would like

to introduce an idea, suggested by Dr. Safar's group [39], namely, intracarotid cold flush (A3). Dr. Safar pointed out that this technique had been tried for nonemergency situations before by neurosurgeons White [62] and Wolfson and Selker [63]. We have shown for the first time how mild hypothermia can be induced rapidly, during prehospital CPR, in a city emergency medical services system, that of Cologne, Germany (unpublished data). First, we measured tympanic membrane temperature in 27 patients, examining spontaneous hypothermia. In the first group, in which restoration of spontaneous circulation was not accomplished, tympanic membrane temperature decreased spontaneously over 30 mins of external CPR. In the second group, which responded with restoration of spontaneous circulation, tympanic membrane temperature was unchanged or increased slightly at first, and slightly decreased later, during transportation. In the third group, in which restoration of spontaneous circulation was accomplished within 2 mins, we punctured the carotid artery during CPR within 3 to 5 mins on the side opposite to tympanic membrane temperature monitoring. In 7 patients, we used 0.5 to 1 L of Ringer's solution at 4 degrees C to 8 degrees C, and forced it in by manual compression of the fluid bag. After approximate 0.5 L was injected into the carotid artery, the tympanic membrane temperature on the opposite side had decreased to 35 degrees C in 2 to 3 mins. The tympanic membrane temperature then decreased further to approximate 32 degrees C, and slowly returned to normothermia.

As to the question of whether the Doppler procedure would be useful to find the carotid artery quicker, I can say that ultrasound has been used by us and others in the hospital to find the internal jugular vein. However, under hectic prehospital emergency conditions, it may not be feasible. These carotid flush trials were done by me personally, with the help of the emergency medical services squad. After the promising dog studies of intracarotid flush [39], that method was found to be feasible in prehospital emergency medical services by us and also by Dr. K. Lindner of the University of Ulm and Dr. F. Sterz of the University of Vienna (personal communications). Dr. Sterz found considerable resistance by some of his colleagues when he performed carotid puncture in a few cardiac arrest patients in the emergency department.

White: Toward designing a simple inhospital technique of intravascular perfusion for rapidly cooling the brain, the cerebral cooling characteristics of blood, dextran, and normal saline solution at 1 degree C, administered intracarotidly, were studied (A7). In 19 heparinized cardiac arrested dogs, these methods, with little difference, lowered intracerebral temperatures from normothermia to 30 degrees C to 33 degrees C within 5 mins. In humans, intracerebral temperature was reduced by 10 degrees C in 10 mins with bilateral intracarotid perfusion of large volumes of dextran at 1 degree C. The ease and efficacy of this simple technique of carotid artery perfusion cooling argue for its use in emergency cardiac arrest situations.

Tisherman: Before intracarotid flush is applied clinically, studies comparing intracarotid with intravenous cold flush, with monitoring of brain vs. core temperature need to be done. Long-term neurologic outcome and risks of carotid injury need to be assessed.

Safar: Mathematical calculations of temperature gradients during surface cooling have been made (Dr. M. Klain, unpublished data), but these calculations cannot reproduce the many biologic variables of heads and organisms, with different body sizes, blood volumes, and blood flows (arrested circulation, low-flow, or normal circulation). There is no substitute for trying out cooling methods in patients inside and outside of the hospital.

A colleague from China indicated that in his country, they are practicing the application of a cooling helmet with seemingly good outcomes. Unfortunately, no data on this experience are available.

Xiao: We in Pittsburgh have been challenged to find a rapid way to induce mild cerebral hypothermia of 34 degrees C within 15 mins of reperfusion [32]. In 1991, we pursued peritoneal cold lavage in large dogs [40]. We feel, as Dr. Lechleuthner does, that peritoneal lavage is commonly practiced. Dr. Marion believes that it is carried out in 80% of severely head-injured patients to rule out abdominal hemorrhage. An informal survey we conducted demonstrated that peritoneal lavage would be readily acceptable for prehospital use by emergency physicians. First, in normal dogs without cardiac arrest, we inserted a large bore tube into the peritoneal cavity and instilled 2 L of Ringer's solution at 8 degrees C to 10 degrees C. The solution was kept in the cavity for 5 mins and then allowed to drain by gravity. In these dogs, weighing approximate 20 to 25 kg, core temperature decreased rapidly, and tympanic membrane temperature (brain temperature) reached 34 degrees C in 12 mins (range 8 to 15 mins). Then, we performed the same procedure on 24 dogs after normothermic cardiac arrest of 11 mins and reperfusion with normothermic low-flow cardiopulmonary bypass (as an experimental tool) [33]. Mild hypothermia was induced by head-neck surface cooling with ice bags, plus peritoneal lavage as above. Peritoneal cooling again reduced tympanic membrane temperature as quickly as in the previous experiments [40]. We maintained tympanic membrane and pulmonary artery temperatures at 34 degrees C for 12 hrs by continuing with head-neck and total body surface cooling and warming as needed. At 96 hrs of postarrest life support, the mild hypothermia-treated animals--which in addition received cerebral blood flow promotion by hypertension (mean arterial pressure of 140 mm Hg instead of 120 mm Hg for 4 hrs with norepinephrine), hemodilution (hematocrit of 30% instead of 40% with a dilute colloid solution), and normocapnia ($Paco_2$ 40 instead of 30 torr [5.3 instead of 4.0 kPa])--achieved the best functional performance and histologic damage scores yet achieved in any of our group's cardiac arrest studies over the past 20 yrs [33]. Although the peritoneal catheter was placed in advance in this study, under clinical conditions, it could be inserted by a skilled physician within 2 to 5 mins. Adult patients are expected to require 4 to 5 L of precooled Ringer's solution. Core temperature should be monitored to avoid a dangerous decrease to less than 30 degrees C. Core temperature and tympanic membrane temperature can be controlled and maintained by draining or reinstilling the cold fluid, and by surface cooling or warming.

Sterz: We recently performed feasibility trials in cardiac arrest patients brought from the city of Vienna to our University Hospital's emergency department after up to 1 hr of resuscitation attempts in the field. Some were mildly hypothermic on arrival. Those patients who were not hypothermic could have their pulmonary artery temperature lowered to approximate 33 degrees C over 1 hr, using whole body surface cooling by refrigeration blankets. This degree of hypothermia was maintained for 24 hrs, and then followed by spontaneous rewarming. We encountered favorable results that were previously not seen. Among 21 patients treated this way, after estimated VF no-flow times of 11 mins (range 5 to 15 mins), and CPR times sometimes as long as 20 to 30 mins, 15 of 21 patients achieved cerebral performance category 1 (normal) or 2 (moderate disability). The remaining six patients died soon thereafter (three patients from cardiovascular failure, two patients from brain failure, and one patient from liver damage caused by external CPR). These exploratory results appear better than those results of historic series without hypothermia in the past. A multicenter randomized clinical trial of mild postarrest hypothermia seems justified. Our observations also suggest that a considerable delay in the onset of hypothermia might still be beneficial.

Safar: Various cooling methods should be reexplored. The popular total body surface cooling with refrigeration blankets or

fanning has achieved core temperatures in anesthetized adult humans of 30 degrees C to 34 degrees C only after 1 to 2 hrs. Total body ice water immersion is rapid, but messy. As for optimal hypothermia levels, more work is needed. We have shown that after experimental traumatic brain injury in our new outcome model in dogs [6,7], moderate hypothermia but not mild hypothermia prevents the often lethal postinsult increase in ICP. During rewarming, however, a lethal ICP increase to herniation may still occur, even after 48 hrs of moderate hypothermia [7].

Research is needed concerning mechanisms by which various levels and durations of cerebral hypothermia, with or without pharmacologic poikilothermia, can produce good vs. bad effects. The observation in rats after incomplete forebrain ischemia, by Dietrich et al. [38], that mild resuscitative hypothermia may give only temporary benefit, should be explored after cardiac arrest in a higher species. Also, limiting outcome evaluation to the counting of neurons in the hippocampus of the rat is in our opinion not adequate. For 20 yrs, we have used in monkeys and dogs a semiquantitative method of scoring histologic ischemic changes in 20 brain regions. We consider this method, which we owe to Drs. J. Moossy and G. Rao of our Department of Pathology, as more representative of global brain damage [23,29-33,64].

This discussion was limited to resuscitation. Protective-preservative hypothermia, with temperature reductions down to just above tissue freezing, is relevant for ``suspended animation,'' the topic of another paper in this issue.

FREE RADICAL REACTIONS

Zar: I feel somewhat out of place presenting perfused liver data to a group of cerebral resuscitation researchers. In our laboratory, we are studying the effect of mild hypothermia on postischemic free radical reactions in the isolated, perfused rat liver (A8). Why study mild hypothermia in the liver? The brain, after all, is the center of cognitive function and determines quality of life after resuscitation. The liver has less lofty functions, such as detoxification, protein production, and serving as a barrier between the intestinal flora and the circulation. As an experimental tool, however, the liver has certain advantages. It does not depolarize and, consequently, has a more constant ionic milieu. There is also no excitotoxicity. These characteristics allow us to separate the effects of free radicals from other processes occurring in the brain.

We monitored free radical reactions, in real-time, with chemiluminescence [65]. We simultaneously monitored perfusion pressure and flow rate, and were able to calculate vascular resistance. Thus, we could measure the effect of free radicals on the vascular physiology of the liver.

We perfused the liver for 30 mins baseline, made it totally ischemic for 2.5 hrs, and then reperfused it for 2 hrs [66]. Since the liver is relatively resistant to ischemic injury and free radical reactions, at least 2 hrs of normothermic ischemia was required to detect sustained increased chemiluminescence with reperfusion. Vascular resistance also increased markedly during reperfusion. When the liver was made ischemic under protective-preservative 34 degrees C hypothermia, chemiluminescence levels remained at or near baseline during reperfusion. Protective-preservative 34 degrees C hypothermia also prevented the increase in vascular resistance with reperfusion seen in normothermic controls. When, after normothermic ischemia, 34 degrees C was induced with reperfusion, the chemiluminescence was at an intermediate level but the increase in vascular resistance was prevented. Our findings have some bearing on organ preservation. Chemiluminescence as a method for detecting on-line free-radical reactions was suggested 10 yrs ago to Safar by Ernster of Stockholm [67]. Within his team,

Dr. Safar promoted the development of this method for brain measurements, which is still technically elusive.

CONCLUSIONS

Marion: During the last 5 to 7 yrs, there has been a surge in research, both basic science and clinical, on the use of therapeutic mild or moderate hypothermia for the treatment of cerebral ischemia and traumatic brain injury. Studies to date have defined many, although by no means all, of the mechanisms through which hypothermia causes preservation of central nervous system tissue and improvement in functional outcome. While the efficacy of hypothermia has most clearly been demonstrated in animal models, recent clinical studies also have confirmed the beneficial effects of this treatment for severe traumatic brain injury. During the next several years, a number of very important issues need to be addressed. We must better define the true role of ischemia in traumatic brain injury. Why does hypothermia completely suppress glutamate in ischemia models, but have no effect on glutamate in contusion models? We must also include long-term outcome studies in our research protocols. The finding of the Ginsberg group that hypothermia may just delay ultimate neuronal death is very concerning. This finding underscores the importance of cerebral apoptosis, and contemporary efforts to define phenomena and the mechanisms responsible for them. The use of multiple therapies for ischemia and traumatic brain injury also must be addressed. As scientists, we must avoid the temptation to simply combine therapies that have been shown to be efficacious by themselves. Combination therapy must be studied with the same scientific rigor applied to the study of single therapies.

CONFERENCE ABSTRACTS*

A1. Xiao F, Safar P, Tisherman S, et al: Peritoneal and other cooling methods for the rapid induction of mild cerebral resuscitative hypothermia in dogs. International Resuscitation Research Center, University of Pittsburgh, Pittsburgh, PA

A2. Katz L, Safar P, Xiao F, et al: Mild cerebral cooling after cardiac arrest in dogs and patients. International Resuscitation Research Center, University of Pittsburgh, Pittsburgh, PA

A3. Lechleuthner A, Grass G, Dallmeyer D: Feasibility of rapid brain cooling during prehospital CPR. Department of Surgery, University of Cologne, Klinikum Koeln-Merheim, Germany

A4. Nemoto EM, Klementavicius R, Yonas H: Hypothermia attenuation of ischemic brain damage. Departments of Anesthesiology/Critical Care Medicine and Neurosurgery, University of Pittsburgh, Pittsburgh, PA

A5. Safar P, Leonov Y, Sterz F, et al: Mild resuscitative cerebral hypothermia mitigates brain damage after normothermic cardiac arrest in dog outcome models. International Resuscitation Research Center, University of Pittsburgh, Pittsburgh, PA

A6. Safar P, Oku K, Kuboyama K, et al: Cerebral blood flow (CBF) and metabolism (CMR) after cardiac arrest. Mild resuscitative cerebral hypothermia. International Resuscitation Research Center, University of Pittsburgh, Pittsburgh, PA

A7. White RJ: A simplified carotid perfusion technique for rapid brain cooling after cardiac arrest. Department of Neurological Surgery, Metropolitan Health Medical Center, Cleveland, OH

A8. Zar H, Tanigawa K, Kim Y, et al: Mild hypothermia decrease postischemic hepatic injury. International Resuscitation

Research Center and Departments of Anesthesiology/Critical Care Medicine and Surgery, University of Pittsburgh, Pittsburgh, PA

*Published in the program of International Resuscitation Research Conference, Pittsburgh, PA, May 1994.

REFERENCES

1. Dripps RD (Ed): The Physiology of Induced Hypothermia. Washington, DC, National Academy Sciences, 1956 [Context Link]

2. Rosomoff HL: Protective effects of hypothermia against pathologic processes of the nervous system. Ann N Y Acad Sci 1959; 80:475-486 [Context Link]

3. Fay T: Observations on generalized refrigeration in cases of severe cerebral trauma. In: Trauma of the Central Nervous System. Proceedings of the Association for Research in Nervous and Mental Disease. Baltimore, Williams & Wilkins, 1945, pp 611-619 [Context Link]

4. Marshall LF, Gautille T, Klauber MR, et al: The outcome of severe closed head injury. J Neurosurg 1991; 75:S28-S36 **ExternalResolverBasic Bibliographic Links** [Context Link]

5. Clifton GL, Jiang JY, Lyeth BG, et al: Marked protection by moderate hypothermia after experimental traumatic brain injury. J Cereb Blood Flow Metab 1991; 11:114-121 **ExternalResolverBasic Bibliographic Links** [Context Link]

6. Pomeranz S, Safar P, Radovsky A, et al: The effect of resuscitative moderate hypothermia following epidural brain compression on cerebral damage in a canine outcome model. J Neurosurg 1993; 79:241-251 **ExternalResolverBasic Bibliographic Links** [Context Link]

7. Ebmeyer U, Safar P, Pomeranz S, et al: Moderate resuscitative hypothermia after brain trauma (simulated epidural hematoma) in new intensive care outcome model in dogs. Abstr. Resuscitation 1994; 28:S13 [Context Link]

8. Palmer AM, Marion DW, Botscheller ML, et al: Therapeutic hypothermia is cytoprotective without attenuating the traumatic brain injury-induced elevations in interstitial concentrations of aspartate and glutamate. J Neurotrauma 1993; 10:363-371 **ExternalResolverBasic Bibliographic Links** [Context Link]

9. Marion DW, White MJ: Treatment of experimental brain injury with moderate hypothermia and 21-aminosteroids. J Neurotrauma, In Press [Context Link]

10. Yaghmai AA, Povlishock J: Traumatically induced reactive change as visualized through the use of monoclonal antibodies targeted to neurofilament subunits. J Neuropath Exp Neurol 1992; 51:158-176 [Context Link]

11. Marion DW, Obrist WD, Carlier PM, et al: The use of moderate therapeutic hypothermia for patients with severe head injuries. A preliminary report. J Neurosurg 1993; 79:354-362 **ExternalResolverBasic Bibliographic Links** [Context Link]

12. Shiozaki T, Hisashi S, Taneda M, et al: Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 1993; 79:363-368 **ExternalResolverBasic Bibliographic Links** [Context Link]

13. Clifton GL, Allen S, Barrodale P, et al: A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 1993; 10:263-271 **ExternalResolverBasic Bibliographic Links** [Context Link]

14. Langfitt TW, Gannarelli TA: Can the outcome from head injury be improved? J Neurosurg 1982; 56:19-25 **ExternalResolverBasic Bibliographic Links** [Context Link]

15. Busto R, Globus MYT, Dietrich D, et al: Effect of mild hypothermia on ischemia-induced release of neurotransmitters and

free fatty acids in rat brain. Stroke 1989; 20:904-910 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

16. Yoshino A, Hovda DA, Kawamata T, et al: Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: Evidence of a hyper-and subsequent hypometabolic state. Brain Res 1991; 561:106-119 **ExternalResolverBasic Bibliographic Links** [Context Link]

17. Nemoto EM, Klementavicius R, Melick JA, et al: Suppression of cerebral metabolic rate for oxygen ($CMRO_2$) by mild hypothermia compared to thiopental. J Neurosurg Anesthesiol, In Press [Context Link]

18. DeKosky ST, Miller PD, Styren S, et al: Interleukin-1 beta elevation in CSF following head injury in humans is attenuated by hypothermia. Abstr. J Neurotrauma 1994; 11:106 [Context Link]

19. Katayama Y, Becker DP, Tamura T, et al: Early cellular swelling in experimental traumatic brain injury: A phenomenon mediated by excitatory amino acids. Acta Neurochir Suppl (Wien) 1990; 51:271-273 [Context Link]

20. Safar P: Cerebral resuscitation after cardiac arrest. Research initiatives and future directions. A review. Ann Emerg Med 1993; 22:324-349. See updated version in: Cardiac Arrest. Chapter 49. Paradis NA, et al (Eds). Baltimore, Williams & Wilkins, 1995 [Context Link]

21. Benson DW, Williams GR, Spencer FC, et al: The use of hypothermia after cardiac arrest. Anesth Analg 1958; 38:423-428 [Context Link]

22. Ravitch MM, Lane R, Safar P, et al: Lightning stroke. Report of case with recovery after cardiac massage and prolonged artificial respiration. N Engl J Med 1961; 264:36-38 **ExternalResolverBasic Bibliographic Links** [Context Link]

23. Gisvold SE, Safar P, Rao G, et al: Multifaceted therapy after global brain ischemia in monkeys. Stroke 1984; 15:803-812 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

24. Leonov Y, Sterz F, Safar P, et al: Moderate hypothermia after cardiac arrest of 17 min in dogs: Effect on cerebral and cardiac outcome. A preliminary study. Stroke 1990; 21:1600-1606 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

25. Safar P, Grenvik A, Abramson N, et al (Eds): International resuscitation research symposium on the reversibility of clinical death, May 1987. Crit Care Med 1988; 16:919-1086 [Context Link]

26. Hossmann KA: Resuscitation potentials after prolonged global ischemia in cats. Crit Care Med 1988; 16:964-971 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

27. Safar P: Resuscitation from clinical death: Pathophysiologic limits and therapeutic potentials. Crit Care Med 1988; 16:923-941 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

28. Brader E, Jehle D, Safar P: Protective head cooling during cardiac arrest in dogs. Abstr. Ann Emerg Med 1985; 14:510 **ExternalResolverBasic Bibliographic Links** [Context Link]

29. Leonov Y, Sterz F, Safar P, et al: Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 1990; 10:57-70 **ExternalResolverBasic Bibliographic Links** [Context Link]

30. Sterz F, Safar P, Tisherman S, et al: Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. Crit Care Med 1991; 19:379-389 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

31. Weinrauch V, Safar P, Tisherman S, et al: Beneficial effect of mild hypothermia and detrimental effect of deep

hypothermia after cardiac arrest in dogs. Stroke 1992; 23:1454-1462 **ExternalResolverBasic Bibliographic Links** [Context Link]

32. 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, controlled study. Crit Care Med 1993; 21:1348-1358 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

33. Safar P, Xiao F, Radovsky A, et al: Improved cerebral resuscitation from cardiac arrest in dogs, with mild hypothermia plus blood flow promotion. Stroke 1996; 27:105-113 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

34. Xiao F, Safar P, Katz L, et al: Mild protective and resuscitative cerebral hypothermia improves outcome after asphyxial cardiac arrest in rats. Abstr Resuscitation 1994; 28:S21 [Context Link]

35. Busto R: Postischemic moderate hypothermia inhibits CA1 hippocampal ischemic neuronal injury. Neurosci Lett 1989; 101:299-304 **ExternalResolverBasic Bibliographic Links** [Context Link]

36. Boris-Moller F, Smith ML, Siesjo BK: Effects of hypothermia on ischemic brain damage: A comparison between preischemic and postischemic cooling. Neuroscience Research Communication 1989; 5:87-94 [Context Link]

37. Chopp M, Chen H, Dereski MO, et al: Mild hypothermic intervention after graded ischemic stress in rats. Stroke 1991; 22:37-43 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

38. Dietrich WD, Busto R, Alonso O, et al: Intraischemic but not postischemic brain hypothermia protects chronically following global forebrain ischemia in rats. J Cereb Blood Flow Metab 1993; 13:541-549 **ExternalResolverBasic Bibliographic Links** [Context Link]

39. Tisherman S, Safar P, Sterz F, et al: Methods for rapid induction of resuscitative cerebral hypothermia. Abstr. Prehosp Disaster Med 1991; 6:207 [Context Link]

40. Xiao F, Safar P, Alexander H: Peritoneal cooling for mild cerebral hypothermia after cardiac arrest in dogs. Resuscitation 1995; 30:51-59 **ExternalResolverBasic Bibliographic Links** [Context Link]

41. Rosomoff HL, Holaday DA: Cerebral blood flow and cerebral oxygen consumption during hypothermia. Am J Physiol 1954; 179:85-88 **ExternalResolverBasic Bibliographic Links** [Context Link]

42. Oku K, Sterz F, Safar P, et al: Mild hypothermia after cardiac arrest in dogs does not affect postarrest multifocal cerebral hypoperfusion. Stroke 1993; 24:1590-1598 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

43. Kuboyama K, Safar P, Oku K, et al: Mild hypothermia after cardiac arrest in dogs does not affect postarrest cerebral oxygen uptake/delivery mismatching. Resuscitation 1994; 27:231-244 **ExternalResolverBasic Bibliographic Links** [Context Link]

44. Dietrich WD, Busto R, Valdes I, et al: Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. Stroke 1990; 21:1318-1325 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

45. Dietrich WD, Busto R, Valdes I, et al: The importance of brain temperatures in alterations of the blood-brain barrier during brain ischemia. J Neuropathol Exp Neurol 1990; 49:486-497 [Context Link]

46. Ginsberg MD, Globus MY-T, Martinez E, et al: Oxygen radical and excitotoxic processes in brain ischemia and trauma. In: Pharmacology of Cerebral Ischemia 1994. Krieglstein J, Oberpichler-Schwenk H (Eds). Stuttgart, Wissenchaftliche Verlagsgellschaft, 1994, pp 255-268 [Context Link]

47. Globus MY-T, Busto R, Lin B, et al: Detection of free radical activity during transient global ischemia and recirculation:

Effects of intraischemic brain temperature modulation. J Neurochem, in press [Context Link]

48. Sternau L, Thompson C, Dietrich WD, et al: Intracranial temperature--observations in the human brain. Abstr. J Cereb Blood Flow Metab 1991; 11:S123 [Context Link]

49. Morikawa E, Ginsberg MD, Dietrich WD, et al: The significance of brain temperature in focal cerebral ischemia: Histopathological consequences of middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 1992; 12:380-389 **ExternalResolverBasic Bibliographic Links** [Context Link]

50. Xue D, Huang Z-G, Smith KE, et al: Immediate or delayed mild hypothermia prevents focal cerebral infarction. Brain Res 1992; 587:66-72 **ExternalResolverBasic Bibliographic Links** [Context Link]

51. Busto R, Dietrich WD, Globus MY-T, et al: Postischemic moderate hypothermia inhibits CA1 hippocampal ischemic neuronal injury. Neurosci Lett 1989; 101:299-304 **ExternalResolverBasic Bibliographic Links** [Context Link]

52. Buchan A, Pulsinelli WA: Hypothermia but not the N-methyl-D-aspartate antagonist MK-801 attenuates neuronal damage in gerbils subjected to transient global ischemia. J Neurosci 1990; 10:311-316 **ExternalResolverBasic Bibliographic Links** [Context Link]

53. Sterz F, Leonov Y, Safar P, et al: Effect of excitatory amino acid receptor blocker MK-801 on overall, neurologic, and morphologic outcome after prolonged cardiac arrest in dogs. Anesthesiology 1989; 71:907-918 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

54. Buchan A, Li H, Pulsinelli WA: The N-methyl-D-aspartate antagonist, MK-801, fails to protect against neuronal damage caused by transient, severe forebrain ischemia in adult rats. J Neurosci 1991; 11:1049-1056 **ExternalResolverBasic Bibliographic Links** [Context Link]

55. Lin B, Dietrich WD, Busto R, et al: Postischemic brain hypothermia combined with delayed MK-801 treatment protects chronically after global ischemia in rats. Abstr. Stroke 1994; 25:254 **ExternalResolverBasic Bibliographic Links** [Context Link]

56. Dietrich WD, Alonso O, Busto R, et al: Post-traumatic brain hypothermia reduces histopathological damage following concussive brain injury in the rat. Acta Neuropathol 1994; 87:250-258 **ExternalResolverBasic Bibliographic Links** [Context Link]

57. Steen PA, Soule EH, Michenfelder JD: Detrimental effect of prolonged hypothermia in rats and monkeys with and without regional brain ischemia. Stroke 1979; 10:522-529 **Ovid Full Text ExternalResolverBasic Bibliographic Links** [Context Link]

58. Tisherman SA, Safar P, Radovsky A, et al: Profound hypothermia (less than 10 degrees C) compared with deep hypothermia (15 degrees C) improves neurologic outcome in dogs after two hours' circulatory arrest induced to enable resuscitative surgery. J Trauma 1991; 31:1051-1062 **ExternalResolverBasic Bibliographic Links** [Context Link]

59. Goss JR, Styren SC, Miller PD, et al: Hypothermia attenuates the normal increase in interleukin 1 beta RNA and nerve growth factor following traumatic brain injury in the rat. J Neurotrauma 1995; 12:159-167 **ExternalResolverBasic Bibliographic Links** [Context Link]

60. Mansfield RT, Schiding JK, Hamilton RL, et al: Effects of hypothermia on traumatic brain injury in immature rats. J Cereb Blood Flow Metab, In Press [Context Link]

61. Katz L, Safar P, Xiao F, et al: Mild cerebral cooling after cardiac arrest in dogs and patients. Abstr. Resuscitation 1994; 28: S10 [Context Link]

62. White RJ: Cerebral hypothermia and circulatory arrest. Review and commentator. Mayo Clin Proc 1978; 53:450-458 **ExternalResolverBasic Bibliographic Links** [Context Link]

63. Wolfson SK, Selker RG: Carotid perfusion hypothermia for brain surgery using cardiac arrest without bypass. J Surg Res 1973; 14:449-458 **ExternalResolverBasic Bibliographic Links** [Context Link]

64. Nemoto EM, Bleyaert AL, Stezoski SW, et al: Global brain ischemia: A reproducible monkey model. Stroke 1977; 8:558-564 **ExternalResolverBasic Bibliographic Links** [Context Link]

65. Boveris A, Cadenas E, Reiter R, et al: Organ chemiluminescence non-invasive assay for oxidative radical reactions. Proc Natl Acad Sci U S A 1980; 77:347-351 **ExternalResolverBasic Bibliographic Links** [Context Link]

66. Zar H, Tanigawa K, Lancaster J: Mild hypothermia (MH) protects against postischemic hepatic endothelial injury and lipid peroxidation (LP). Abstr. FASEB J 1994; 8:A128 **ExternalResolverBasic Bibliographic Links** [Context Link]

67. Ernster L: Biochemistry of reoxygenation injury. Crit Care Med 1988; 10:947-953 [Context Link]