

Baltimore, 1997.
123. Grahn D, Brock-Utne JG, Watenpaugh DE, Heller HC. Recovery from mild hypothermia can be accelerated by mechanically distending blood vessels in the hand. *J Appl Physiol* 1998;85:1643–8.

124. Smith CE, Parand A, Pinchak AC, et al. The failure of negative pressure rewarming (Thermostat) to accelerate recovery from mild hypothermia in postoperative surgical patients. *Anesth Analg* 1999;89:1541–5.

Therapeutic Hypothermia

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Learning Objectives: 1) to familiarize the reader with contemporary studies on the application of resuscitative hypothermia in the treatment of traumatic brain injury and hemorrhagic shock, 2) to describe the potential mechanisms for the beneficial effects of hypothermia in these settings, 3) to present some recent findings from both laboratory and clinical studies of resuscitative hypothermia conducted at the University of Pittsburgh, 4) to discuss possible side effects and limitations of the application of therapeutic hypothermia, and 5) to discuss future directions for novel applications of hypothermia.

Abstract

There have been some exciting advancements in the field of therapeutic hypothermia during the past 7 years. Studies have shown the beneficial effects of mild hypothermia after ventricular fibrillation cardiac arrest and its use has been recommended by two leading medical groups. Ongoing work in the areas of the therapeutic efficacy of mild cooling and methods for rapid reduction and use during field resuscitation have been presented. The importance of mild cooling during CPR—a subject of intense investigation by the late Dr. Peter Safar near the end of his career—is beginning to become evident in laboratory studies. Mild hypothermia is also under additional investigation for use as treatment of severe traumatic brain injury. Further work is needed in this area in both children and adults because of controversial findings in the recent adult multicenter clinical trial. There also have been developments in the area of the potential applications of hypothermia in resuscitation from hemorrhagic shock. The studies of this controversial use are still in the experimental stage. Finally, we discuss a novel approach to treatment of exsanguination cardiac arrest by application of suspended animation with delayed resuscitation.

In 1997, our group at the Safar Center for Resuscitation Research consulted on an article for the ITACCS-sponsored monograph on hypothermia in trauma that was entitled *Therapeutic Hypothermia After Traumatic Brain Injury or Hemorrhagic Shock: From Mild Cooling to Suspended Animation*.¹ Having been asked to update that article for *TraumaCare* in 2004, we take a look back and a glimpse forward on the topic of therapeutic hypothermia in the collective field of resuscitation medicine.

From 1997 to 2004

Unquestionably, the most exciting and important development in the field of therapeutic hypothermia for resuscitation medicine came in February 2002. In that month, two separate studies were reported in the *New England Journal of Medicine* demonstrating beneficial effects of mild hypothermia (~33°C) after ventricular fibrillation (VF) cardiac arrest (CA) in adults.^{2,4} Sterz and his multicenter group in Europe² and Bernard et al³ in Australia reported significant beneficial effects on outcome when hypothermia was initiated after restoration of spontaneous circulation. In the study by Sterz and colleagues,² to prevent one unfavorable outcome, six patients would need to be treated with hypothermia. Cooling was continued for either 12 hours in the study by Sterz and colleagues² or 24 hours in the study by Bernard and colleagues.³ Even more surprising to our group in Pittsburgh was the fact that cooling was effective even though the time to target temperature was about 12 hours in the study by Sterz and colleagues.² This suggests benefit of hypothermia after cardiac arrest even with delayed application. One mechanism that may be involved is the ability of mild cooling to block delayed neuronal death, which is likely to develop as part of an activated apoptosis cascade after CNS injury.^{5,7} Blockade of the release of the key initiator of the mitochondrial intrinsic pathway of apoptosis—cytochrome C—by mild hypothermia was recently shown in experimental brain ischemia.⁷ Of interest, successful delayed application of mild hypothermia has been shown in experimental animal models.⁸ These two clinical studies prompted a recent Level I recommendation of the American Heart Association (AHA) and the International Liaison Committee on Resuscitation (ILCOR) for the use of mild hypothermia after VFCA in adults.⁹

It is, however, widely recognized that therapeutic hypothermia is most efficacious when applied either before or early after CNS insults. In this regard, there have been two important studies that we believe will further expand the therapeutic efficacy of mild cooling. In 2003, in a study of 22 adults, Bernard et al¹⁰ reported that 30 mL/kg bolus over 30 min of an ice cold (4°C) lactated Ringer's solution is safe and reduces core temperature by ~2°C when administered after establishing stable restoration of spontaneous circulation (ROSC) in CA victims. This is a simple, inexpensive, and very feasible approach to rapid induction of mild hypothermia. Ambulances should develop systems to have several liters of ice cold fluid readily available. More recently, in an experimental laboratory model of CA in dogs simulating field resuscitation, Nozari et al¹¹ carried this concept further and

reported that mild hypothermia was powerfully effective in improving survival and outcome when initiated during protracted CPR and ACLS. Clinical trials of the use of mild cooling during CPR should be pursued. Of note, that work was one of several that CPR pioneer Dr. Peter Safar believed to be of special importance to the optimization of hypothermia, during his investigation in the final 15 months of his life.¹²

Traumatic Brain Injury

Remarkably, in 1997 there was little hope that hypothermia would be effective in CA, but much optimism that it would become standard of care in the setting of severe traumatic brain injury (TBI). That optimism was based on the study of the beneficial effect of moderate hypothermia (32°C) on outcome published by Marion et al.¹³ This study followed a long series of positive reports on the effect of moderate hypothermia in experimental TBI. However, Clifton et al.¹⁴ in 2001, reported on the failure of moderate hypothermia (32°C) in 392 patients in a study that staggered the momentum behind the application of this therapy in CNS injury. Mild and moderate hypothermia had been shown consistently to have the most powerful beneficial effect on outcome of any therapy in experimental TBI; why had it failed? And now, in light of the positive trials in CA, why would therapeutic hypothermia be effective in CA but not in severe TBI? This topic was recently reviewed.¹⁵ One of the answers may lie in the mire of the challenges of carrying out a multicenter study of this magnitude and in the complex therapeutic setting of severe TBI. Issues such as differences in the approaches taken between centers to achieve the target cerebral perfusion pressure and intracranial pressure (i.e., fluid versus pressor) along with the fact that a number of patients in both groups presented with hypothermia on admission have been discussed in separate reports.^{16,17} Another intriguing possibility is the fact that unlike TBI, there is generally no application of other brain-oriented therapies (ICP monitoring, mannitol, hypertonic saline) in CA. Thus, hypothermia was compared with a number of other brain-oriented therapies in TBI that may already be mitigating most or all of the secondary damage that is therapeutically manipulable by cooling.

The optimal temperature, duration, and rate of rewarming could also be factors that need to be defined for successful application of therapeutic hypothermia. It is interesting that in CA mild hypothermia (33–36°C) is generally used, while in TBI moderate hypothermia (32°C) is generally the target. Recently, Tokutomi et al.¹⁸ reported that extremely mild hypothermia (35.5°C) may be optimal in clinical TBI. Similarly, rapid rewarming may be particularly harmful to traumatically injured brains.¹⁹ Finally, sex may be an important factor in determining the efficacy of hypothermia in TBI. Bayir et al.²⁰ recently reported that lipid peroxidation (assessed by CSF levels of F₂-isoprostane) after severe TBI in adults was markedly increased on day 1 in male patients, but not in female patients. Hypothermia was only able to affect this mechanism in men. Further clinical and laboratory study of hypothermia in TBI is needed.

An additional area of investigation that is ongoing in Pittsburgh in the area of hypothermia in TBI is the multicenter safety and feasibility study of infants and children by P. David Adelson and his group.²¹ This work actually includes two studies: a multicenter trial in cases in which the time of injury is less than 6 hours before enrollment and a second trial that includes children presenting with secondary deterioration and child abuse victims where the time of injury is not defined. As

these studies are being carried out by Dr. Adelson and colleagues, our investigators at the Safar Center have performed a comprehensive assessment of the effect of therapeutic hypothermia (32–33°C) applied for 48 hours on CSF biochemistry in these infants and children. Our data support a powerful beneficial effect of hypothermia on a battery of markers of oxidative injury.²⁰ However, the effect of hypothermia appears to be selective since we did not observe reductions in the posttrauma increase in a number of other markers of secondary damage.²² As additional data emerge from this trial, we hope we will be able to better understand and tailor the use of hypothermia in pediatric and adult TBI.

Hypothermia in Hemorrhagic Shock

Since publication of our review in 1997, there have been a number of developments in the area of the potential applications of hypothermia in resuscitation from hemorrhagic shock. These studies have been exclusively carried out in experimental models since the use of mild cooling during traumatic hemorrhagic shock is more controversial than its use in cerebral resuscitation and preservation. Tisherman and co-investigators at the Safar Center^{23–28} have led the way in the investigation of this potential use of mild hypothermia.

In a series of studies in rats, mild cooling during shock was found to increase survival in both uncontrolled and pressure-controlled models.^{23–28} In this setting, cooling appears to confer a systemic benefit since local gut cooling was insufficient to confer protection.²⁷ One possible mechanism for the benefit of hypothermia in this setting is shown by the work of Weisser et al.²⁹ They reported that mild cooling improves myocardial contractility during shock. Finally, in a recent study, Wu et al.²⁸ demonstrated a beneficial effect of mild IV cooling on survival in a pig model of trauma and hemorrhagic shock. A surprising finding in that study was the fact that rapid cooling with IV iced saline was not as effective as somewhat slower controlled cooling with room temperature IV fluids. Although additional investigation of this controversial but interesting application of mild hypothermia is needed in large-animal models of hemorrhagic shock, clinical feasibility trials could be initiated.

Suspended Animation with Delayed Resuscitation for Exsanguination Cardiac Arrest

Finally, our group has been intensely studying a very novel approach to the treatment of victims of exsanguination CA. This work has been recently reviewed,³⁰ but has been developed as part of a novel approach to the high field mortality from rapid exsanguination seen in combat casualties. Using an aortic flush of iced (~2°C) saline initiated at 2 minutes after established exsanguination CA in a dog model that includes 72 hours of contemporary ICU care, preservation times of up to 2 hours have been achieved with normal long-term outcome.³¹ A brain temperature of ~10°C is used with this approach to achieve good outcome for arrest times beyond 60 minutes. The effect of profound hypothermic preservation has been also found to be efficacious even in the setting of exsanguination CA with superimposed tissue trauma (splenic laceration and laparotomy); however, the addition of postresuscitation plasma exchange was necessary for optimal outcome.³² In current studies in our laboratory we are testing if this suspended animation approach is still successful in

achieving normal outcome if prolonged hemorrhagic shock (1.5–2.5 hours) precedes exsanguination CA. The beneficial effects of this extremely novel approach to trauma resuscitation are remarkable. The first clinical application of suspended animation with delayed resuscitation is being considered in the civilian of exsanguination CA from penetrating trauma.³⁰

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References

- Kochanek PM, Safar P, Marion DW, Tisherman SA, DeKosky ST. Therapeutic hypothermia after traumatic brain injury or hemorrhagic shock: From mild cooling to suspended animation. In: *Hypothermia in Trauma: Deliberate or Accidental. What is New?* 10th Annual Trauma Anesthesia and Critical Care Symposium (ITACCS), Baltimore, MD, May 17, 1997, pp 17–20.
- Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
- Safar PJ, Kochanek PM. Therapeutic hypothermia after cardiac arrest. *N Engl J Med* 2002;346:612–3.
- Edwards AD, Yue X, Squier MV, et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. *Biochem Biophys Res Commun* 1995;217:119–9.
- Phanithi PB, Yoshida Y, Santana A, et al. Mild hypothermia mitigates post-ischemic neuronal death following focal cerebral ischemia in rat brain: immunohistochemical study of Fas, caspase-3, and TUNEL. *Neuropathology* 2000;20:273–82.
- Yenari MA, Iwayama S, Cheng D, et al. Mild hypothermia attenuates cytochrome c release but does not alter Bcl-2 expression or caspase activation after experimental stroke. *J Cereb Blood Flow Metab* 2002;22:29–38.
- Hickey RW, Ferimer H, Alexander HL, et al. Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats. *Crit Care Med* 2000;28:3511–6.
- Nolan JP, Morley PT, Vanden Hoek TL, et al; International Liaison Committee on Resuscitation. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003;108:118–21.
- Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003;56:9–13.
- Nozari A, Safar P, Stezoski SW, et al. Mild hypothermia during prolonged cardiopulmonary-cerebral resuscitation increases conscious survival in dogs. *Crit Care Med*, in press, 2004.
- Grenvik A, Kochanek PM. The incredible career of Peter J. Safar, MD: The Michelangelo of acute medicine. *Crit Care Med* 2004;32(2 suppl):S3–S7.
- Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997;336:540–6.
- Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001;344:556–63.
- Kochanek PM, Safar PJ. Therapeutic hypothermia for severe traumatic brain injury. *JAMA* 2003;289:3007–9.
- Clifton GL, Miller ER, Choi SC, et al. Hypothermia on admission in patients with severe brain injury. *J Neurotrauma* 2002;19:293–301.
- Clifton GL, Choi SC, Miller ER, et al. Intercenter variance in clinical trials of head trauma—experiences of the National Acute Brain Injury Study: Hypothermia. *J Neurosurg* 2001;95:751–5.
- Tokutomi T, Morimoto K, Miyagi T, et al. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. *Neurosurgery* 2003;52:102–11.
- Suehiro E, Povlishock JT. Exacerbation of traumatically induced axonal injury by rapid posthypothermic rewarming and attenuation of axonal change by cyclosporin A. *J Neurosurg* 2001;94:493–8.
- Bayir H, Adelson PD, Kagan VE, et al. Therapeutic hypothermia attenuates oxidative stress after traumatic brain injury in infants and children. 32nd SCCM Critical Care Congress, January 2003, *Crit Care Med* Suppl 2002;30:A7.
- Adelson PD, Ragheb J, Muizelaar JP, et al. Prospective multicenter randomized Phase II trial of moderate hypothermia in children following severe TBI. *Neurosurgery* 2004, in press.
- Shore PM, Jackson EK, Clark RSB, et al. Therapeutic hypothermia does not affect markers of injury, cellular energetics, inflammation, and regeneration in cerebrospinal fluid after severe traumatic brain injury in infants and children. 4th World Congress on Pediatric Intensive Care (WFPICCS), Boston. *Pediatr Crit Care Med* Suppl 2003;4:A143.
- Kim SH, Stezoski SW, Safar P, Capone A, Tisherman S. Hypothermia and minimal fluid resuscitation increase survival after uncontrolled hemorrhagic shock in rats. *J Trauma* 1997;42:213–22.
- Kim SH, Stezoski SW, Safar P, Tisherman SA. Hypothermia, but not 100% oxygen breathing, prolongs survival time during lethal uncontrolled hemorrhagic shock in rats. *J Trauma* 1998;44:485–91.
- Prueckner S, Safar P, Kentner R, Stezoski J, Tisherman SA. Mild hypothermia increases survival from severe pressure-controlled hemorrhagic shock in rats. *J Trauma* 2001;50:253–62.
- Kentner R, Rollwagen FM, Prueckner S, et al. Effects of mild hypothermia on survival and serum cytokines in uncontrolled hemorrhagic shock in rats. *Shock* 2002;17:521–6.
- Wu X, Stezoski J, Safar P, et al. Systemic hypothermia, but not regional gut hypothermia, improves survival from prolonged hemorrhagic shock in rats. *J Trauma* 2002;53:654–62.
- Wu X, Stezoski J, Safar P, Nozari A, Tisherman SA. After spontaneous hypothermia during hemorrhagic shock, continuing mild hypothermia (34 degrees C) improves early but not late survival in rats. *J Trauma* 2003;55:308–16.
- Weisser J, Martin J, Bisping E, et al. Influence of mild hypothermia on myocardial contractility and circulatory function. *Basic Res Cardiol* 2001;96:198–205.
- Tisherman SA. Suspended animation for resuscitation from exsanguinating hemorrhage. *Crit Care Med* 2004;32:S46–50.
- 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* 2003;31:1523–31.
- Nozari A, Safar P, Tisherman S, et al. Suspended animation and plasma exchange (SAPEX) enables full neurologic recovery from lethal traumatic exsanguinations, even after 2h period of no-flow. 33rd SCCM Critical Care Congress, February 2004. *Crit Care Med* Suppl 2003;31:A9.