Therapeutic Hypothermia: The Safar Vision

Patrick M. Kochanek,1,2 Tomas Drabek,1,3 and Samuel A. Tisherman1,2,4

Abstract

At the 2nd International Brain Hypothermia conference, in Miami, the late Dr. Peter Safar was honored for his many contributions to the field of therapeutic hypothermia. Therapeutic hypothermia played a central role in his overall vision for optimized resuscitation and neurointensive care, across a large number of potential insults. The successful use of therapeutic hypothermia in comatose patients after cardiac arrest, for example, was already included in the historic first “ABCs” of resuscitation, published by Safar in 1964. This review addresses key historical events in the development and implementation of therapeutic hypothermia across a number of central nervous system insults. A discussion of future potential uses of this therapy in a variety of applications as part of the Safar vision is also presented.

Key words: cerebrospinal fluid; clinical trial; glia cell response to injury; human studies; hypothermia; pediatric brain injury; regeneration; stem cells; therapeutic approaches for the treatment of CNS injury; traumatic brain injury; traumatic spinal cord injury

At the 2nd International Brain Hypothermia conference, in Miami, the late Dr. Peter Safar was honored for his many contributions to the field of therapeutic hypothermia. Safar was a remarkable man, generally recognized as the “Father of Modern Resuscitation.” Therapeutic hypothermia played a central role in his overall vision for optimized resuscitation and neurointensive care, across a large number of potential insults. The importance of this therapy in Safar’s overall vision for optimized critical care for acute life-threatening insults goes back to work by Drs. Hugh Rosomoff and Safar in the early 1960s at the University of Pittsburgh School of Medicine. Indeed, Safar built upon a body of work already established by Rosomoff (Rosomoff and Gilbert, 1955), and the early work of Williams and Spencer on the use of therapeutic hypothermia in clinical cardiac arrest, also in the 1950s (Williams and Spencer, 1958). In that era, Rosomoff and Safar routinely used therapeutic hypothermia as outlined in their incredible treatise from 1965 on management of the comatose patient (Rosomoff and Safar, 1965). In that review, Rosomoff and Safar provided a roadmap for therapeutic hypothermia and temperature control in neurointensive care that in many ways holds up remarkably well by today’s standards. On the topic of fever control after central nervous system (CNS) insults, they indicated that “hyperpyrexia is disastrous if uncontrolled” and suggested that “we prevent temperature rises above 38°C by the use of external cooling and/or vasodilators.” For comatose patients, they suggested that “hypothermia seems indicated in any patient who has brain damage severe enough to produce unconsciousness—usually the temperature is kept at 32°C.” On the topic of rewarming, they indicated that “re-warming should be accomplished by simply removing hypothermia blankets” and indicated that “patients may take 12–48 hours.” They also discussed hypothermia’s use as a therapeutic adjunct.

The key role of therapeutic hypothermia in comatose patients after cardiac arrest, for example is also readily seen in the historic first “ABCs” of resuscitation, published by Safar in 1964 (Safar, 1964). In that document, Safar presciently states that “hypothermia should be started within 30 minutes if there is no sign of CNS recovery.” Safar regularly stated that few things in medicine represent new discoveries; most are re-discoveries. Certainly that is the case for therapeutic hypothermia, where there are many earlier examples of potential value of the use of hypothermia in acute life threatening insults. Mild or moderate hypothermia was recognized as being potentially beneficial in trauma victims even by Napoleon’s respected surgeon, Baron Dominique-Jean Larrey, in 1814 (Larrey, 1814). Similarly, Dr. Charles Phelps in 1897 (Phelps, 1897) recommended the use of the “ice cap” in his treatise, “Traumatic Injuries of the Brain and Its Membranes.” Many others support the use of hypothermia in CNS insults in the 1950s and 1960s (Williams and Spencer, 1958; Lundberg et al., 1965).

As discussed elsewhere in this issue, many reports on the potential value of hypothermia—with astounding recoveries in some cold water drowning victims further fueling the resurgence of moderate hypothermia in clinical practice in the

1Safar Center for Resuscitation Research, 2Department of Critical Care Medicine, and 3Department of Anesthesiology, 4Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.
of mechanical support (Reich et al., 1990). He often stated that, with emergency extracorporeal support, blood flow and temperature can be optimized, and potentially beneficial drugs that might otherwise not be tolerated could be readily administered.

In traumatic brain injury (TBI), Safar felt that the current push to define, with a randomized controlled trial (RCT), a single protocol for use of therapeutic hypothermia was misguided. He suggested that therapeutic hypothermia in TBI be initiated early, but that its use in the intensive care unit (ICU) should be titrated to intracranial pressure (ICP), particularly during re-warming (Kochanek and Safar, 2003). Certainly, the idea of titrated cooling to physiological, biochemical, or other endpoints is worthy of exploration. Safar also believed that it was long overdue for therapeutic hypothermia to be applied in spinal cord injury and frequently cited early experimental work on this by his colleague Dr. Maurice Albin (Albin et al., 1965). He would have been pleased to see the work out of Miami on this therapy in experimental models (Yu et al., 2000) and the bold application in clinical care by the clinicians in Buffalo (www.cnn.com/HEALTH/blogspaging.dr.gupta/2007/12/tuning-in-to-watch-miracle.html).

Safar also felt that it would be logical for mild hypothermia to be used in focal ischemic insults such as stroke, where it could play a neuroprotective role, but he felt strongly that reperfusion was critical in that condition, and that hypothermia should serve as a bridge and/or adjunct in that regard. He would often say we must address the plumbing in stroke; otherwise, other acute therapies are not likely to be successful. Much of Safar’s final years were spent on the potential use of therapeutic hypothermia in the setting of hemorrhagic shock and exsanguination cardiac arrest. Work in this area was stimulated related to the obvious fact that conventional resuscitation (CPR/ACLS) is ineffective in the setting of exsanguination cardiac arrest—an important problem in civilian and military trauma. Given Safar’s seminal role in the development and implementation of CPR, this represented an obvious additional target for a new breakthrough approach. The

FIG. 1. Plot of approximate number of citations on PubMed resulting from the use of the search terms “cardiac arrest” and “hypothermia” on April 10, 2008. Key citations beginning in 1960 relevant to the application of hypothermia to clinical practice in cardiac arrest are identified. A remarkable increase in the area of therapeutic hypothermia (both research and clinical applications) is reflected by the increase in citations since 2002. VF, ventricular fibrillation; CPR, cardiopulmonary resuscitation.
extensive experience acquired from cardiac surgery became a cornerstone for experiments initiated by Tisherman and Safar in the late 1980s at the Safar Center for Resuscitation Research (formerly the International Resuscitation Research Center at the University of Pittsburgh) (Tisherman et al., 1990, 1991). The concept emerged to rapidly induce a state of “suspended animation” with profound hypothermia to buy a short period of time for damage control surgery for otherwise hopelessly injured trauma victims of exsanguination cardiac arrest. This approach, using an aortic ice-saline flush to induce emergency preservation, after years of study, has been demonstrated to be feasible for periods up to 3 h in several species (Behringer et al., 2000, 2003; Wu et al., 2006, 2008; Drabek et al., 2007), and is now moving forward, under the moniker Emergency Preservation and Resuscitation (EPR), as a clinical trial.

In addition to the work with the induction of profound hypothermia in exsanguination cardiac arrest, Safar and his team of investigators also pioneered the use of mild hypothermia to prolong the golden hour in hemorraghic shock. Although he recognized that spontaneous hypothermia epidemiologically is associated with unfavorable outcome in large trauma series (Wang et al., 2005), Safar and his investigative team demonstrated in experimental models of hemorrhagic shock that early application of mild cooling can indeed prolong the golden hour and delay the time to cardiac arrest in hemorrhagic shock (Crippen et al., 1991; Tisherman et al., 1999; Takasu et al., 2000; Prueckner et al., 2001; Wu et al., 2002). It may be that the induction of mild hypothermia is able to protect against tissue and organ injury in the setting of ischemia during shock and prevent acute death, prolonging the golden hour, but potential deleterious acute effects on coagulopathy and subsequent effects on infection may confound its potential benefit in hemorrhagic shock. In addition, induction of mild hypothermia with controlled polikilo-thermia (with deep sedation and neuromuscular blockade) may, in part, explain the different effects of therapeutic hypothermia versus the exposure hypothermia that frequently occurs in trauma victims. This is another area that deserves further exploration and represents an area of use of mild therapeutic hypothermia that may be able to be optimized by other adjuncts or therapies.

Finally, although Safar did not directly work in all the areas in which he believed that therapeutic hypothermia had potential utility, he supported exploration of its application in myocardial infarction. Indeed some of his own work showed that mild cooling in the setting of a cardiac arrest had beneficial effects outside of the CNS, including improved myocardial recovery and prevention of multiple organ failure (Nozari et al., 2006). Other potential conditions that he felt should be explored in this regard included refractory septic shock and acute lung injury, in prevention of multiple organ failure, and in cerebral protection in metabolic encephalopathy (Safar et al., 1978).

In conclusion, renewed interest in the use of therapeutic hypothermia is exciting and logical, given its powerful effects across many models and clinical conditions germane to acute medicine. Although many salient questions remain with regard to details of the use of this therapy—such as optimal target temperature and duration in various conditions, the best approach to re-warming, defining the most effective pharmacological adjuncts, the best target populations, and understanding how many issues in our routine clinical intensive care interface with therapeutic hypothermia (i.e., sedation, drug metabolism, outcome prediction, among others) (Tortorici et al., 2006, 2007; Haque et al., 2006)—a larger number of the facets of the Safar vision for therapeutic hypothermia are gaining acceptance, and the original roadmap of Rosomoff and Safar from 1965 is worthy of re-exploration and re-discovery.

Acknowledgments

This research was supported in part by the U.S. Army/ Telemedicine and Advanced Technology Research Center (to S.T.), the Society for Cardiovascular Anesthesiology (to T.D.), the Laerdal Foundation (to T.D.), and NINDS (grants NS 30318 and NS 38087, to P.M.K.). Drs. Kochanek and Tisherman are co-holders of a patent on the Emergency Preservation and Resuscitation method.

References


Address reprint requests to: Patrick M. Kochanek, M.D.

Department of Critical Care Medicine

Safar Center for Resuscitation Research

University of Pittsburgh School of Medicine

3434 Fifth Avenue

Pittsburgh, PA 15260

E-mail: kochanekpm@ccm.upmc.edu