Therapeutic Hypothermia in Resuscitation: The Safar Vision

Patrick M. Kochanek, MD,[1-4,7] Xianren Wu, MD,[1,3,7] Robert S. B. Clark, MD,[1-4] C. Edward Dixon, PhD,[1,2,5] Larry Jenkins, PhD,[1,2,5] Lyn Yaffe, MD,[8] and Samuel A. Tisherman, MD[1,3,6]
[1]Safar Center for Resuscitation Research,
[2]Brain Trauma Research Center,
Departments of [3]Critical Care Medicine, [4]Pediatrics,
[5]Neurosurgery, [6]Surgery, and [7]Anesthesiology
University of Pittsburgh School of Medicine,
Pittsburgh, PA 15260 USA,
and [8]Alion Science and Technology, McLean, VA 22102 USA
kochanekpm@ccm.upmc.edu

Much has been written about the incredible life of Peter Safar (Fig. 1), inventor of modern-day CPR, pioneer in anesthesiology, critical care medicine, emergency medicine, and disaster reanimatology, and humanist and mentor to countless clinicians, scientists, and students. For any of you who are interested in learning more about this incredible man, a comprehensive review of Peter's contributions to resuscitation can be found in a two-part series written by Peter Baskett and published in the journal *Resuscitation*.[1,2] Peter Safar's autobiography is also available through the Wood Library-Museum of Anesthesiology, and provides remarkable detail on both his academic and personal endeavors.[3] Finally, Drs. Patrick Kochanek, Ake Grenvik, and John Schaefer and Ms. Fran Mistrick assembled a Festschrift in honor of Dr. Safar, published in February 2004, as an entire freestanding supplement to the journal *Critical Care Medicine*.[4] That document provides a pictorial synopsis of his career, and quotes from over 30 individuals on their recollections of Peter Safar.

In light of the focus of this issue of *TraumaCare* on the use of therapeutic hypothermia in resuscitation and trauma, we thought that it would be worthwhile to write a short tribute to Peter specifically focused on some of his thoughts about the development and application of therapeutic hypothermia across the spectrum of resuscitation medicine.

Safar's Definitions of Hypothermia and Its Use in Resuscitation

On the topic of therapeutic hypothermia in resuscitation, Peter Safar would always begin by pointing out two issues that he believed were critical about this area of study, namely, accurate and consistent terminology concerning the depth of hypothermia and the situation surrounding its use. He believed that hypothermia should be categorized into mild (34–36°C), moderate (27–33°C), deep (15–26°C), profound (10–14°C), and ultraprofound (<10°C), and that the consistent use of this terminology was important since different mechanisms are affected in each of these temperature ranges. Similarly, he emphasized the importance of categorizing the use of hypothermia (and other therapies in the field of resuscitation medicine) as used for protection (applied before the insult), preservation (applied during the insult), or resuscitation (applied after the insult). These were part of the language of resuscitation, and he emphasized that we must speak it consistently to optimally communicate in our field. He disliked the term "neuroprotection" that is so often used by scientists and clinicians when discussing therapies that might be used in cerebral resuscitation after traumatic brain injury or cardiopulmonary arrest. As one can infer from the foregoing statements, these would be resuscitative rather than protective or preservative therapies.

Figure 1. Peter Safar, MD (See cover for portrait details)

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Peter Safar and Resuscitative Hypothermia in the 1960s to 1980s

Peter Safar was intimately involved in the use of therapeutic hypothermia in the 1960s in the treatment of patients across a broad spectrum of disorders during the birth of modern-day neurointensive care. He was heavily influenced by the work of Dr. Hugh Rosomoff in the Department of Neurological Surgery at the University of Pittsburgh, who was one of the pioneers in the investigation and application of therapeutic hypothermia in the 1950s and 1960s.[5-7] Peter Safar came to Pittsburgh in 1961 and always respected Rosomoff's work. In subsequent years, he fondly discussed the interaction between anesthesiology and neurological surgery in the use of hypothermia in patients with cerebral swelling. Safar often described the importance of titration of the hypothermia used in these patients. For example, he often indicated that in the 1960s, they routinely applied moderate hypothermia to patients with intracranial hypertension and severe traumatic brain injury, and would reinstate it if a secondary rise in intracranial hypertension occurred during rewarming. In traumatic brain injury, he did not believe that a single value for temperature control made sense, rather, that the depth of hypothermia should be continuously titrated to optimize its effect on a physiologically relevant bedside parameter, namely, intracranial pressure.

Safar also learned a great deal about therapeutic hypothermia in the early 1960s from the work of others outside Pittsburgh. For example, he was always intrigued by the work of Dr. Robert White in Cleveland, Ohio, who performed a number of pioneering studies of the use of hypothermia to preserve the isolated dog brain.[8,9] Similarly, he also discussed the early use of hypothermia by Lundberg and co-workers[10] in Lund, Sweden, and early use of spinal cord cooling by Albin et al.[11] However, in retrospect, Peter Safar recognized that there was inadequate information available about how to optimize the application of hypothermia in that early era and that the side effects seen with the use of moderate hypothermia for prolonged periods (particularly pulmonary infection and sepsis) gradually led to its abandonment in clinical use.

In reviewing the collected works of Peter Safar, the earliest description of his thoughts on the use of therapeutic hypothermia are provided in an amazing article written by him and published in a 1964 issue of the *Journal of the Iowa Medical Society.*[12] Peter Safar's "ABCs" (and beyond) of resuscitation in the early 1960s are described in this article—and of course Peter Safar was not satisfied with just ABC. He provided the resuscitator an entire alphabet of interventions for the victim in cardiac arrest. Prophetically, this describes the letter "H" in his resuscitation alphabet as the application of therapeutic hypothermia. This description is not all that far from what recently received a Level I endorsement from the International Liaison Committee on Resuscitation (ILCOR)[13] and the American Heart Association (AHA).[14] The figure outlining Peter's ABCs from 1964 and the use of hypothermia is shown in Figure 2.

Figure 2. Figure from a 1964 publication by Peter Safar in the *Journal of the Iowa Medical Society* describing the Safar ABCs and beyond of resuscitation. Over 40 years ago Peter Safar included the postresuscitation induction of hypothermia (see arrow) in victims of cardiopulmonary arrest. This concept was recently endorsed into standard of care (see text for details).

In the laboratory, one of the earliest documentations of therapeutic hypothermia in the collected works of Dr. Safar is an interesting report by Gisvold et al[15] in 1984 that described the use of a multifaceted therapeutic approach to cerebral resuscitation in an experimental model of complete global cerebral ischemia in monkeys. The approach used hemodilution, transient hypertension, pentobarbital, dexamethasone, and 6 hours of hypothermia, which significantly improved intact survival in 7 of 10 versus 2 of 9 controls. The concept and testing of a multifaceted approach to cerebral resuscitation, including hypothermia, was certainly ahead of its time, and contributed to the rejuvenation in the use of hypothermia that was also stimulated by the work of Busto et al,[16] who showed that very small reductions in brain temperature improved outcome in experimental cerebral ischemia in rats. The resurgence in interest in hypothermia that followed is recent history, with which you all are surely familiar.

In the last 20 years, Peter Safar focused on the use of hypothermia since it was the only therapy that he found to consistently demonstrate a "breakthrough" effect in his experimental models. In 2002, two large clinical trials demonstrated the efficacy of mild hypothermia after ventricular fibrillation (VF) cardiopulmonary arrest in humans[17-19] and, as previously described, this has now been recommended for clinical use by the key endorsing societies worldwide.[13,14]

On the day that the ILCOR and AHA guidelines were published, endorsing mild hypothermia after VF cardiac arrest in adults, I (PK) went into Peter Safar's office to share with him this exciting news. In typical Safar fashion he stated, "What took them so long?" When a therapy was shown to be effective—based on sound experimental evidence in large-animal studies that included clinically relevant long-term outcome and intensive care unit (ICU) care, and that accurately modeled the clinical condition—Peter Safar believed that randomized clinical trials were needed only to show feasibility. Peter Safar was not convinced that randomized clinical trials (RCTs) were very helpful in the difficult setting of resuscitation medicine, where it is challenging to control any of the key physiological parameters or underlying disorders. He believed that if a therapy was shown to be feasible and safe in clinical trials, and effective in relevant laboratory models, we were depriving patients of a valuable therapy that may never be able to be proven effective in the morass of an RCT. Fortunately, mild hypothermia was powerful enough to demonstrate a beneficial effect in two RCTs. Based on Peter's understanding of the problems that we face in resuscitation research, other agents able to demonstrate a benefit in an RCT are likely to need to possess similar breakthrough effects in laboratory studies.

Peter Safar and Resuscitative Hypothermia: Recent Investigation

Peter Safar also carried out a considerable body of work in the last 20 years to support the use of hypothermia on three additional fronts that are relevant to readership of *TraumaCare*. First, he worked closely with trauma surgeon and critical care physician Samuel Tisherman on the use of mild hypothermia to prolong the "golden hour" of shock. That work is in a highly controversial area because retrospective clinical studies associate exposure/secondary hypothermia with increased mortality rate. However, the studies of Safar and Tisherman in this area represent a substantial series of experiments in rodent and pig models of hemorrhagic shock, demonstrating that mild or moderate hypothermia can delay the time to exsanguination cardiopulmonary arrest in this condition.[20-25] Second, he developed, after discussions with Colonel Ronald Bellamy of the United States Army, a novel approach to the resuscitation of victims of exsanguination cardiopulmonary arrest. He proposed inducing a brief (several-hour) state of suspended animation using an aortic flush of a cold preservative solution that could buy time for transport and surgical repair, which could be followed by delayed resuscitation using cardiopulmonary bypass.[26-29] We at the Safar Center have been fortunate to participate in this landmark project, which, to date, has been able to successfully achieve good outcome in dogs after an exsanguination cardiopulmonary arrest of 2 hours' duration using profound hypothermia (10°C).[30] It will be interesting to see over the years that follow if clinical trials are carried out in either of these two extremely novel areas of research.

Finally, Peter Safar and co-workers also carried out some of the only contemporary work on the application of therapeutic hypothermia to the treatment of traumatic brain injury using large-animal models. Despite the considerable number of studies in contemporary models of experimental traumatic brain injury in rodents, few studies supported its use in large-animal models, with clinically relevant long-term outcome, ICU care, and intracranial pressure (ICP) monitoring and control. Peter's group published two such papers on the efficacy of moderate hypothermia in a canine model of epidural hematoma.[31,32] He believed that it was essential to test resuscitation-related therapies in large-animal models that mimicked the clinical condition as closely as possible.[33]

Some of Peter Safar's final experimental work demonstrated the incredible vision that he possessed, the value that he placed on translational studies, and his obsession that one cannot be satisfied until a therapy is optimized—and used. With the acceptance of mild hypothermia as a therapy after successful restoration of spontaneous circulation (ROSC), Peter questioned why we were waiting to apply this therapy "after" ROSC. Indeed, applied during advanced cardiac life support in a model of prolonged experimental VF in dogs, Nozari et al[34] demonstrated that mild hypothermia was dramatically beneficial to both cerebral and myocardial outcome. Mild hypothermia applied during resuscitation, in a preservative rather than resuscitative manner, is a therapy that deserves to be tested in clinical trials.

Peter Safar was also interested in understanding the mechanism(s) underlying the beneficial effects of therapeutic hypothermia in protection, preservation, and resuscitation. Some of his last work was done in collaboration with Drs. Larry Jenkins and Mandeep Chadha on the use of proteomics to determine if profound hypothermia was preventing proteolysis during prolonged ischemia.[35] However, it was the study of the effect of therapies on outcome in clinically relevant experimental models that Dr. Safar believed was the most important.

Peter Safar's Overall Vision on the Potential of Therapeutic Hypothermia

Peter's vision on hypothermia in resuscitation was that it was the most effective agent that was currently available in resuscitation medicine—and that it had important potential applications in at least 10 different disease processes, including 1) VF, asphyxial, and exsanguination cardiopulmonary arrest; 2) traumatic brain injury; 3) stroke; 4) acute myocardial infarction; 5) elective surgical procedures; 6) refractory status epilepticus; 7) septic shock; 8) spinal cord injury; 9) hemorrhagic shock; and 10) possibly even septic shock. He also believed that rigorous temperature control with prevention of fever in neurointensive care was logical and should be implemented. He believed that clinical feasibility and safety studies should be performed in each of these settings, followed by clinical application.

Conclusions

In 2003, Drs. Kochanek and Safar wrote an editorial on the use of therapeutic hypothermia in traumatic brain injury that was published in the *Journal of the American Medical Association*.[36] Although other articles with Dr. Safar as co-author will continue to appear over time in the literature, since many works that he sparked are still in progress, that article represents the final paper that Peter Safar worked on before his death. The need to titrate, optimize, and better understand the mechanistic effects of hypothermia while we use it to improve outcome in our patients resonates from his final work.

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The Physiology of Mammalian Temperature Homeostasis

Dennis Grahn, PhD, and H. Craig Heller, PhD
Department of Biological Sciences
Stanford University
Stanford, CA 94305 USA
dagrahn@stanford.edu

Learning Objectives: 1) to describe the unique features of mammalian thermoregulation, 2) to emphasize the importance of behavior and passive heat transfer as thermoregulatory mechanisms, and 3) to propose a noninvasive alternative to general surface temperature manipulation as a means for effective treatment of heat- and cold-stressed individuals.

Abstract

The thermoregulatory system of mammalians is such that minimal energy expenditure is required to maintain a relatively stable internal thermal condition, despite large variations in environmental conditions and internal heat generation. Primary heat exchange occurs through specialized heat exchange-vascular structures that underlie the noninsulated body surfaces. In humans, these heat exchange-vascular structures are found exclusively underlying the palms of the hands, soles of the feet, the ears, and the hairless skin surfaces of the face. The treatment of hypo- and hyperthermia requires effective delivery of a thermal load to the body core. Heat may be delivered directly to the thermal core in a noninvasive manner via the heat exchange-vascular structures. To effectively utilize these structures, it is necessary to control blood flow through them. Future studies will focus on utilization of a combined application of subatmospheric pressure and an appropriate thermal load directly to the heat exchange surfaces of the hands and feet to treat heat- and cold-related maladies.

Mammalian temperature regulation has been the subject of scientific investigation since the advent of thermometers that could be inserted into an orifice of the body. Thousands of research articles, review articles, and book chapters have been written on the subject. A substantial portion of the *Handbook of Physiology: Section 4: Environmental Physiology*[1] deals with temperature regulation and is a comprehensive reference resource. Several more condensed,

Patents have been issued for the technology disclosed in this manuscript [D. Grahn and H.C. Heller (Inventors); Stanford University (Assignee)], and Stanford University has entered into licensing agreements with AVAcore technologies, Inc., and Dynatherm Medical, Inc., for the commercialization of the technology. Included in the license is a royalty agreement that grants Stanford University a percentage of the net sales of the technology, which will be shared by the University and the inventors. D. Grahn and H.C. Heller are founders of AVAcore Technologies but receive no ongoing compensation from the company.