ments) to clinical practice. The decrease in tissue/organ water content and increased diuresis with hypertonic saline are not new information and are somewhat expected in light of the fluid shifts that occur following hypertonic saline resuscitation.

Also, the use of hypertonic saline to increase serum osmolality and decrease brain swelling is not new information. The novelty of the present study is related to the level of osmolality (>350 mOsm/L) proposed by the authors as safe and "clinically" sound. Interestingly, they stated that their resuscitation strategy is safe although this was not a safety study, and they have not provided histologic or any other measure of brain function, perfusion, or intracranial pressure to document safety.

Studies in larger animals providing data on brain function, perfusion, and intracranial pressure are necessary to demonstrate safety of the proposed strategy.

Although the data presented by Dr. Toung and colleagues (21) are provocative, more evidence is needed to support a resuscitation strategy that has serum osmolality >350 mOsm/L as a target.

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To cool or not to cool, that is the question*

To be or not to be, that is the question." Perhaps the most famous soliloquy in literature, these words reflect the state of desperation in which Hamlet, the Prince of Denmark, finds himself as he contemplates suicide. Any trauma surgeon who has lost a patient on the operating table despite his best efforts, especially when the underlying injury was fixable, can appreciate desperation. How many times have we said, "All I needed were a few more minutes . . . .Could I have done something different to save this patient's life?"

Desperate situations demand radical solutions. And behind every drastic change in medicine you can find a visionary who had not only the conviction to stand up to the establishment but also the scientific acumen to actually prove his ideas. Peter Safar was indeed such a visionary (1), who along with numerous other contributions to critical care medicine gave us the concept of therapeutic hypothermia. In this issue of the *Critical Care Medicine*, Dr. Drabek and colleagues (2) from the Safar Center for Resuscitation Research have conducted another well-designed experiment that establishes the feasibility of using hypothermic arrest and cardiopulmonary bypass (CPB) resuscitation in rats subjected to lethal

***See also p. 532.**

Key Words: induced hypothermia; hypothermia secondary to shock; cardiac arrest

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hemorrhage. As this approach has previously been used successfully in large animals (3), the findings presented here are clearly not novel. But the investigators must be congratulated for designing a small animal model that decreases the cost and complexity of the experimentation and opens up this area of investigation to labs that may not possess the capacity to perform large animal studies. Furthermore, this study makes it feasible to determine the impact of temperature modulation on key cellular/molecular mechanisms that are difficult to study in swine (due to lack of appropriate molecular biology tools).

Up to 80% of trauma deaths occur in the early posttraumatic phase (4), with exsanguination as the dominant etiology (5). Profound shock from blood loss does not respond well to conventional methods of resuscitation (6). Even when the underlying cause can be treated and circulation restored, cerebral ischemia lasting ≥5 mins invariably results in severe brain damage. Often the underlying injuries are reparable but the patient dies of irreversible shock or severe brain damage. In this setting, strategies to maintain cerebral and cardiac viability long enough to gain control of hemorrhage and restore intravascular volume could be lifesaving. This requires an entirely new approach to the problem, with emphasis on rapid total body preservation, repair of injuries during metabolic arrest, and controlled resuscitation: emergency preservation and resuscitation (EPR). Currently, hypothermia is the most effective method for preserving cellular viability during prolonged periods of ischemia. Although no clinical studies have been conducted to test the therapeutic benefits of hypothermia in trauma patients, numerous well-designed preclinical studies clearly support this concept. It should be emphasized up front that *induced hypothermia* and *hypothermia secondary to shock* are very different entities. Induced hypothermia is therapeutic in nature, whereas hypothermia, seen in severely traumatized patients, is a sign of tissue ischemia and failure of homeostatic mechanisms to maintain normal body temperature. It is clear from the literature that rapid induction of deep/profound hypothermia (<15°C) can improve otherwise dismal outcome after exsanguinating cardiac arrest (7–9). Depending on the degree of hypothermia, good outcomes have been achieved with cardiac arrests of 15, 20, 30, and even 90 mins in canine models (10, 11). Furthermore, the period of hypothermia can be safely extended to 180 mins if blood is replaced with organ preservation fluids and low-flow cardiopulmonary bypass is continued (as opposed to no-flow) during the arrest period (12).

Although groundbreaking, the clinical relevance of these original studies was somewhat limited by reliance on pressure-controlled models of hemorrhagic shock (or no hemorrhage), an absence of major injuries, and lack of surgical interventions. To fill these gaps, our group has used clinically realistic large animal models of lethal vascular injuries and soft tissue trauma to demonstrate that profound hypothermia can be induced through an emergency thoracotomy approach for total body protection, with excellent long-term survival and no neurologic damage or significant organ dysfunction (13). In a follow-up study, it was established that lethal vascular injuries, above and below the diaphragm, can be repaired under hypothermic arrest with >75% long-term survival (14). More important, it was shown that hypothermia could be used successfully even after 60 mins of normothermic shock (transport time) and that the surviving animals not only were neurologically intact but also had normal cognitive functions. Subsequent studies have determined that to achieve the best results, profound hypothermia must be induced rapidly (2°C/min) and reversed at a slower rate (0.5°C/min) (15, 16). Induction of hypothermia has been shown to preserve various cell types in the central nervous system, while providing some immunologic advantages (17, 18). The optimal depth of hypothermia is 10°C, and decreasing the temperature to ultraprofound levels (5°C) may actually worsen the outcome (19). Technically it is now feasible to induce hypothermia using small, battery-operated, portable equipment (suitable for austere settings and prehospital environment) (20). This is associated with excellent "total body preservation," which may have significant implications not only for treatment of traumatic injuries but also for preserving organs for transplant (21). There are also some data from small animal models to suggest that similar metabolic arrest (and tissue preservation) can be achieved with other methods, such as inhaled hydrogen sulfide (22).

It may sound futuristic, but the expertise to preserve the viability of key organs during repair of otherwise lethal injuries is now available. What is needed now is not yet another well-designed animal experiment but rather a clinical trial that can save lives by translating these findings into trauma practice. Desperate situations demand radical solutions, but more than anything else they require bold leadership. Are we up to the challenge?

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Low-dose perfluorocarbon: A revival for partial liquid ventilation?*

In April 2006, Kacmarek et al. (1) reported in the *American Journal of Respiratory and Critical Care Medicine* the results of a phase III trial assessing the safety/efficacy of partial liquid ventilation using perfluorocarbon (PFC) in the acute respiratory distress syndrome (ARDS) (1). This report was long awaited, since the trial had ended >5 yrs before. Obviously, such a delay fueled the worries that this "negative" trial, sponsored by a pharmaceutical company, might never be published. At last, it was submitted and accepted for publication. But, unfortunately, the somewhat futuristic novel treatment did not appear to be superior to conventional ventilation. Actually, it did even worse, with less ventilator-free days, more adverse effects, and a trend toward higher mortality. This was the end of a dream—liquid ventilation (remember the movie *Abyss*?)—nurtured by a succession of highly sophisticated animal experiments and promising phase II trials. But, ultimately, what went wrong?

Dr. Ricard and colleagues (2), in this issue of *Critical Care Medicine*, give us a clue that could revive the entire story, hopefully in a much safer way. They convincingly demonstrate in an animal model of ventilator-induced lung injury (VILI) that a low dose of PFC, 3 mL/kg, much lower than the dosages used in the human trial (10 and 20 mL/kg), could actually be beneficial.

This study concludes a series of experiments from the same laboratory that dissected the multiple components of the interaction of PFC with alveolar lining, respiratory mechanics, and gas exchange. In their first report, published back in 1999, Dreyfuss et al. (3) showed in rats with VILI that PFC instillation was able to reduce the amount of edema (lung weight), to oppose the alveolar permeability increase (albumin space) and to restore respiratory pressure-volume curves. The unique dose of PFC that they initially tested was a low one, 3 mL/kg. Then, in their next article, Ricard et al. (4) assessed in rats with normal lungs the effects of different dosages of PFC (from 3 to 20 mL/kg), with 0 and 5 positive end-expiratory pressure. They demonstrated that the higher dosage of PFC actually aggravated the capillary leak, which, conversely, decreased with the lower dose. Respiratory mechanics were also markedly altered, with end-inspiratory pressure reaching 60 cm H_2O when 20 mL/kg PFC was instilled. Tomodensitometry imaging, in five additional rats, revealed that the deterioration of respiratory mechanics was accompanied by massive gas trapping. In their latest experiment (this issue), Dr. Ricard et al. (2) used this time a model of VILI and confirmed that alpha-naphtylthiourea and hyperventilation had a synergistic deleterious action and that, once again, low-dose PFC reversed ventilator-induced permeability alteration and decreased plateau pressure. They hypothesized that low doses of PFC homogenized the ventilation distribution, thus suppressing pockets of local overdistension, the probable cause of aggravation of VILI. In this respect, the linear relationship that this article shows between end-inspiratory plateau pressure and albumin space is especially compelling.

Now, what does it tell us about the previous clinical trials?

In addition to the specific complications (acute episodes of hypoxia, hypotension, cardiac arrests) linked to the filling of the tracheobronchial tree by PFC, which should be lessened by a diminution of the dosing, the two main published trials (1, 5) have been jeopardized by an abnormally high occurrence of barotrauma: 34% pneumothoraces in the phase II trial (20% in the control group) and 29% and 28% in the phase III trial (control, 9%). We do not know whether this high rate of barotrauma is statistically linked to mortality, since it was not explored in the trial by Kacmarek et al (1). But it is a notoriously bad event in the course of ARDS. Moreover, the data provided by Dr. Ricard and colleagues (2) suggest that PFC instillation may have aggravated the preexisting alveolar permeability alteration. From the beginning, several authors, particularly pediatricians, warned that partial liquid ventilation could generate a "baby lung" effect, due to the migration of an incompressible liquid in the dependent lung (6) and the resulting overdistension of the nondependent zones (7). But there was at that time an unsolved dilemma between using high doses of PFC, yielding great Pa_{O_2}s at the expense of lung compliance, and using low ones, much better for the respiratory mechanics but deleterious to gas exchange (8). This explains the design of the Kacmarek trial, with two

*See also p. 561.

Key Words: acute respiratory distress syndrome; partial liquid ventilation; ventilator-induced lung injury; perflubron; barotrauma

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