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13. ABSTRACT (Maximum 200 Words)

We have been working since the 1980s, for the past 5 yrs under DOD support, on novel ways to resuscitate "unresuscitable" trauma victims. We focus on combat casualties who exsanguinate internally resulting within a few min in cardiac arrest (CA). We have conceived and documented the concept of "suspended animation (SA) for delayed resuscitation" using a hypothermic saline flush into the aorta after rapid (over 5 min) exsanguination (Ex) CA, using novel clinically relevant outcome models in dogs. With the use of saline flush we have achieved complete recovery after ExCA of up to 120 min at 7-10°C. This is the report on yr 6. In yr 6, we carried out studies to determine if SA could be effective in the setting of ExCA preceded by a prolonged period (1.5-2.5 h) of hemorrhagic shock. This scenario mimics the important situation where a casualty may be pinned down for a prolonged period of time prior to the arrival of either the medic or transport to a field hospital. To this end, we applied SA for 1 h after prolonged hemorrhage –which we produced for durations between 1.5 and 2.5 h. Prior to the induction of SA, the dogs were moribund with a marked metabolic acidosis. Nevertheless, SA was successful in achieving intact neurological outcome in this setting when it was followed by a 48 h period of mild hypothermia. This further supports the potential feasibility of SA in military and civilian ExCA. In Yr 6, we also developed a full rat model of SA that included resuscitation using miniaturized cardiopulmonary bypass. With this new rat model, we began investigation of the effect of reperfusion on the rat brain proteome after a 30 min period of normothermic and deep hypothermic CA. These studies will also allow us to define key secondary injury targets during prolonged SA and reperfusion and ultimately screen novel pharmacological adjuncts to hypothermia. We also advised industries for novel smart catheter insertion and cooling devices that we will need to bring SA to patients, and tested several prototypes. Finally, we published several manuscripts based on this work.

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A. ABSTRACT

NOVEL RESUSCITATION FROM LETHAL HEMORRHAGE
Suspended Animation (SA) for Delayed Resuscitation
Keywords: Hemorrhagic shock, cardiopulmonary arrest, trauma, hypothermia, resuscitation, ischemia, proteomics, reperfusion, delayed neuronal death, combat casualty, terrorism, transport

This study concerns presently unresuscitable military and civilian trauma-induced hemorrhage to severe hemorrhagic shock (HS) and cardiac arrest (CA). We have shown that mild hypothermia (tympanic T, Tty 34°C) increases survival time and rate after HS in rats. Our suspended animation (SA) studies in dogs in years 1-5 (1998-2003) used rapid exsanguination over 5 min to CA. We documented that aortic flush with cold saline to Tty 10°C at the start of CA can preserve viability of the organism during up to 90 min CA without trauma (120 min with special preservation solutions), and 60 min CA with trauma. Fourteen drugs failed to approach the breakthrough effect of hypothermia. We reduced flush solution volume requirement by re-circulating diluted venous blood via a heat exchanger. In yr 5 (2003) we increased the preservation limit for traumatic CA from 60 min to 120 min with post-CA plasma exchange to mitigate or prevent the coagulopathy and multiple organ failure associated with trauma. For year 6 (2004), we proposed two major lines of investigation. First we proposed to explore *in dogs* with trauma, slow continuous, controlled exsanguination over prolonged periods (1.5-2.5 h) to CA, to determine if SA (60 min or longer) could still be effective in preserving the organism for transport and delayed resuscitation –even if the organism was in shock for an extended period prior to arrest. This scenario mimics the situation observed in the Mogadishu conflict (as depicted in "Black Hawk Down") to maximize preservation time for transport and repair, under special analgesia. Remarkably, we were able to achieve successful SA of 1 h in dogs with profound metabolic acidosis, and marked elevations of lactate and potassium levels in serum. The use of conventional SA followed by 48 h of mild (34°C) systemic hypothermia during ICU care resulted in survival with intact neurological outcome in most dogs in this series. The remarkable advantage of SA over conventional CPR in preservation was also convincingly shown. Second, in a parallel set of experiments, we developed a full rat model of SA that included resuscitation using miniaturized cardiopulmonary bypass. With this new rat model, we began investigation of the effect of reperfusion on the rat brain proteome (using proteomics as assessed by 1D and 2D gel electrophoresis of the rat hippocampus) after a 30 min period of normothermic and deep hypothermic CA. Our initial results with this new model suggest that there is little obvious protein degradation during SA, however, reperfusion after a normothermic 30 min ischemic insult results in obvious protein degradation. These studies will also allow us to define key secondary injury targets during prolonged SA and reperfusion and ultimately screen novel pharmacological adjuncts to hypothermia. We also advised industries for novel catheter insertion and cooling devices that we will need to bring SA to patients, and we tested several prototypes for our industrial consultants. Finally, we published a number of manuscripts and chapters and presented numerous abstracts based on this work.

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PI: Patrick Kochanek, MD

ANNUAL RESEARCH REPORT FOR USAMRMC/TATRC
September 2003 – September 2004

NOVEL RESUSCITATION FROM LETHAL HEMORRHAGE
Suspended Animation (SA) for Delayed Resuscitation
Project Year 6

INTRODUCTION

This research report for 2003/04 concerns our US Army funded research project on "Novel resuscitation from severe hemorrhage, suspended animation (SA) for delayed resuscitation" (PI: Dr. Kochanek, Co-PI: Dr. Tisherman), project yr 6 (academic yr 2003/04, FY-03). The work carried out during yr 6 involved studies in 2 separate models: Study I) SA induced in our established dog model after an exsanguination cardiac arrest (ExCA) preceded by prolonged (1.5-2.5 h) of hemorrhagic shock (HS), and study II) establishment of a rat model of SA including resuscitation using miniaturized cardiopulmonary bypass (CPB). This model will allow us to study mechanisms of secondary damage including protein and lipid degradation (using proteomics and lipidomics, respectively) and facilitate the screening of novel therapies. Overall, for these studies, a total of 41 about 1 wk-long dog experiments and 159 rat SA modeling experiments were carried out. These are described in detail below.

In this yr 6 we continued using a systematic approach, aiming for a breakthrough in resuscitation attempts for the presently considered unresuscitable condition of 2 h traumatic ExCA. In yr 1 (1998-99) we established the non-traumatic ExCA model (1,2). In yr 2 (1999-00), we explored pharmacologic adjuncts to hypothermic flush, achieving no breakthrough effect with any of 14 drugs (3). Some benefit came from the antioxidant tempol (4). In yr 3 (2000-01) we pushed profound hypothermic preservation with aortic large-volume saline flush to tympanic temperature (Tty) 5-10°C; we achieved intact survival after a CA of either 60 min or 90 min at 10°C, and inconsistently after CA 120 min (5-7). In yr 4 (2001-02) we documented a 5 min limit to flush delay, pushed the limit of SA to 120 min, and documented problems with coagulopathy when severe tissue trauma was superimposed on our standard exsanguination CA protocol and SA. In yr 4, separate studies also documented the efficacy of SA in a dog model of refractory ventricular fibrillation (VF) CA (17)—setting the stage for the use of this approach even in normovolemic CA victims with sudden cardiac death—those patients that do not respond to standard advanced cardiac life support (ACLS) protocols. In yr 5, using the dog model of ExCA, we built upon the strong foundation of work and carried out 2 important studies. Using re-circulation of the initial flush, we were able to reduce the flush volume from ~400 mL/kg to 50 mL/kg (14). We also successfully tackled the critical challenge of designing an approach that allowed SA to be successfully applied to a 2-h CA with superimposed severe trauma in dogs. We used a contemporary therapy—plasma exchange—to control coagulopathy and facilitate intact survival after 120 min of exsanguination CA with superimposed severe trauma (laparotomy, splenectomy, and thoracotomy) (15). In yr 5, we also began an important additional line of investigation using a rat model of decapitation ischemia–and applying a state-of-the-art proteomic analysis (12,13,18). These studies were designed to define the cascade of global protein degradation that occurs despite profound cooling. Knowing the proteins that are

injured during SA will help us define the limits of resuscitability—possibly aiding in the titration of hypothermia (depth, duration), and uncovering the best adjuncts to SA. These studies were carried out under the direct supervision of Larry Jenkins, PhD at the Safar Center.

Germane to work in yr 6, it is recognized that conventional resuscitation after ExCA is often unsuccessful, particularly when prolonged HS produces the arrest. Previously, we reported the success of SA with delayed resuscitation in ExCA. SA of up to 2 h was induced via rapid aortic flush with ice-cold (2°C) saline followed by delayed resuscitation via CPB. This would buy time for transport and/or surgical repair. In the past, we used SA to achieve intact survival of dogs after rapid hemorrhage (over 5 min) to ExCA. We hypothesized that SA would allow survival with good neurological outcome in the setting of prolonged hemorrhage prior to ExCA. Dogs underwent spleen transection and controlled, continuous bleeding until CA. Two min after CA, dogs were randomized into 3 groups (n=7 each): 1) the CPR group resuscitated with conventional CPR and rapid infusion of blood and LR; 2) SA-I, or 3) SA-II Groups, both of which received 20 L of 2°C saline flushed into the aorta. CPR or SA lasted 60 min, and was followed by 2h of CPB and splenectomy. CPR dogs were maintained at 38°C, while SA dogs were controlled at 34°C for either 12h with standard rewarming (SA-I) or 36 h with slow rewarming (SA-II). Outcome was evaluated with Neurological Deficit Scores (NDS) (0%=normal, 100%=brain death) and Overall Performance Category (OPC) (1=normal, 5=death). CA occurred after 124±16 min of hemorrhage. Arterial pH, lactate, and K^+ were remarkably abnormal, and did not differ between groups. In the CPR group, spontaneous circulation could not be restored without CPB; none achieved long-term survival (range: 11.5-16.5 h). In contrast, 12 of 14 SA dogs survived ($p<0.01$ vs the CPR group). The SA-II Group had better NDS than SA-I (1.5 [0-89%] vs 42 [10-92%)], $p=0.04$) and a trend toward better OPC (5 vs 1 dog recovered to normal, $p=0.06$). **Based on this work, we concluded that SA facilitated survival with good neurological outcome in a model of otherwise unresuscitable prolonged hemorrhage with ExCA.** Surprisingly, extending the duration of mild hypothermia followed by slow rewarming after SA was critical to achieving intact neurologic outcome.

Near the end of yr 6, we also began pilot experiments to set the stage for our proposed studies in yr 7, which will tackle the difficult challenge of extending the duration of SA beyond the 2 h barrier. Most promising appears to be the addition of energy substrates such as oxygen and glucose to the flush solution. Approximately 10 successful pilots were carried out that helped define the definitive study of this approach for yr 7.

Also during yr 6, we carried out two series of studies (IIa and IIb) to begin to define mechanism of secondary damage during normothermic and profound hypothermic circulatory arrest (as used in SA). Based on the wealth of molecular agents available in rats (vs dogs), we chose to carry out these mechanistic studies in rats–specifically focusing on global protein degradation (degradomics) in rat brain (hippocampus). Initial work in this area used a decapitation model of complete global brain ischemia (GBI). After decapitation, we isolated the hippocampi, and studied paired hippocampi maintained at target temperature (either 37°C or 10°C—mimicking the temperatures used for either a normothermic insult or SA) for 30 min. Remarkably, during 30 min of ischemia at either normothermia or 10°C, assessment of protein degradation using proteomics (2D gel electrophoresis) revealed minimal degradation (12,13,18). Several possible explanations for these findings included, 1) that reperfusion was critical to the development of

protein degradation, 2) that 2D proteomic approaches were not sensitive enough to detect changes in important low copy proteins, or 3) that other targets, such as damage to lipids, DNA, or RNA were more critical to secondary injury after SA. To begin to answer these important questions, we felt it was necessary to develop a complete SA model in the rat—including delayed resuscitation. To achieve delayed resuscitation after these long ischemic times, it was necessary to use a CPB system for use in the rat. We adapted an established miniaturized CPB system for rats that was used by our consultant (David Warner, MD) at Duke University and we successfully established a complete rat model of SA. We have now been able to achieve survival with intact functional outcome in rats after 30 min of SA at 10°C (20). Current studies are optimizing this model and formally evaluating histopathology.

During yr 6 we had 7 publications from work on the SA project, building on a remarkable body of publications from this program (1-23). Fellows working on this project also presented 10 abstracts of this work during yr 6 (abstracts 13-22). Dr. Kochanek, with the research team, also published a chapter in a specific textbook on hypothermia that was presented at an international symposium on hypothermia that was held in Tokyo, Japan (19). Dr. Tisherman was also the lead editor of a textbook on "Therapeutic Hypothermia" (see bibliography).

BODY OF REPORT (yr 6)

Study I) Is SA effective after a prolonged period of HS resulting in ExCA in dogs?

Conventional resuscitation is often unsuccessful after ExCA, particularly when prolonged HS produces the arrest. Previously, we reported the success of SA with delayed resuscitation in ExCA. SA of up to 2 h was induced via rapid aortic flush with ice-cold saline followed by delayed resuscitation via CPB. This would buy time for transport and surgical repair. In the past, we used SA to achieve intact survival of dogs after rapid hemorrhage (over 5 min) to ExCA. The success of SA relies on timely initiation of preservation during CA. It is speculated that different durations of HS before CA may affect efficacy of SA. Rapid Ex does not cause severe tissue acidosis over 5 min while longer duration of HS may exhaust compensatory reserve and build up extremely severe tissue acidosis and tissue injury. Although the CNS is generally damaged minimally during HS, superimposing a transient normothermic CA and a prolonged profound hypothermic CA, i.e. SA, upon prolonged HS may importantly complicate the ability to preserve and resuscitation. **Thus we designed a clinically model particularly relevant to military and civilian trauma that is characterized by a controlled continuous bleeding, trauma (laparotomy and spleen transaction), limited fluid resuscitation, and resultant CA. Allowing volume depletion and circulatory decompensation to finally cause CA was intended to create a setting that is non-salvageable with conventional CPR.**

The dog model (Fig 1) included 3 phases: 1) HS and CA phase: bleeding was continuous until CA; 2) CPR/SA phase: 2 min after CA, dogs were resuscitated with either conventional CPR or SA; and 3) delayed resuscitation phase, including 2 h CPB, and up to 72-96 h intensive care. Dogs were assigned to 1 of 3 groups 2 min after CA: 1) the CPR group was resuscitated with conventional CPR; 2) the SA-I group was resuscitated with arterial flush of 20 L ice-cold saline, followed by delayed resuscitation with CPB, 12 h of post-ischemia mild hypothermia, and was sacrificed at 72 h; and 3) the SA-II group was identical to the SA-I group except that 1) the duration of post-ischemic hypothermia was 36 h, 2) mild hypothermia was reversed by slower rewarming, and 3) these dogs were sacrificed at 96 h.

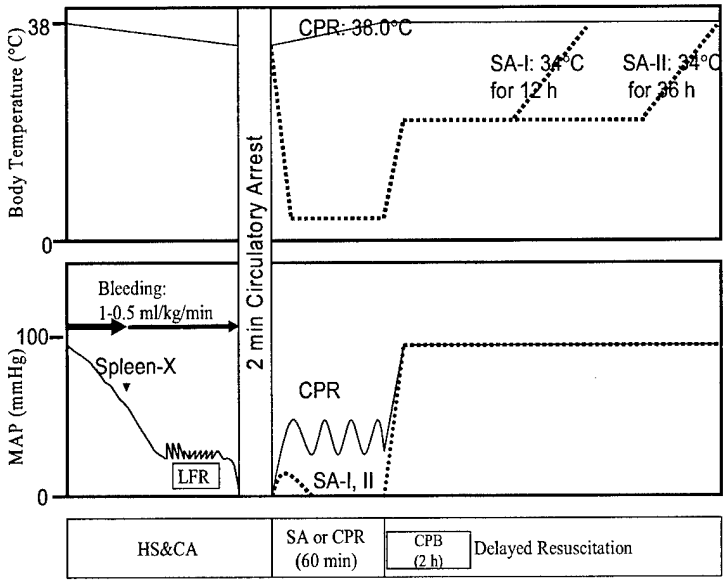


Figure 1. Experimental protocol for testing the efficacy of SA after prolonged HS in dogs. SA-I = conventional SA; SA-II = conventional SA followed by 48 h of mild hypothermia during ICU care.

At HS 0 min, venous blood was withdrawn via the right femoral vein catheter at a rate of 1 ml/kg/min over 40 min. Out-going blood was spiked with 0.125 ml/kg/min citrate delivered via a PE 60 catheter that ran inside the femoral vein catheter lumen. From HS 40 min, blood withdrawal rate was set at 0.5 ml/kg/min. At HS 40 min, the spleen was transected. When MAP was lower than 30 mmHg, limited fluid resuscitation was started with infusion of 100 ml of LR over 2 min. The maximum amount of LR was 500 ml. ExCA was defined as: 1) MAP <10 mmHg, and severe bradycardia (<20 bpm) or, 2) asystole or VF confirmed by EKG and arterial blood pressure tracing.

The original design included only the CPR and SA-I Groups. The SA-II Group was added into the study for randomization after 10 dogs in the CPR and SA-I Groups were completed. Two min after CA, dogs were randomized into the CPR or SA Groups. In the CPR Group, the conventional ACLS was started. Briefly, chest compression with a thumper was started at 60 beats per min, and the compressing distance was adjusted in an attempt to generate a systolic blood pressure of 100 mmHg. Ventilation with 100% O_2 was provided at 12 breaths per min, and the airway pressure was set at 40 cm H_2O. Epinephrine 0.01 mg/kg was given every 5 min (maximum 5 times). After epinephrine administration, defibrillation with 150 J was given when EKG showed VF; increment of 50 J was given after 2 unsuccessful defibrillations. Sodium bicarbonate and $CaCl_2$ were given if BE<-6 mmoml/L and

Table 1. Physiological parameters during CA preceded by prolonged HS

	CPR Group	SA-I Group	SA-II Group
Hemorrhage Time (min)	124.4±10.5	118.4±19.7	126.4±19.8
pH	6.88±0.24	6.99±0.16	6.93±0.12
PCO_2 (mmHg)	86±39	58±30	73±28
PO_2 (mmHg)	58±8	85±31	79±24
BE (mmol/L)	-16.6±2	-16.4±1.3	-15.5±1.8
K+ (mmol/L)	7.6±1.2	6.8±1.3	7.3±0.9
Glucose (mg/dl)	449±150	563±110	522±207
Lactate (mmol/L)	15.1±1.6	14.6±2.8	14.1±2.3
BUN (mg/dl)	23.4±6.1	27.6±6.5	25.6±8.1
Hematocrit (%)	16.2±2.2	18.1±2.3	19.6±1.8

Ca^{2+} <1 mmol/L. At CPR 0 min, LR 1 L was infused over 10 min, and shed blood 30 ml/kg was given over 5 min. Additional LR (250 ml/15 min for 3 times) was given afterwards. In the SA Groups, aortic flush of 20 L of 2°C saline via CPB cannula was initiated at a rate of 1.6 L/min via a roller pump (Ardiem, Indiana, PA). The dog was then covered with ice after the flush.

Sixty min after the onset of aortic flush or CPR, CPB was started. At RT 0 min, splenectomy was performed. The abdominal wounds were closed in 3 layers. The temperature in the CPR Group was kept at 38°C, while it was rewarmed to 34°C in about 1 h in the SA Groups. Defibrillation was attempted when splenectomy was completed in the CPR Group and the core temperature reached 32°C in the SA Groups. ICU care was provided for 24 h in the CPR and SA-I Groups, and for 48 h in the SA-II Group. In the CPR Group, the body temperature was kept at 37.5-38.5°C. In the SA-I Group, the body temperature was kept at 34°C until RT 12 h, which was followed by standard rewarming (1°C/h) to 37.5°C. In the SA-II Group, mild systemic hypothermia (34°C) was maintained for 36 h, followed by a slower rewarming (0.3°C/h) to 37°C than in the SA-I Group. Outcome was evaluated according to OPC. Neurologic function was evaluated as NDS. In selected dogs, paraformaldehyde fixed brain sections were stained with H&E or Fluoro-Jade B and analyzed by a neuropathologist blinded to treatment.

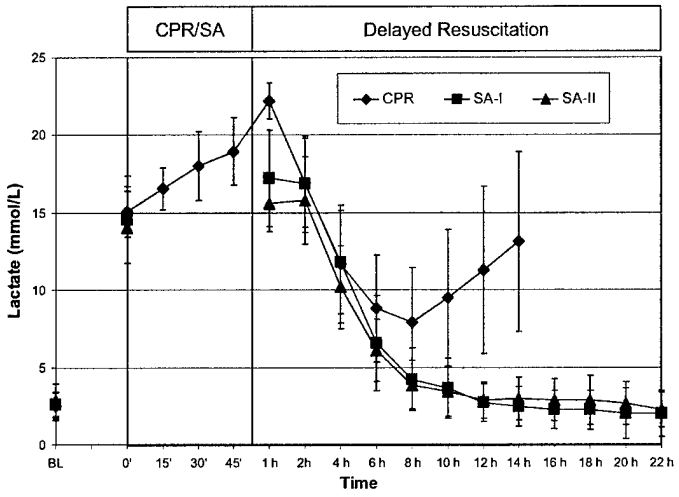


Figure 2. Blood lactate levels after ExCA preceded by prolonged HS. Blood lactate was markedly elevated in all 3 groups at the time of arrest, but recovered in the SA group. In contrast, lactate never completely recovered after conventional CPR and there was a secondary rise that accompanied the development of multiple organ failure and death in the CPR group.

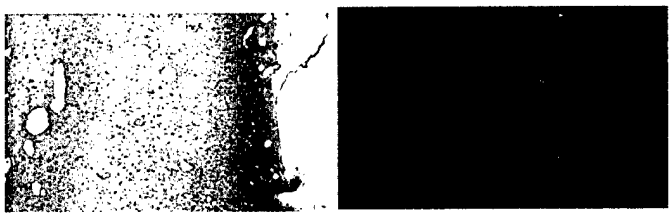
The averages of hemorrhage time before CA were 124±16 min in all groups, and there was no difference between groups (Table 1). Arterial pH, PCO_2, PO_2, BE, K^+, lactate, and glucose values at 1 min after CA were markedly abnormal, but similar in 3 groups (Table 1).

During chest compression, MAP was kept >50-60 mmHg over 1 h. However, return of spontaneous circulation was not achieved by CPR/ACLS in any dog in spite of vigorous resuscitation efforts with chest compression, ventilation, medications (epinephrine, calcium chloride, bicarbonate), fluid, blood, and defibrillation.

Return of spontaneous circulation was achieved in all dogs 15±16 min after initiation of CPB with 157±181 J defibrillation. However, substantial fluid losses developed during recovery phase from the rectum, orogastric tube, and abdominal drainage catheter (all $p<0.01$ vs the SA Groups)

and multiple organ failure ensued. The lactate levels decreased transiently, but increased sharply again until death ($p<0.01$, vs the SA Groups) (Fig 2).

At the end of aortic flush with 20 L of ice-cold saline, Tty was decreased to similar levels in both SA Groups. It remained almost unchanged during preservation. Dogs were rewarmed to 34°C within 1 h by CPB. When the core temperature reached 32°C, defibrillation successfully restored circulation in all dogs at 30±12min in the SA-I Group, and 32±23 min in the SA-II Group (NS).



A: Frontal lobe, H&E B: Cerebellum, Fluoro-Jade B

Figure 3. Brain histology in SA-1. See text for details.

Preliminary Brain Histology: In 2 SA-I dogs that developed generalized seizures after 48 h, extensive laminar necrosis was seen in the cortex (Fig 3A) and synaptic damage was seen throughout the cerebellum (Fig 3B). A complete histopathological analysis of 19 brain regions in each dog is ongoing.

Outcome: All CPR dogs died with a median survival time of 14.7 h (range 11.5-16.5h) ($p<0.01$, vs the SA Groups). In contrast, all SA-I dogs survived to 72 h except 1 that died at RT 29.5 h ($p<0.01$ vs the CPR Group). Similarly, in the SA-II Group, 6/7 survived to 96 h ($p<0.01$, vs the CPR Group). Of all survivors, 2 SA-I dogs developed generalized seizures 48 h after extubation. One had seizures shortly after weaning of sedation at RT 24 h. At 72 h, there was only one dog that recovered to normal. In contrast, none of SA-II survivors exhibited seizures and 5 of 6 recovered to normal at 96 h ($p=0.06$, vs the SA-I Group) (Table 3). **The final NDS at the 96 h in the SA-II Group was significantly better than that in the SA-I Group at RT 72 h ($p=0.04$).**

In this study we established an ExCA model that is unsalvageable using contemporary conventional resuscitation. At the time of CA, ~60-90% of the blood volume was removed. Arterial blood gases taken at the beginning of CA showed severe acidosis ($pH<7.0$), hyperkalemia, and hyperlactemia. As expected, none could be resuscitated despite an aggressive contemporary resuscitation. Although all of the dogs could be resuscitated with CPB, all subsequently died of severe multiple organ failure, including renal failure, extensive gastrointestinal mucosa necrosis and sloughing, and cardiovascular dysfunction. This pattern is what was anticipated in the setting of conventional resuscitation after prolonged HS and CA. In contrast, SA with delayed resuscitation significantly improved survival. Twelve of 14 dogs survived without apparent extra-cerebral organ injuries. However, dogs in the SA-I Group had severe neurological injuries. Three dogs had generalized seizures after weaning from mechanical ventilation and sedation. Initially, two of them regained consciousness but became comatose following episodes of seizures that occurred after 48 h. This is a unique pattern that we had not

previously encountered in the long history of investigation of rapid ExCA models. Extensive laminar necrosis was found in the cortexes, and synaptic injuries were found in the cerebellum. This is very different from the histopathology observed after rapid ExCA in which almost no brain damage was seen after 60 min of SA. The SA and delayed resuscitation protocols were almost identical between these two studies. Apparently, the pre-existing prolonged HS substantially decreased the efficacy of SA.

Table 2. Survival Rates and OPC in Survivors of SA preceded by prolonged HS

	CPR N=7	SA-I N=7	SA-II N=7
OPC 1		•	•••••#
OPC 2		•	
OPC 3		•••	
OPC 4		•	•
OPC 5			
Death <72 h	•••••••##	•	•

#p=0.06, vs 1/6 in the SA-I Group;## p=0.001 for survival for SA-I or SA-II.

The mechanism of delayed neurological deterioration after prolonged HS and prolonged hypothermic CA that was seen with our standard rewarming protocol may be related to delayed cytotoxic brain edema that peaks around 48 h after reperfusion. Different from rapid ExCA, the blood glucose level at time of CA was >500 mg in most dogs. Based on a similar histological pattern coupled with previous reports of hyperglycemia-associated brain injury, it is speculated that the high blood glucose levels may contribute to the delayed neurological deterioration. Alternatively, rapid rewarming of the traumatically injured brain can markedly exacerbate injury. **Regardless of what exact mechanisms may be responsible, hypothermia has been found to be very effective in protecting against ischemic brain injuries**. Remarkably similar to our finding in profound hypothermic CA, Gunn et al (1997) documented that delayed brain edema that peaked at 48 h after 30 min cerebral ischemia in fetal lamb was abolished by prolonged (72 h) hypothermia. Shorter term (48 h) cooling was associated with rebound of epilepitiform activity. Similarly, Colbourne et al (1994) found that to salvage CA1 neurons after 5 min of ischemia in gerbils, hypothermia (32°C), induced 1 h after ischemia, needed to be maintained for 24 h rather than 12 h. **In our study, when the duration of hypothermia was extended to 36 h, followed by slow rewarming (0.3°C/h), 6 of 7 dogs regained consciousness, and seizures were not seen, even when observation was extended to 96 h.**

We were surprised by the dramatic mild effects of post-ischemic mild hypothermia in our clinically-relevant model. The success of resuscitation of CA after prolonged HS as demonstrated in this study may have important implications. First, it is suggested that the potential application of SA is not limited by the duration of pre-existing HS. This may facilitate application of a novel therapeutic approach for otherwise lethal ExCA. Second, SA may provide an effective treatment for a specific situation in modern urban wars as the one in Somalia in 1993

in which several US soldiers were wounded and pinned down for >14 h until they could be evacuated (Mabry et al., 2000). Such a prolonged uncontrolled HS poses as a new challenge to military medical care. As suggested in our study, SA is much more reliable in preserving tissue viability during CA than conventional CPR. It is plausible that SA may allow intact survival in the setting of prolonged HS. Third, the surprising benefits of prolonged post-ischemic mild hypothermia and slow rewarming may also provide neuroprotective effects after deep hypothermic CA (DHCA) as used in cardiac or neurological surgeries. This could have potential value, for example, in cases where neurologic injury is suspected after open-heart surgery. Currently, rapid rewarming is commonly practiced after DHCA. In conclusion, SA facilitated survival with good neurological outcome in a model of otherwise unresuscitable prolonged hemorrhage with ExCA. Surprisingly, extending the duration of mild hypothermia and reversing it at a slower rate after SA was critical to achieving intact neurologic outcome.

Study II) Mechanistic studies of SA in rats
(IIa) Proteomic assessment of global protein degradation (degradomics) in SA and (IIb) Development of a complete rat model of SA

(IIa) Proteomic/degradomics assessment of protein degradation in SA
In FY6, we first chose to build on our work assessing protein degradation in rat brain hippocampus after prolonged periods of complete global brain ischemia (GBI) using two dimensional (2D) gel electrophoresis without recirculation. Complete GBI without recirculation is an ideal model to evaluate homogeneous CNS changes since the ultrastructural responses vary little among different brain regions or cell types. We examined hippocampal proteomic changes after 30 min of GBI at normothermia vs hypothermia to identify any predictive patterns of protein degradation or post-translation modification. Hypothermia at 10°C is optimal in our dog SA model—and was thus selected for use in these studies. In yr 5, using large format 2D gel, we noted surprisingly minimal differences in protein degradation with comparing 30 min of GBI at either 38 or 10°C (). However, weaker solubilization buffers are required for 2D gel vs 1D gel analysis. We sought to further evaluate global protein degradation during prolonged complete GBI with and without hypothermia using more powerful solubilization buffers and 1D gel analysis. Our hypothesis was that protein degradation is minimal during prolonged normothermic or hypothermic ischemia in rat brain.

Using a decapitation complete GBI model in Sprague-Dawley rats (n=6 per group), both hippocampi were rapidly dissected and randomized to 30 min of complete ischemia at either 38 or 10°C. A third group of hippocampi (no ischemia) served as controls. Separation of proteins from hippocampal lysates by molecular weight was accomplished with medium format (16X18 cm) SDS-PAGE. Paired samples were run in triplicate on the same gel to reduce variability, stained with Sypro Ruby, imaged and quantified.

No differences in protein levels were found between either normothermic or hypothermic ischemia groups—or controls—without reperfusion (Fig 4).

We observed little degradation of the rat hippocampal proteome during prolonged normothermic or hypothermic complete ischemia without reperfusion. These data confirm (using a separate method) and extend our prior work with 2D gel analysis. In that multiple studies have shown important neuroprotection by profound hypothermia during complete GBI, we are currently

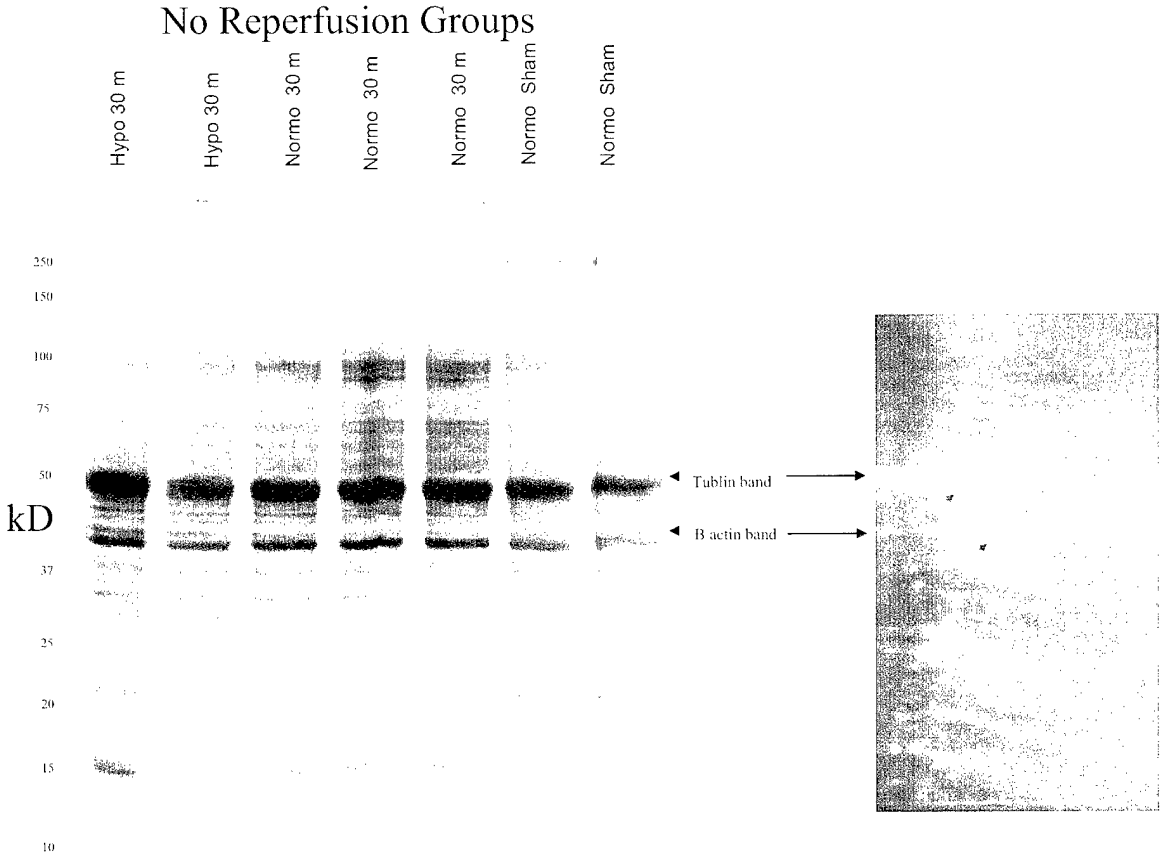


Figure 4. Protein degradation in rat hippocampus after 30 min complete GBI without reperfusion. Left panel shows 1D analysis of each group in triplicate stained with sypro ruby. Right panel shows Sypro Ruby stained 2D gel showing that each of the 1D bands represent a large number of proteins, for example in the high copy tubulin and β-Actin identified.

examining the effect of reperfusion on hippocampal protein degradation after prolonged normothemic cardiac arrest and SA using our newly established complete rat SA model (described below).

(IIb) Development of a complete rat model of SA

SA with delayed resuscitation is a novel approach that we have developed for resuscitation of ExCA victims. SA utilizes cold aortic flush to induce a state of hypothermic preservation, followed by resuscitation with CPB. In prior reports, we have used a dog model to study long-term outcome and maximize clinical relevance. However, because of the limited availability of molecular tools in dogs, development of a rat model of SA would enable further investigation of the mechanisms underlying secondary neuronal injury during SA and delayed resuscitation. We tested two hypotheses; first, that SA would be achievable in a rat model, and second, that plasmalyte would be a more favorable aortic flush solution than normal saline.

HS was induced with rapid exsanguination of 12.5 ml of blood over 5 min, followed by KCl-induced CA. After 2 min of no-flow, cooling to 10°C (target temperature) was initiated with ice-

cold flush (30 ml/min flow rate, total volume 500 ml), and topical cooling. After 30 min of DHCA, reperfusion and re-warming were achieved with a miniaturized CPB system over 60 min. In all rats, arterial blood gases, Hct, electrolytes, glucose, lactate, BUN and Osm were serially monitored. Rats were extubated 2 h later and body temperature controlled at 34°C with telemetry. Survival to 24 h was the primary outcome variable. Outcome was also assessed at 7 d using an OPC and a NDS modified for rats.

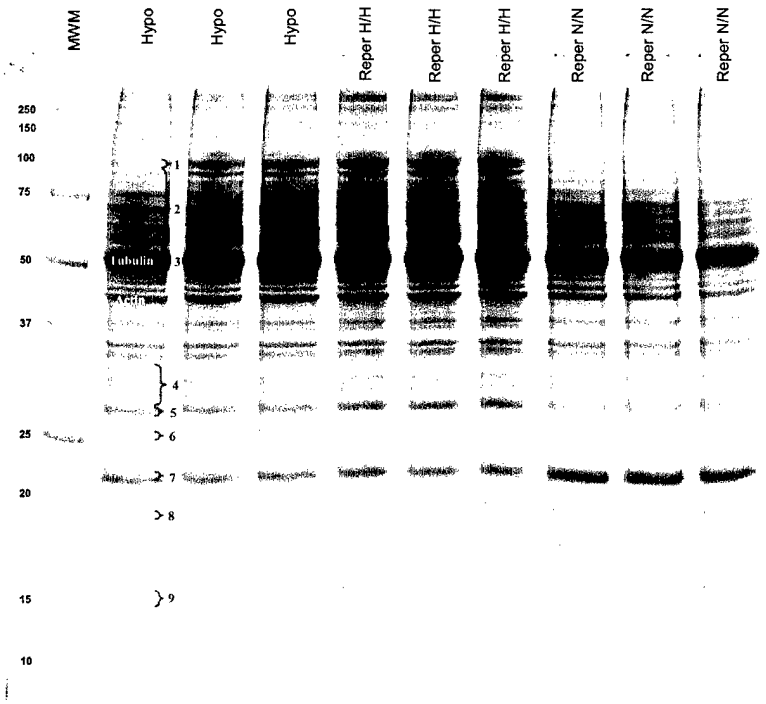


Figure 5. Preliminary data using 1D gel electrophoresis showing the effect of reperfusion on protein degradation after 30 min of normothermic CA vs 30 min of SA (at 10°C) in rat hippocampus. From left to right the vertical lanes show SA without reperfusion (Hypo, 3 lanes), SA with reperfusion (Reper H/H, 3 lanes) and normothermic CA with reperfusion (Reper N/N, 3 lanes). Reperfusion was achieved for 30 min using CPB. As seen in Fig 4, prolonged ischemia without reperfusion produced not obvious protein degradation. In contrast, reperfusion after normothermic CA resulted in obvious loss of high molecular weight proteins (in areas 1-2) and increases in lower molecular weight proteins (such as in areas 7 and 9). This suggests a critical role of reperfusion to protein degradation in SA.

Eighteen rats were used; 4 rats died from technical reasons. Flush with ice-cold normal saline or plasmalyte rapidly decreased the temperature to 10°C. 4/7 rats survived to 24 h in both normal saline and plasmalyte groups. Favorable outcome (NDS <10%) at 7 d was achieved in 2/7 rats in the normal saline and 4/7 in plasmalyte group.

We have successfully established an SA model in rats that includes 30 min of profound hypothermia and resuscitation using miniaturized CPB. To our knowledge, this is the first successful description of either SA or DHCA in a rat. The model is technically demanding but can achieve intact long-term survival. Our preliminary results suggest a favorable outcome with Plasmalyte vs normal saline as the flush solution. Successful establishment of this model of SA in rats should facilitate application of molecular tools for studying the effects of both SA and DHCA and reperfusion on mechanisms of neuronal death. Our preliminary data using this model suggest that reperfusion is critical to protein degradation in SA (Fig 5). As discussed previously in this report, this model may also serve to screen approaches to neuronal preservation in both SA and DHCA with obvious relevance to cardiac surgery and transplantation medicine.

Other accomplishments of the SA program during yr 6

Devices developments: In yr 5, we established a steering committee with Dr. Lyn Yaffe as administrative chairman, to coordinate laboratory results from this Army project, developments of methods and devices, and planning clinical trials of mild hypothermia for traumatic HS and profound hypothermic aortic flush SA for exsanguination CA. This steering committee includes the Pittsburgh team (Kochanek, et al, for SA, and Tisherman, et al, for HS), Yaffe (smart catheter project), McMurray, Ardiem (portable cooler project), and Dr. Tisherman, et al, for planning clinical trials. That steering committee continued to meet via telecom throughout the year in conference calls at a minimum of every other week, and in person with Dr. Yaffe visiting Pittsburgh about once per month. The project of Dr. Yaffe includes Dr. Klain, and as advisors, Drs. Kochanek and Tisherman, and Mr. S. W. Stezoski. These conference calls have proven invaluable to our team.

Several dog experiments were also used for testing of adjunctive methods and devices, before euthanasia, to save extra dog lives. These efforts (which are approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh) continue to lead to prototypes of aortic balloon catheters that are now being improved. Ardiem delivered its first prototype of a portable cooler to us in Sept. 2003. That cooling device was used to induce SA in each of the dog experiments performed in the prolonged HS study described above.

Miscellaneous: For clinical trials, Dr. *Tisherman* continues to communicate with 6 potentially participating major trauma hospital groups.

Xianren Wu, MD continued to serve as senior fellow on the dog SA project in 2004 under the mentorship of Drs. Kochanek and Tisherman. He has remarkable experience, particularly for a fellow, in the field of HS including work in dog, pig, and rat models. His productivity regarding publications has been exceptional.

Mandeep Chadha, MD a fellow working under the direction of Drs. Jenkins and Kochanek is using proteomics to study protein degradation and modification during complete global cerebral ischemia with profound hypothermia. Dr. Chadha is a critical care medicine fellow who is funded separately by a T-32 entitled Pediatric Neurointensive Care and Resuscitation Research from the NICHD/NIH on which Dr. Kochanek is PI and Dr. Jenkins is a trainer. This project on proteomics in SA has broad implications across the field of resuscitation and is an outstanding opportunity for fellowship training. Dr. Chadha has presented numerous abstracts of his novel work in proteomics and an initial full manuscript is in preparation.

Tomas Drabek, MD joined our group this year as the fellow in charge of development of the rat SA model. Dr. Drabek is a practicing cardiac anesthesiologist in Prague, Czech Republic, and his experience in that regard is perfect to expand the relevance of our rat SA model to the study of DHCA in cardiac surgery. He has submitted an initial abstract of the complete rat SA model to the 2004 meeting of the Society of Critical Care Medicine.

During yr 5, our group gave over 13 presentations on our work on the SA project. This included abstracts presented by Drs. Wu, Chadha, Drabek, and invited lectures by Drs. Kochanek, Tisherman, and Jenkins.

Second Annual Safar Symposium at the University of Pittsburgh School of Medicine: On October 30, 2003, the second *Annual Safar Symposium* was held at the University of Pittsburgh School of Medicine. This event was attended by ~150 clinicians and scientists. The morning session focused on "Breakthroughs in Resuscitation" and again focused on resuscitative hypothermia. The afternoon focused on the use of simulation in resuscitation research. The symposium featured prominent national and international speakers and was supported in part by this grant. The program is attached in the appendix. We again thank the US Army for supporting this symposium in honor of Dr. Safar.

Books and monographs: Dr. Tisherman was the lead editor of a textbook on hypothermia in acute medicine entitled 'Therapeutic Hypothermia." That book is in press and will be published by Kluwer. In addition, Dr. Kochanek was the lead editor of a supplement to the February 2004 issue of the journal Critical Care Medicine that was assembled as a special Festschrift in honor of Dr. Peter Safar. That supplement highlighted a number of aspects of this SA project. We are indebted to the US Army (TATRC) for supporting this publication.

KEY RESEARCH ACCOMPLISHMENTS

Accomplishments for funding yr 6

Study I: We showed that SA is still effective even when a remarkably prolonged 1.5-2.5 h period of HS precedes the CA. This has important implications for potential clinical use in the field hospital, trauma bay, or armored far-forward field hospital. This expands the potential target of casualties for which SA might be applicable.

Study IIa: Our initial studies on the application of proteomics to SA suggest that protein degradation during the hypothermic insult is minimal. This is an unexpected finding and suggests that reperfusion after the insult is likely the time of significant protein degradation providing an expanded therapeutic window to intervene and better preserve protein function with novel therapies.

Study IIb: Our group has been able to successfully develop a complete rat model of SA, including application of miniaturized CPB to resuscitate after 30 min of DHCA. To our knowledge, these are the first successful studies of DHCA in the rat. These studies should greatly facilitate the study of the effect of reperfusion after SA, and provide the ability for us to screen novel therapies.

REPORTABLE OUTCOMES

Specific reportable outcomes for yr 6 are defined in the report and identified with an asterisk (*) in the reference list—including publications and presentations.

CONCLUSIONS

Work in yr 6 of this project has continued to expand the scope of the potential application of SA for combat and civilian casualties. Specifically in yr 6, we have demonstrated that SA is still effective even when a remarkably prolonged 1.5-2.5 h period of HS precedes the CA. We also carried out parallel mechanistic studies in a rat model of decapitation global brain ischemia to identify key assess protein degradation using novel proteomics methods. Finally, in yr 6, we were able to establish a complete rat model of SA. Future studies will further refine SA in our

dog and rat models and also mild hypothermia to optimize "Emergency Hypothermia" in lethal HS while we begin to plan and implement feasibility clinical trials.

References and Appendices

This reference and appendix list includes all items generated by the SA project during years 1-6. *Denotes items generated during funding yr 6. Reprints of these specific items from yr 6 are attached in the appendix, which has been sent under separate cover, since some of these items (books, etc) are not available on PDF. Reprints from prior years are available upon request.

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For *Critical Care Medicine*
Crit Care Med
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MILD HYPOTHERMIA DURING PROLONGED CARDIOPULMONARY CEREBRAL RESUSCITATION INCREASES CONSCIOUS SURVIVAL IN DOGS

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ABSTRACT

Objective: Therapeutic hypothermia *during* cardiac arrest (CA) and *after* restoration of spontaneous circulation enables intact survival after prolonged cardiopulmonary cerebral resuscitation (CPCR). The effect of cooling *during CPCR* is not known. We hypothesized that mild to moderate hypothermia *during* CPCR would increase the rate of neurologically intact survival after prolonged CA in dogs.

Design: Randomized, controlled study using a clinically relevant CA outcome model in dogs.

Setting: University research laboratory.

Subjects: Twenty-seven custom-bred hunting dogs (19-29 kg) (3 were excluded from outcome evaluation).

Interventions: Dogs were subjected to CA no-flow of 3 min, followed by 7 min basic life support and 10 min of simulated unsuccessful advanced life support (ALS) attempts. Another 20 min of ALS continued with 4 treatments: In control group 1 (n=7) CPCR was with normothermia; in group 2 (n=6, 1 of 7 excluded), with moderate hypothermia via veno-venous extracorporeal shunt cooling to tympanic temperature (Tty) 27°C; in group 3 (n=6, 2 of 8 excluded), the same as group 2 but with mild hypothermia, i.e., Tty 34°C; and in group 4 (n=5), with normothermic veno-venous shunt. After VF 40 min, reperfusion was with cardiopulmonary bypass for 4 hours, including defibrillation to achieve spontaneous circulation. All dogs were maintained at mild hypothermia (Tty 34°C) to 12 h. Intensive care was to 96 h.

Measurements and Main Results: Overall performance categories (OPC) and neurologic deficit scores were assessed from 24 h to 96 h. Regional and total brain histologic damage scores (HDS) and extracerebral organ damage were assessed at 96 h.

In normothermic groups 1 and 4, all 12 dogs achieved spontaneous circulation but remained comatose and (except one) died within 58 h with multiple organ failure. In hypothermia groups 2 and 3, all 12 dogs survived to 96 h without gross extracerebral organ damage ($p < 0.0001$). In group 2, all but one dog achieved OPC 1 (normal); 4 of 6 dogs had no neurologic deficit and normal brain histology. In group 3, all dogs achieved good functional outcome with normal or near-normal brain histology. Myocardial damage scores were worse in the normothermic groups compared to both hypothermic groups ($p < 0.01$).

Conclusion: Mild or moderate hypothermia *during* prolonged CPCR in dogs preserves viability of extracerebral organs and improves outcome.

Key words: Cardiac arrest, resuscitation, hypothermia, extracorporeal circulation, survival, neurologic deficit, dog

INTRODUCTION

Sudden cardiac death remains the principal killer in industrialized countries.[1,2] The potential physiologic potency of standard external cardiopulmonary-cerebral resuscitation (CPCR) far exceeds the current rates of achieving conscious survival after out-of-hospital CPCR attempts. In about 50% of cases, restoration of spontaneous circulation (ROSC), i.e., spontaneous heart beat, is not achieved in the field and resuscitation efforts are abandoned.[1-3] Among patients who reach the hospital intensive care unit (ICU), about one-half die in the ICU, primarily from cardiac, cerebral or multiple organ failure.[1-3] Among long-term survivors, 10-30% have permanent brain damage. Rapidly induced mild hypothermia *after* ROSC from prolonged normothermic ventricular fibrillation (VF) cardiac arrest (CA), i.e., no flow, has improved cerebral outcome in dogs[4-8] and patients.[9-11] For cases resistant to ROSC attempts, we searched for a method to preserve the organism during transport to, and preparation for, prolonged circulatory support using cardiopulmonary bypass (CPB), which would allow the heart to recover from ischemic stunning or be evaluated, repaired or replaced.[12-16]

For CPCR-resistant cases of CA we considered "suspended animation for delayed resuscitation" during no-flow, with tympanic temperature (Tty) of 10°C, which is being explored primarily for preservation of the exsanguinating trauma victim to allow transport and resuscitative surgery during pulselessness.[17-19] In clinical cases, however, with hearts resistant to ROSC attempts (perhaps only temporarily), clinicians would hesitate to create no-flow deliberately with aortic cold flush, instead of continuing basic and advanced life support (BLS-ALS) with steps A (airway), B (breathing), and C (circulation by chest compressions) with the hope that the heart may resume beating. Other ways to "buy time" might include mild (33-36°C)

or moderate (27-32°C) hypothermia during steps A-B-C until CPB is initiated. Others and we have used these definitions for temperature levels of therapeutic hypothermia.

We *hypothesized* that: 1) Maintaining viability of brain, heart and organism during prolonged CPCR basic and advanced life support (BLS-ALS) steps A-B-C (low flow) can be a bridge during transport to initiation of CPB in the hospital; 2) induction of mild hypothermia during CPCR can maintain viability for at least 40 min of VF-CA; and 3) mild hypothermia (which is safe) is as effective as moderate hypothermia (which has more risk of complications) in preserving the viability of the heart during CPCR.

MATERIALS AND METHODS

The experimental protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. The care and handling of the animals followed guidelines of the National Institutes of Health. All surgery was performed by the same team in our animal intensive care unit, using sterile techniques.[20-21]

Protocol

The model's protocol ~~(Fig. 1)~~ with life support to 96 h after reperfusion, simulated a scenario of prolonged VF resistant to defibrillation attempts utilizing CPCR steps A-B-C over 40 min to "bridge" from collapse via transport to initiation of CPB in the hospital emergency department. Twenty-seven custom-bred hunting dogs (19 - 29 kg body weight, age 8 - 12 months) were used. They were sedated with ketamine 10 mg/kg i.m. Anesthesia was induced with halothane 2-4% in N_2O/O_2 50/50% via a cone mask. The dogs were then positioned supine, intubated, and mechanically ventilated to maintain an arterial PCO_2 at 35-40 mmHg. A positive end-expiratory pressure of 5 cm H_2O was applied. Anesthesia was maintained during preparation with halothane 0.5 - 1.5% and N_2O/O_2 50/50% without neuromuscular blockade. Temperature probes were inserted for measuring tympanic membrane (Tty), esophageal (Tes) and rectal temperatures (Tr). Tty was controlled at 37.5 ± 0.1°C with heating blankets and heating lamps before the insult. We chose to control Tty since the brain was the primary target organ for our therapy. We recognize that the correlation between Tty and brain temperature is poor, although one recent study suggested good correlation between Tty and brain temperature in the neurosurgical patients.[22] The correlation between core and brain temperatures is also variable.[23] Gastric and bladder catheters were inserted. Dextrose 5% in sodium chloride 0.45%

was administered at 5 mL/kg/h via a peripheral i.v. cannula (18 Gauge). A 10 French catheter was inserted into the left femoral artery for monitoring of arterial pressure and for blood sampling. A 7-8 gauge cannula was inserted 3 cm into the right femoral artery for later use for CPB. A pulmonary artery catheter (7.5 French) was inserted via the left femoral vein and advanced into wedge position for pressure and temperature monitoring (Tpa), continuous cardiac output determination and blood sampling. Arterial and central venous pressures and electrocardiogram were continuously recorded on a polygraph. Due to technical issues, venous pressures were not measured accurately during chest compressions.

For controlling Tty in groups 2, 3 and 4, via veno-venous extracorporeal shunt cooling, a 13 French catheter was inserted via the femoral vein 20 cm into the *inferior* vena cava and connected to 15 m long tubing (3 mm inner diameter; primed with isotonic saline 120 mL and 500 IU heparin) immersed in ice-water. This simple system was utilized instead of conventional heat exchangers specifically because of its simplicity. Only one pump was needed. The system could readily be utilized outside of the hospital. There was no additional systemic heparinization. A shunt flow of 10 mL/kg per min by a roller pump returned the cooled blood via the right external jugular vein into the *superior* vena cava using a multiple-holed 19 French catheter.

Randomization for group assignments was performed after surgical preparation, but before the insult began so that one team member could prepare materials for cooling if necessary. Attempts were made to keep the other team members blinded to group assignments until during the insult.

After stabilization and two baseline measurements, intravenous fluids were discontinued, heating devices were turned off and the dogs were weaned to spontaneous breathing via a T-tube. VF was induced with a 95-volt AC, 60 Hz transthoracic shock of 2 sec, using subcutaneous

needles. The shock was repeated as needed. Pulselessness was allowed to persist for 3 min before initiation of CPR. CPR BLS steps A-B-C, with air for ventilation to simulate bystander CPR, was then initiated, using left parasternal chest compressions (dogs turned 45° to the right of supine to exert more direct pressure on the heart) with a mechanical thumper (Michigan Instruments, Grand Rapids, MI), rate of 80/min. The depth of compression was titrated to maximize systolic blood pressure. There was no active decompression of the chest. Tidal volumes of approximately 15 ml/kg (larger than the standard in humans based on greater compliance of the dogs' chest and lungs) at an FiO_2 of 0.21 were delivered with a self-inflating bag (Laerdal Medical Co., Stavanger, Norway) at a ratio of 5 compressions to 1 ventilation. In previous experiments with this model, this ratio provided better hemodynamics and ventilation during CPR than the 15:2 ratio. There was no interruption of compressions for ventilation. After 7 min of BLS (10 min of VF), to simulate arrival of paramedics and futile ROSC attempts, ALS was continued for another 10 min of normothermic VF, using three external transthoracic DC countershocks of 50 J in rapid sequence. In pilot experiments, even countershocks of ≥150 J after 3 min of untreated VF and 7 min of BLS were unsuccessful. ~~These d~~Deliberately weak shocks (50 J) were used in the study to avoid premature defibrillation which would have made that experiment unusable. These shocks never caused defibrillation; VF persisted. Chest compressions were continued at a rate of 60/min (decreased per protocol to maximize ~~blood~~ systolic blood pressure based upon previous experience with this model) and ventilation with FiO_2 1.0, at a ratio of 5:1 was used. The primary goal was to maximize cerebral perfusion pressure. Epinephrine 20 μg/kg was administered i.v. at 5 min intervals ~~until~~ from 10 min VF to~~of~~ 20 min, without any additional defibrillation attempts. The dogs were to be maintained in

VF for a total of 40 min. Lidocaine (1-1.5 mg/kg IV) was administered for recurrent or refractory ventricular fibrillation or ventricular tachycardia.

At VF 20 min, the dogs were assigned to one of four *treatment groups*: Control group 1 (n = 7) received continued normothermic CPR-ALS until VF 40 min, without veno-venous shunt flow, with Tty maintained at 37.5°C using heating blankets as necessary. Moderate hypothermia group 2 (n = 7) received veno-venous shunt cooling to Tty 27°C during 20 min CPR-ALS. Mild hypothermia group 3 (n = 8) was treated as group 2, but cooling to Tty 34°C. Cooling in groups 2 and 3 was induced with a bolus of 20 ml/kg of normal saline at 2°C into the superior vena cava, followed by veno-venous extracorporeal pumping at 200 ml/min (estimated to be 10% of cardiac output). In normothermic group 4 (n = 5) the initiating i.v. flush (at 37°C) and veno-venous pumping were similar to groups 2 and 3, but were maintained at normothermia. No additional epinephrine or countershocks were administered during this time.

Reperfusion after VF 40 min was with CPB as an experimental tool since ROSC attempts with external CPCR would not be reliable after such a severe insult. The use of CPB for resuscitation also simulates a possible clinical scenario for cases of refractory VF. The CPB system utilized a centrifugal pump to circulate venous blood from the superior vena cava catheter into the femoral artery cannula via a membrane oxygenator.[12-16] The CPB system had been primed with lactated Ringer's solution 400 mL with sodium bicarbonate 2 mEq/kg. CPB flow was maintained at 100 mL/kg/min. After 15 min of recirculation with CPB, defibrillation attempts were initiated with external DC countershocks of 150 J (which could now be successful since the heart has been reperfused), increased if needed by 50 J for repeated shocks. If ROSC was achieved (defined as the presence of arterial pulsations on the arterial pressure tracing), CPB was continued for assisted circulation. By protocol, Tty ~~was~~ should be approximately 34°C at

this time point. ~~If necessary for ROSC, e~~Epinephrine 5 μg/kg was administered i.v. before countershocks and then~~,~~ repeated as needed every 5 min until ROSC. After ROSC, norepinephrine was titrated to maintain the MAP at 90-120 mmHg. Flow of 100% O_2 through the oxygenator was adjusted to keep $PaCO_2$ at 30-35 mmHg. The CPB flow rate was kept at 100 mL/kg/min until 120 min then reduced to 50 mL/kg/min until weaning from CPB at 4 h. Weaning was initiated earlier if the dogs achieved ROSC and were hemodynamically stable without inotropic support. The temperature of the water bath of the CPB heat exchanger was set to 34°C. After CPB, Tty 34°C was maintained by external means until 12 h in all 4 groups.

When CPB was initiated, controlled ventilation was resumed with 100% O_2, which was maintained until weaning from CPB. The i.v. maintenance fluid was restarted. A base deficit of > 6.0 mEq/L was treated with sodium bicarbonate i.v.

Intensive care was continued until 96 h or earlier death by technicians and critical care physicians. Controlled ventilation was continued to at least 48 h. Neuromuscular blockade was maintained with intermittent doses of pancuronium (0.1 mg/kg i.v). Analgesia was with N_2O/O_2 50/50%. In addition, throughout the experiment of 96 h, i.v. boluses of morphine (0.1-0.3 mg/kg) and diazepam (0.1-0.3 mg/kg) were titrated to prevent signs of pain (reactive wide pupils or hypertension). Hypotension (MAP < 80 mmHg) was treated with normalization of CVP (5-8 mmHg) and i.v. titration of norepinephrine. Standard intensive care included airway suctioning, periodic deep lung inflations and position change (rotation). The dogs received cefazolin (250 mg i.v.) every 8 h for infection prophylaxis. At 44 - 48 h, neuromuscular block was reversed with neostigmine (50 μg/kg) plus atropine (25 μg/kg) and the dogs were weaned to spontaneous breathing via T-tube and extubated by previously reported criteria.[13-20] Dogs that required continued circulatory support were ventilated for an additional 24 h. Successfully weaned dogs

were transferred to a step-down ICU for observation and treatment to 96 h, with O_2 by mask, continuous monitoring of pulse rate and arterial O_2 saturation. The maintenance fluid was dextrose 5% in NaCl 0.45% until 48 h and dextrose 10% in NaCl 0.45% thereafter, until the dog either could drink adequately, died, or completed the experiment via euthanasia at 96 h.

Outcome Evaluation

Performance was evaluated according to overall performance categories (OPC 1 = normal (able to walk and eat); 2 = moderate disability (able to sit, but not stand or walk); 3 = severe disability (unaware of surroundings, withdraws to pain); 4 = coma (some reflexes or pathologic movements, but no response to pain); and 5 = death).[13-16,20] This scoring system is designed to be similar to the Glasgow Outcome Scale used clinically (ref). Neurologic function was evaluated as neurologic deficit scores (NDS 0 - 10% = normal; 100% = brain death), which includes evaluation of consiousness, breathing, cranial nerves, sensory/motor function, and behavior.[13-21] Our group, and others, ~~has~~ have used these outcome measures for over 20 years for large animal outcome experiments. OPC and NDS were evaluated every 8 h after extubation for best (at any time) and final values (at 96 h). Attempts were made to discontinue any sedation at least 4 h prior to final evaluations at 96 h. If necessary, sedation was reversed with naloxone (1.5-6.0 μg/kg i.v.) and/or flumazenil (0.1 mg i.v.), repeated if needed. The 96 h NDS evaluation was the average of 4 evaluators.

After final evaluation at 96 h, the dogs were re-anesthetized for morphologic studies. Via a left thoracotomy, brain perfusion fixation, with infusion of paraformaldehyde into the aortic arch, for cutting, staining and histologic damage scoring, was performed as described previously.[17,20,21] The same six brain slices were stained with hematoxylin-eosin-phloxine.

Using light microscopy, the same pathologist, blinded for treatment assignments, scored 19 distinct anatomic brain regions for severity and extent of ischemic neuronal changes, infarcts, and edema.[21] A total histopathologic damage score (HDS) of > 40 represents moderate damage, and > 100 represents severe damage.

A complete necropsy was performed. Macroscopic lesions in the myocardium were scored as absent, minimal, mild, moderate, marked or severe and scored taking into account the pattern, appearance and anatomic distribution (0 = no damage, 100 = severe damage). Although a score was given, this was a qualitative appraisal of overall myocardial damage, without a true quantitative scoring system.

Statistical Analysis

Repeated measures analyses of variance were performed followed by Bonferroni/Dunn post-hoc tests to identify differences in hemodynamic parameters and temperature data between groups over time. NDS, HDS and myocardial damage scores were analyzed using Mann-Whitney U Test, with the sequentially rejective Bonferroni test being used to preserve the experiment-wise type-I error rate at 0.05. Fisher's exact test was used to assess differences in OPC proportions (dichotomized to OPC 1 and 2 = good outcome (similar to the Glasgow Outcome Scale with potential for independent functioning), and OPC 3, 4 or death = bad outcome) between groups. A p-value < 0.05 was considered statistically significant.

RESULTS

Three of the 27 dogs were excluded from analysis. One each in groups 2 and 3 had severe, exsanguinating hemorrhage from major liver lacerations secondary to chest compressions. These were clearly direct, severe liver injuries, not minor injuries complicated by coagulopathy. One in group 3 had subarachnoid hemorrhage and *Dirofilaria immitis* infection.

There were no significant differences between groups in baseline measurements, including hemodynamic parameters and blood gas, electrolytes, serum glucose, hemoglobin and hematocrit values.

In spite of 3 countershocks of 50 J during ALS, all 24 dogs remained in VF until reperfusion was initiated with CPB and countershocks with >150 J were delivered. All dogs then achieved ROSC after 15 - 120 min of CPB (Table 1). Temperatures (Fig. 1~~2~~) and blood pressures (Fig. 2~~3~~) changed as expected, according to protocol. Coronary perfusion pressures (diastolic arterial pressure – central venous pressure) after ROSC were initially slightly above baseline (Fig. 2), but returned to baseline values by 12 h. All 12 normothermic dogs (groups 1 and 4) died with cardiovascular and multiple organ failure during intensive care, with the exception of one dog in group 1 that survived to 96 h in coma (Figs. 3~~4 and 5~~). Median survival time was 25 h (range 4-96) in group 1 and 15 h (4-24) in group 4 (NS between these 2 groups). All 12 hypothermic dogs (groups 2 and 3) were successfully weaned from CPB and controlled ventilation and survived to 96 h ($p < 0.0001$ vs. normothermia groups 1 and 4) with normal or near-normal function ~~(Fig. 4)~~ and brain histology (Fig. 3~~5~~). If the excluded animals were included (intention to treat analysis), the survival in the hypothermia groups would still be significantly greater than that in the normothermic groups ($p<0.0001$).

During CPCR, mean arterial pressures were 39 - 63 mmHg and mean diastolic pressures were 24 - 39 mmHg without difference between groups (Fig. 23). In groups 2, 3 and 4, these pressures increased after the intravenous flush of normal saline at VF 20 min and returned to pre-infusion levels within 8 min, without statistical differences between groups. After ROSC and after weaning from CPB, heart rate values were significantly higher in normothermic flush group 4 versus hypothermic flush groups 2 and 3 ($p < 0.001$ and $p = 0.006$, respectively), despite adequate analgesia, normalization of central venous pressure, and avoidance of drugs with chronotropic effects. No other differences were observed in the hemodynamic parameters between the groups. MAP was controlled per protocol. Cardiac output was not available in several dogs because of difficulty advancing the catheter. After weaning from CPB, cardiac output was quite variable within groups. Values were not statistically different from baseline, nor were they different between groups.

Arterial PCO_2 values were also variable. These values were frequently high (50-60 torr) at the time of initiation of CPB, but returned to baseline levels per protocol by CPB 15 min. PCO_2 ranged from 30-40 torr during CPB and early resuscitation. There were no differences between groups.

Veno-venous shunt cooling in groups 2 and 3 was initiated by an i.v. saline flush, which decreased Tty from 37.5°C to 36.1 ± 0.7°C (Fig. 12). Tpa was 26 ± 0.2°C and Tes 35.8 ± 1.5°C at the end of the i.v. flush. The time needed for shunt cooling after the flush to achieve Tty 34°C in groups 2 and 3, was only 2 min (a decrease in Tty of 1°C/min). In group 2, continued veno-venous shunt cooling decreased Tty to a nadir of 26.6 ± 0.6°C at the end of CPCR ALS (VF 40 min). Within 15-20 min after recirculation with CPB, these temperatures reached 34°C in all groups and were maintained at that level until 12 h.

Extracerebral organ failure, after CPB and ROSC, was the main reason for irreversible deterioration in normothermic groups 1 and 4. Arrhythmias appeared within the first hour after ROSC in all 4 groups. The most frequent form of arrhythmia was multifocal runs of ventricular extrasystoles, appearing intermittently in all dogs, especially during the first day after the insult. During CPB (assisted circulation), after ROSC, ventricular arrhythmias increased gradually in 2 dogs in each of the normothermia groups 1 and 4. Shortly after these 4 dogs were weaned from CPB, they died in VF that was resistant to vigorous CPR and up to 25 countershocks. Two dogs in normothermia group 1 and the remaining 3 dogs in normothermia group 4 died within 38 h after recirculation in vasopressor-resistant shock. Two other dogs in normothermic group 1 developed an increasing need for large doses of norepinephrine (despite adequate left ventricular filling pressures), severe metabolic acidemia, anuria and respiratory failure. These dogs were euthanized at 25 and 38 h, respectively, when it was recognized that they were not salvageable, to obtain their brains for histologic scoring.

Myocardial injury was present in all 4 groups, despite patent coronary arteries. Milder lesions were restricted to the subendocardium and subepicardium with a patchy, multicentric pattern that coalesced into larger, focally extensive lesions. Superficial subendocardial hemorrhage and papillary muscle necrosis were more frequently observed in the left than in the right ventricle, and more frequently in the normothermia groups than in the hypothermia groups. Microscopically, the areas of myocardial damage were characterized by the loss of fiber cross-striation, decreased nuclear definition and prominent contraction band necrosis. Intensely eosinophilic transverse bands representing hypercontracted myofibrils span these degenerative cells. In some areas, there was frank associated individual myofiber coagulation necrosis with associated disintegration and loss of fiber integrity. Another finding seen in areas adjacent to

frankly degenerative myocardium, especially in sub-endocardial and sub-epicardial perivascular locations, was focal myocytolysis (vacuolar degeneration). Some hearts also had large amounts of prominent basophilic stippling of myofibers.

The total myocardial damage scores were significantly lower in the hypothermia groups 2 and 3 than in the normothermic groups 1 and 4 ($p = 0.0083$), but did not differ between the two hypothermia groups ($p = 0.1548$, Figure 34).

Cerebral outcome (Fig. 34 ~~and 5~~): There was 100% agreement among observers regarding OPC scoring. The only dog in normothermic groups 1 and 4 that survived to 96 h remained comatose (OPC 4) and required controlled ventilation. In contrast, all surviving dogs in group 3 and all but 1 dog in group 2 ~~were~~ had good functionall~~y normal~~outcome (OPC 1 or 2) (Fig. 34). Because of early deaths, only 4 brains of the normothermic groups could be studied histologically: 3 in group 1 and 1 in group 4. Histologically, the brains in the normothermic groups were characterized by multifocal infarctions, with vasculitis/encephalitis adjacent to the infarcted areas. These lesions were noted in the frontal, parietal, and occipital cortices, as well as the putamen and caudate nucleus. Multifocal vasculitis was also observed adjacent to an infarcted area in the occipital cortex of one dog in hypothermia group 3. Histopathologic changes in groups 2 and 3 were mild and consisted mainly of isolated ischemic neurons and, in 2 dogs, focal vasculitis. The only region in which the regional HDS was not zero was the caudate nucleus. Except for the above lesions, total brain HDS was normal (0-4%) in all but 2 dogs in group 2 and in all dogs in group 3 ($p < 0.001$ for hypothermia groups versus normothermic groups). ~~Median regional brain HDS was zero in 15 of 19 regions in group 2 and in all 19 regions in group 3 (Fig. 5).~~

DISCUSSION

This study strongly supports all three hypotheses posed in the Introduction. The results show outcome benefit for simulated "refractory" CA cases, in terms of overall organ preservation, survival time and survival rate, with mild (34°C) or moderate (27°C) hypothermia, induced by veno-venous extracorporeal shunt cooling, *during* prolonged CPCR-ALS steps A-B-C, as a bridge to temporary, prolonged CPB. The benefit derived from mild hypothermia *after* ROSC for cerebral recovery has been well documented.[4-11] All 4 groups in the present study with VF of 40 min were treated with mild hypothermia *after* ROSC; this alone did not prevent organ failure and early death in groups 1 and 4. Demonstration of the added benefit (without negative side effects) of mild (group 3) or moderate (group 2) hypothermia, when introduced *during* CPR steps A-B-C (low flow), not only for the brain but also for preservation of extracerebral organs, is new. The finding that the impact of hypothermia was so pronounced on extracerebral organ preservation was not expected.

Mild hypothermia initiated *before* CA in rats was shown to be more beneficial than after CA.[2,12] The results of the present study in a clinically realistic dog model, document that therapeutic hypothermia should be initiated as soon as possible, even before ROSC, to provide effective protection from, or to mitigate, post-CA damage to all vital organs. Even though one of us recommended resuscitative *moderate* hypothermia as a step in the CPCR system as early as 1961,[2,13] it has not been practiced because of a fear of causing arrhythmias, depressing the myocardium, causing coagulopathy and infection, and because of practical limitations with slow surface cooling.[2,6,4,2,7,5] Moderate hypothermia (30°C) has been considered detrimental during CPCR, as it may worsen the chance for achieving ROSC, in addition to aggravating the

myocardial damage.[6,28~~6~~] The cardiovascular safety of even 27°C in this study in healthy animals may not apply to patients with diseased hearts.

In the present study we not only documented an effective and feasible technique for the rapid induction of mild (34°C) to moderate hypothermia (27°C) during CPCR steps A-B-C, but also demonstrated that hypothermia significantly improves outcome without cardiovascular side effects during prolonged VF, in a model of ~~unresuscitable~~ refractory CA. The finding that mild hypothermia is as effective as moderate hypothermia in preserving the viability of the organism obviates the need for lowering the temperature beyond the relatively safe limit of 34°C. We recognize that studies are needed to evaluate the effect of mild hypothermia on the ability to achieve ROSC without CPB in experimental models with diseased hearts. Recent clinical studies suggest that in patients with diseased hearts, post-arrest mild hypothermia induced by infusion of large volume (30 ml/kg) of intravenous iced (4°C) crystalloids does not cause arrhythmias and may actually improve hemodynamics.[29~~7~~] Ideally, hypothermia should be induced immediately after CA. However, experience from clinical studies of out-of-hospital CA indicates that 8-10 min is required in many urban areas for the ambulance to arrive and for paramedics to initiate ROSC attempts.[2,3,~~,2~~30~~8~~,31~~29~~] Therefore, in the present study the dogs were subjected to 3 min of no flow, simulating the reaction time for a bystander, followed by 7 min of BLS, to approximate the time required for the ambulance to arrive. Hypothermia was not induced until after another 10 min at normothermia, simulating ROSC attempts and the time needed to gain vessel access.

Alternative explanations for the results of this study should be considered. The excellent neurologic outcomes in the hypothermia groups may, theoretically, have been the result of better perfusion pressures during CPR. Indeed, the flush administered at the start of the veno-venous

shunt cooling did increase blood pressure, similar to what has been seen clinically.[29,7] The normothermic shunt group 4, however, had similar blood pressure responses as the hypothermia groups, but had significantly worse outcome. Thus, it appears that hypothermia improved outcome. Similarly, the hypothermia groups had less myocardial damage than the normothermia groups. Hypothermia presumably had a protective effect on the heart. Mechanisms of this protection may include decreased heart rate, decreased oxygen demands, decreased apoptosis[32], and increased production of heat shock proteins[33]. The resultant improved hemodynamics could have contributed to the improved neurologic outcome.

One potential criticism of the study is that the control (normothermic) group was actually actively warmed during CPCR. This was done to be sure that temperatures were tightly controlled during the insult. Clinically, however, patients tend to cool spontaneously during CA and CPCR. Thus, the protocol may have exaggerated the effects of mild hypothermia since the control group may have actually been *hyper*thermic compared to patients. The results of this study suggest that perhaps exposure of the victim or other measures should be used during CA to enhance this spontaneous cooling.

Limitations of this study also include the fact that the researcher who evaluated the functional outcome (OPC, NDS) could not be blinded for the treatment groups, although the pathologist who evaluated cerebral histologic outcome was blinded. These experiments require a large team of personnel, who consequently become aware of the group assignments. There were no other personnel available to routinely perform neurologic assessments in every animal. In previous studies, agreement between team members on outcomes scores was good. This is not surprising since the differences between the overall performance categories, the primary

functional outcome variable, are not subtle. In addition, the fact that the histopathologic findings correlate with the OPCs suggest a lack of bias in OPC determination.

For clinical use, the catheters used in this study for the veno-venous shunt cooling could be replaced by a double-lumen central venous catheter, inserted through a large vein (basilic, cephalic, internal jugular, femoral), with inflow and outflow sites separated. In our pilot experiments we found that the veno-venous cooling during CPR is less effective if the tips of the catheters are less than 20 cm apart. Another alternative is a standard central venous catheter for inflow into the heat exchanger and any peripheral venous catheter for delivery of cooled blood to the patient. Our improvised cooler (heparinized tubing in ice water) might be replaced by a still-to-be-developed, FDA-approved miniaturized pump-cooler for field use. Although the 10 min allowed in this protocol for achieving venous access and initiation of cooling seems unrealistic with standard techniques, we are working with catheter and imaging companies to develop novel approaches to vessel cannulation that could be more rapid and reliable, even in the hands of physician extenders.

CONCLUSIONS

We *conclude* that in normovolemic "refractory" VF-CA of 40 min in dogs, cooling to mild (Tty 34°C) or moderate (Tty 27°C) hypothermia *during* ROSC attempts of 20 min with external CPCR steps A-B-C (for BLS and ALS) as a bridge to prolonged CPB can results in survival with full neurologic recovery. This was not achievable in the same scenario with normothermic closed-chest CPCR, in spite of mild hypothermia *after* ROSC. A clinically acceptable portable device for blood cooling during CPCR should be developed.

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LEGENDS TO FIGURES

~~Figure 1~~

~~Study protocol. Three min of normovolemic ventricular fibrillation was followed by 7 min of basic life support (BLS) and 30 min of advanced life support (ALS). CPB = cardiopulmonary bypass; Tty = tympanic temperature (°C).~~

Figure 12

Tympanic temperature during 3 min of normovolemic ventricular fibrillation (no flow), followed by 7 min of basic life support (BLS) and 30 min of advanced life support (ALS). CPB = cardiopulmonary bypass; V-v shunt = veno-venous shunt cooling; Tty = tympanic temperature (°C).

Figure 23

Mean (MAP) and diastolic arterial pressures (DAP) and coronary perfusion pressure (CPP) during and after ventricular fibrillation (VF) cardiac arrest. Data are presented as means and SD.

Figure 34

Final 96 h outcome. Overall Performance Categories OPC 1 = normal; OPC 2 = moderate disability; OPC 3 = severe disability; OPC 4 = coma; OPC 5 = brain death. NDS = Neurologic deficit Score; HDS = Total Brain Histologic Damage Score; MDS = Gross Myocardial Damage Score. Each dot represents a dog. Values of NDS, HDS, and MDS are expressed as median (range). [ ] represents individual HDS scores at 22 - 58 h of reperfusion.

Figure 5

Regional brain histologic damage scores (HDS) at 96 h in hypothermia groups 2 and 3. Median values were 0 in all regions except the caudate nucleus. Groups 1 and 4 are not shown because only one dog survived to 96 h. The three available brains of group 1 had regional HDS of 0 in all regions except in frontal, parietal, and occipital cortices (range 0-32), and in putamen and caudate nucleus (range 0-12). The one available brain of group 4 also had cortical histologic damage in the above mentioned areas but HDS 0 in other brain regions.

Table 1.

Resuscitation variables.

Group	1) Control	2) Tty 27°C	3) Tty 34°C	4) Tty 37.5°C
Countershocks, total number	2 (1-19)	1	1 (1-16)	14 (1-25)
Countershocks, total energy (J)	300 (150-3990)	150	150 (150-3200)	2550 (150-4000)
Time of ROSC (min after start of CPB)	22 (15-120)	15	17 (15-33)	32 (15-105)
Total Bicarbonate (mEq)	115 (50-215)	95 (50-175)	107 (50-130)	100 (95-275)
Total epinephrine (mg)	0.9 (0.4-6.4)	0.5 (0.4-1.1)	0.8 (0.5-1.7)	0.9 (0.4-1.7)
Total Norepinephrine (mg)	6.68 (2.32-85.46)	2.05 (1.26-5.40)	7.49 (2.01-36.32)	23.09 (10.88-49.58)
Duration of NE infusion, min	3.5 (1-38)	6 (0.25-44)	2.25 (0.5-80.25)	12 (4-24)
Lidocaine (mg)	20 (0-280)	25 (20-184)	30 (20-40)	20 (20-30)
Survival time (h)	25 (4-96)	96	96	15 (4-24)

ROSC = restoration of spontaneous circulation; CPB = cardiopulmonary bypass. Tty = tympanic temperature. NE = norepinephrine. Data are given as median (range).

~~Fig. 1~~

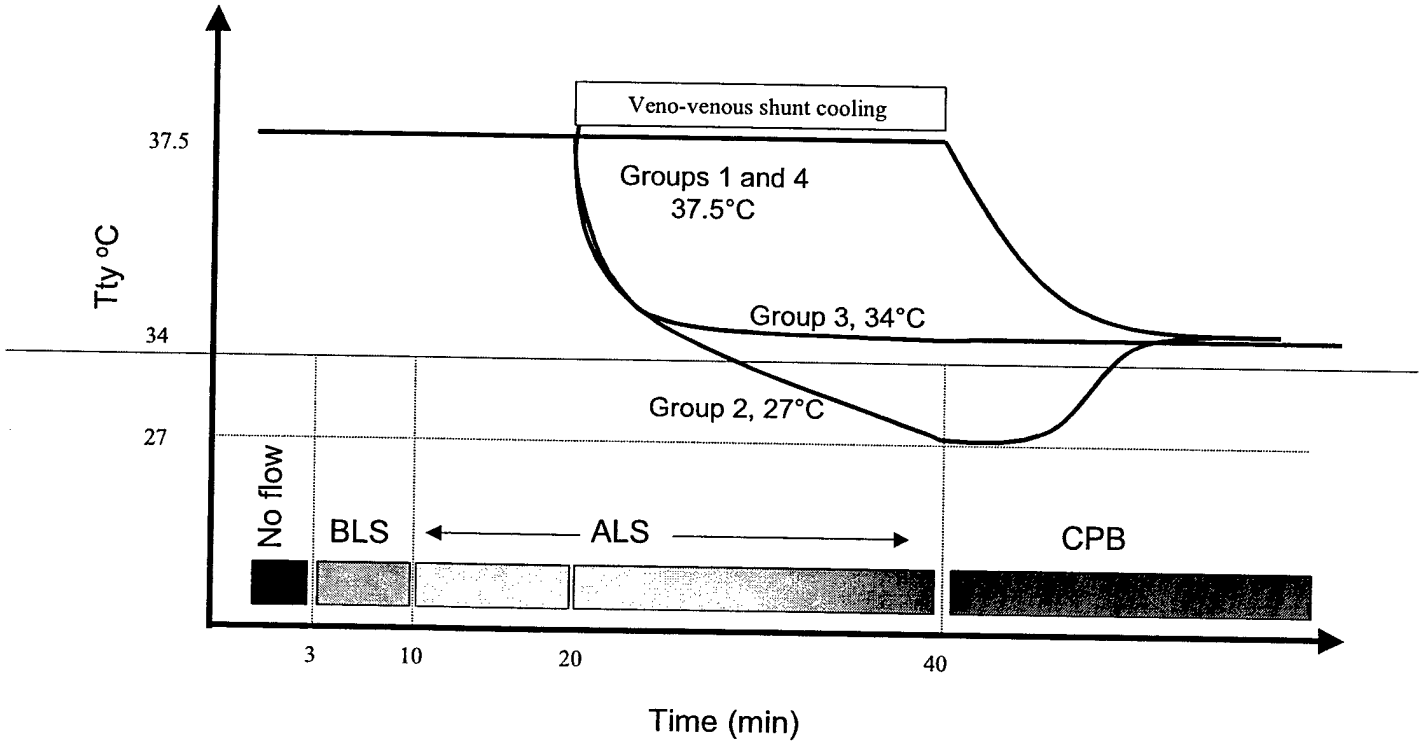
Veno-venous shunt cooling
37.5
Groups 1 and 4
37.5°C
Tty °C
Group 3, 34°C
34
Group 2, 27°C
27
No flow
BLS
ALS
CPB
3
10
20
40
Time (min)

Fig. 12

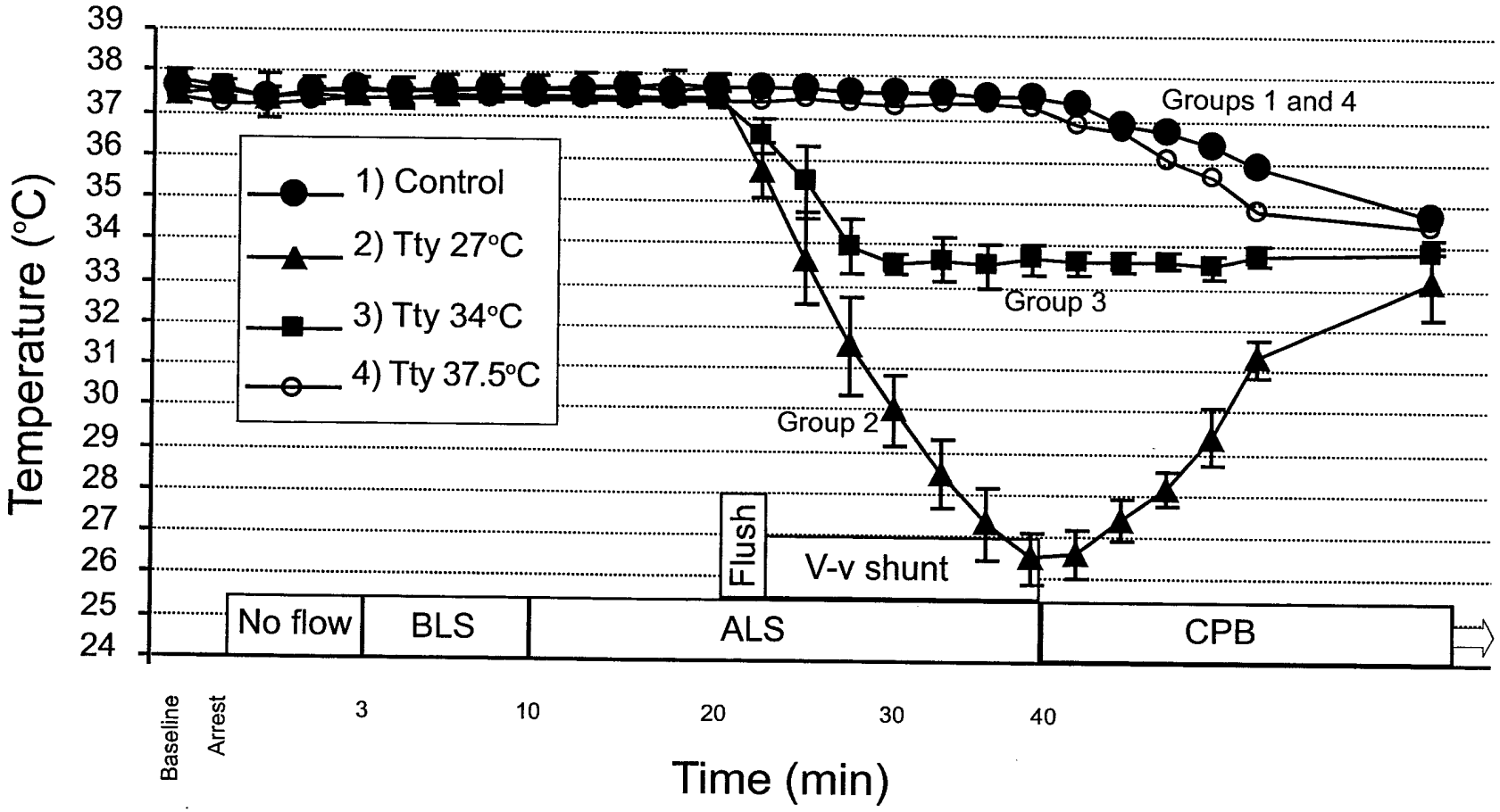
Temperature (°C)
39
38
37
36
35
34
33
32
31
30
29
28
27
26
25
24
1) Control
2) Tty 27°C
3) Tty 34°C
4) Tty 37.5°C
Groups 1 and 4
Group 3
Group 2
Flush
V-v shunt
No flow
BLS
ALS
CPB
Baseline
Arrest
3
10
20
30
40
Time (min)

Fig.32

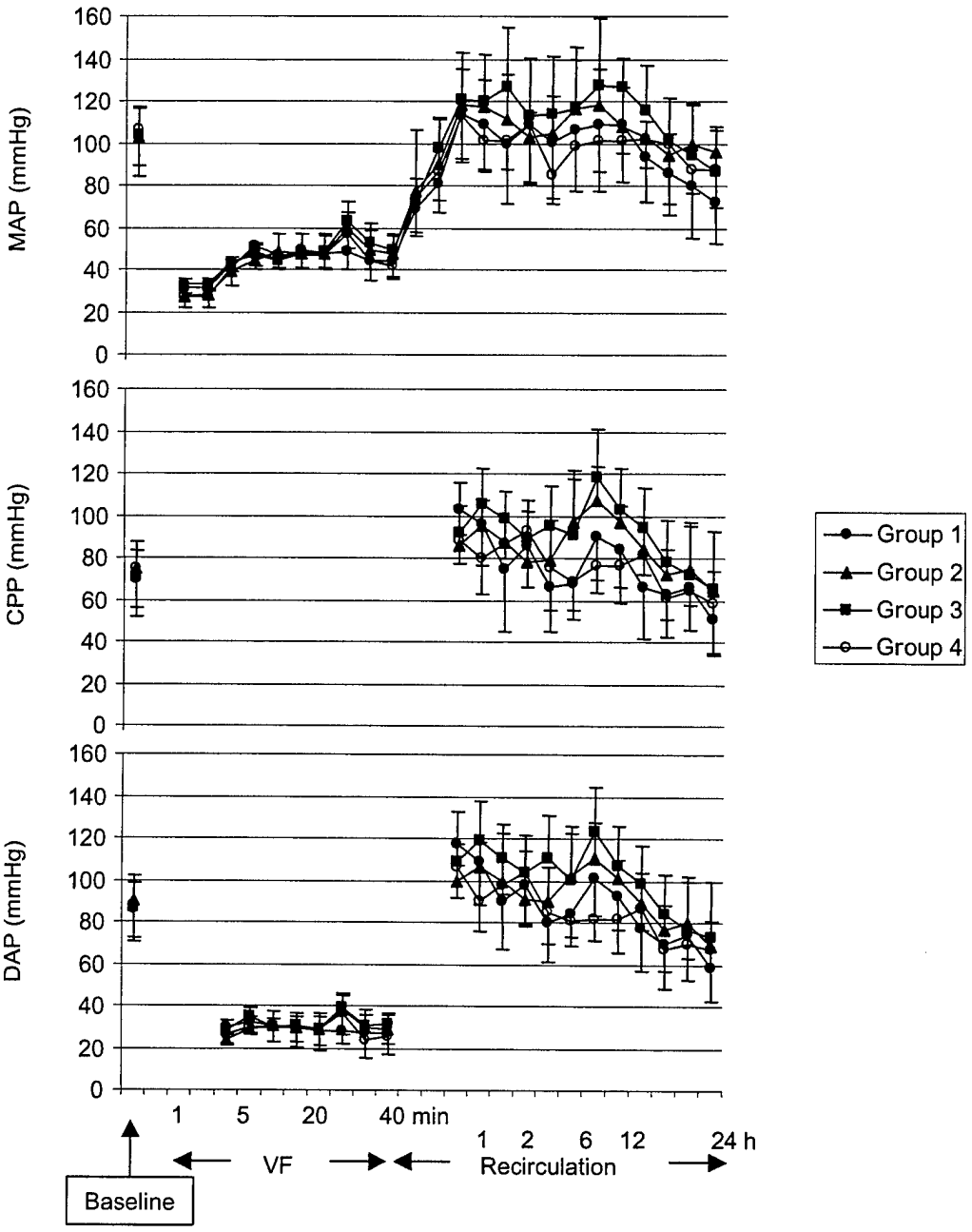
MAP (mmHg)
CPP (mmHg)
DAP (mmHg)
160
140
120
100
80
60
40
20
0
1
5
20
40 min
1
2
6
12
24 h
VF
Recirculation
Baseline
Group 1
Group 2
Group 3
Group 4

Fig 34

	Group1	Group 2	Group 3	Group 4
OPC 5 or death	⌘⌘⌘⌘⌘⌘⌘			⌘⌘⌘⌘⌘⌘
OPC 4	⌘	⌘		
OPC 3				
OPC 2			⌘⌘⌘	
OPC 1		⌘⌘⌘⌘⌘⌘	⌘⌘⌘	
NDS (%)	92	1 (0-92)	1 (0-11)	
HDS	[26, 78, 0]	1 (0-66)	0 (0-4)	[46]
MDS	85 (73-97)	30 (13-87)	55 (27-80)	90 (80-93)

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Suspended Animation Can Allow Survival Without Brain Damage After Traumatic Exsanguination Cardiac Arrest Of 60 Min In Dogs

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Disclosure Statement

The following authors of this manuscript, entitled, "Suspended Animation Can Allow Survival Without Brain Damage After Traumatic Exsanguination Cardiac Arrest of 60 Min in Dogs," from the University of Pittsburgh, have no financial or proprietary interest in the subject matter or materials discussed in the manuscript. This includes (but is not limited to) employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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ABSTRACT

Background: We have previously shown in dogs that exsanguination cardiac arrest of up to 120 min without trauma under profound hypothermia induced by aortic flush (suspended animation) can be survived without neurologic deficit. In the present study the effects of trauma are explored. This study is designed to better mimic the clinical scenario of an exsanguinating trauma victim, for whom suspended animation may buy time for resuscitative surgery and delayed resuscitation.

Methods: Fourteen dogs were exsanguinated over 5 min to cardiac arrest. Flush of saline at 2°C into the femoral artery was initiated at cardiac arrest 2 min and continued until a tympanic temperature (Tty) of 10°C was achieved. The dogs were then randomized into a control group without trauma (n=6) or a trauma group (n=8) which underwent, at start of cardiac arrest, spleen transection and left thoracotomy. During cardiac arrest, splenectomy was performed. After cardiac arrest of 60 min no flow, reperfusion with cardiopulmonary bypass was followed by intensive care to 72 h.

Results: All 14 dogs survived to 72 h with histologically normal brains. All control dogs were functionally neurologically intact. Four of 8 trauma dogs were also functionally normal. Four had neurologic deficits, although 3 required prolonged mechanical ventilation because of airway edema and evidence of multiple organ failure. Blood loss from the chest and abdomen was variable and was associated with poor functional outcomes.

Conclusions: Rapid induction of profound hypothermic suspended animation (Tty 10°C) can enable survival without brain damage after exsanguination cardiac arrest of 60 min no flow even in the presence of trauma. This technique may allow survival of exsanguinated trauma victims who now have almost no chance of survival.

INTRODUCTION

Despite advances in resuscitation techniques and in surgical management of trauma victims, survival rates remain extremely low in trauma patients who exsanguinate to cardiac arrest [1,2]. Emergency department thoracotomy to treat cardiac tamponade, control intra-thoracic hemorrhage, perform open-chest cardiac massage, and cross-clamp the aorta to optimize cerebral and myocardial perfusion and decrease intra-abdominal hemorrhage is often performed but the surgical team's race against the clock to achieve hemostasis is rarely successful, even when the underlying injury is technically repairable. Most patients die or suffer severe brain injury because these extraordinary efforts are not adequate to restore blood flow before the limit of tolerance under normothermia of 5 min circulatory arrest for the brain [3,4] and about 20 min for the heart [4,5].

In 1984, Bellamy and Safar considered these issues when reviewing data from the Vietnam War. It was clear that a new approach to resuscitation is needed [2]. Suspended animation, i.e., rapid induction of pharmacologic-hypothermic preservation, was introduced as a new concept for attempting resuscitation from cardiac arrest in presently unresuscitable victims [2,6]. The viability of brain and organism is preserved with suspended animation during cardiac arrest, to buy time for transport and resuscitative surgery, until restoration of spontaneous circulation or prolonged artificial circulation is possible. Using dog outcome models of exsanguination cardiac arrest, the Pittsburgh group has systematically explored suspended animation potentials. The initial studies included pressure-controlled hemorrhagic shock, rapid cooling via cardiopulmonary bypass (CPB), 60-120 min deep (15°C) or profound (<10°C) circulatory arrest, and resuscitation via CPB [7,8]. Since CPB can not be initiated rapidly enough, we have more recently explored induction of suspended animation via a rapid flush of ice-cold saline into the aorta. Hypothermic preservation induced within 5 min of circulatory arrest

through aortic or femoral cold saline flush has allowed long-term survival without brain damage after up to 120 min of no-flow cardiac arrest [9-12].

The experimental model in these studies involved exsanguination, but not major tissue injury. However, the majority of patients who experience hemorrhage severe enough to cause exsanguination cardiac arrest have a major vascular or solid organ injury with significant tissue trauma. The potential efficacy of suspended animation in traumatic exsanguination cardiac arrest has therefore been questioned, as trauma may affect the distribution of preservative cold flush, cause coagulopathy, and elicit inflammatory and other deleterious responses. In the present study, we aimed to determine the outcome after suspended animation in a clinically realistic dog model of exsanguination cardiac arrest with abdominal injury and thoracotomy. We hypothesized that additional trauma would worsen the chance of intact survival.

METHODS

This study was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh and the Department of Defense and was conducted in accordance with the Animal Welfare Act and other Federal statutes and national guidelines for the treatment of animals. All surgical procedures were performed by the same team in a designated veterinary surgical suite with sterilized instruments and aseptic procedures.

A total of 35 custom-bred hunting dogs (21 - 28 kg body weight, age 8 - 12 months) were used; 16 were used for pilot experiments to determine the trauma, hemorrhage and flush, 5 were used as blood donors, and 14 were used for the definitive study with exsanguination cardiac arrest of 60 min with or without laparotomy, splenic injury, and thoracotomy. Whole blood of donor dogs was collected into 1000 mL bags with 50 mL sodium citrate through a 19 Fr, right external jugular vein catheter, inserted under general anesthesia, and was stored at 6 °C for up to 7 days.

Preparation

The dogs were fasted overnight with free access to water. After sedation with ketamine (10 mg/kg i.m.), anesthesia was induced with halothane (2-4%) in N_2O/O_2 (50/50%) via a cone mask. The dogs were then intubated and mechanically ventilated (Harvard Piston Ventilator model 613, Harvard Apparatus, South Natick, MA) with a tidal volume of 15 mL/kg and the rate adjusted to maintain $PaCO_2$ 35 - 40 mmHg. A positive end-expiratory pressure of 5 cm H_2O was applied. Anesthesia was maintained during preparation with halothane 0.5 - 1.5% in N_2O/O_2 (50/50%) without neuromuscular blockade.

Temperature probes were inserted for measuring tympanic membrane (Tty), esophageal (Tes) and rectal temperatures (Tr). Tty was controlled at 37.5 ± 0.1 °C with heating blankets and heating lamps before the insult. Gastric and bladder catheters were inserted. Dextrose 5% in 0.45% sodium chloride was administered at 5 mL/kg/h via a peripheral i.v. cannula (18 gauge). A 10 Fr catheter was inserted into the left femoral artery for monitoring arterial blood pressure and blood sampling. A pulmonary artery catheter (7.5 Fr, Intellicath Continuous Cardiac Output Thermodilution Catheter, Baxter Co., Irvine, CA) was inserted via the left femoral vein and advanced into wedge position for pressure and temperature monitoring (Tpa), cardiac output determination and blood sampling. Arterial and central venous pressures and electrocardiogram were continuously recorded on a polygraph (Grass Model 7D Polygraph, Quincy, MA). Pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac output, arterial and mixed venous blood gases, hemoglobin, hematocrit, serum sodium, potassium, glucose, and lactate levels were measured at regular intervals. Coagulation abnormalities were assessed using thromboelastography (TEG) (Thromboelastograph, Haemoscope Co., Morton Grove, IL). Reaction time (r), clot formation time (K), alpha angle and maximum amplitude (MA) were measured and recorded for each animal at baseline, and at 1, 3, 6, 9, 15, 24 and 72 h after reperfusion, using celite-activated whole blood at 37°C.

A 7-8 gauge cannula was inserted 3 cm into the right femoral artery for arterial cold flush after induction of circulatory arrest and, after cardiac arrest of 60 min, to return arterialized blood to the animal from the CPB circuit (CPB arterial cannula)[13,14]. The right external jugular vein was cannulated with a multiple-holed 19 Fr catheter, which was advanced to the level of the right atrium, for venous bleeding during exsanguination and later, for venous return to the CPB system.

Insult

In the trauma group, a midline laparotomy was performed providing exposure for the splenic injury. The abdomen was temporarily closed with towel clips.

In both groups, after two baseline measurements, halothane and intravenous fluids were discontinued, heating devices were turned off and the dogs were weaned to spontaneous breathing of N_2O/O_2 (70/30%) via a T-tube. When the canthal reflex returned, hemorrhage was initiated. Over a 5 min period the dogs were bled via the jugular venous cannula, and the blood was collected in 1000 mL bags with 50 mL sodium citrate for later reinfusion. The hemorrhage was controlled to achieve mean arterial pressure (MAP) of 40 mmHg at 2 min, 30 mmHg at 3 min, and 20 mmHg at 4 min, at which time, in the trauma group, the abdomen was re-opened and a standardized complete transection of the spleen was performed at its midpoint. At 5 min, to assure zero blood flow, ventricular fibrillation (VF) was induced with a 95 volts AC, 60 Hz transthoracic shock through subcutaneous needles for 2 sec, repeated as needed. Cardiac arrest was defined by identification of VF on the EKG and the loss of arterial pulsation. Total arrest time (no-flow) was 60 min.

Preservation and surgical hemostasis

After two min of no-flow (cardiac arrest), normal saline at 2°C was flushed in both groups through the CPB arterial cannula into the femoral artery at a rate of 1.7 L/min, using a roller pump, until Tty reached 10°C. In the trauma group, at 2 min no-flow, a left lateral thoracotomy was performed at the sixth intercostal space, exposing the intra-thoracic organs. At cardiac arrest 20 min, simulating the time needed for transport, splenectomy was performed. The

abdominal wall and the thoracotomy incision were, however, left open to detect possible bleeding after initiation of CPB.

Resuscitation

Reperfusion after cardiac arrest no-flow of 60 min was achieved in both groups with CPB [13,14], using heparin-coated circuits to avoid systemic heparinization (Medtronic – Carmeda bonded circuits, Grand Rapids, MI). The CPB system was primed with 400 mL of lactated Ringer's solution with 2 mEq/kg sodium bicarbonate. The flow was adjusted with a centrifugal pump (Biomedicus, Eden Prairie, MN), at 100 mL/kg/min. Reinfusion of the shed blood was titrated, aiming to maintain a MAP of 90 to 150 mmHg, and a central venous pressure of 10-15 mmHg. If necessary, epinephrine boluses of 5 μg/kg were administered and norepinephrine infusion was titrated to maintain the MAP within the targeted range. Gas flow through the CPB oxygenator was adjusted to keep $PaCO_2$ at 30-35 mmHg. The temperature of the water bath of the CPB heat exchanger was set to 5°C above Tty, until Tty reached 34°C. Controlled ventilation was resumed with 100% O_2, at a rate of 8 - 10 inspirations/min. The i.v. maintenance fluid was restarted with a flow of 100 mL/h. A base deficit of >6.0 mEq/L was treated with sodium bicarbonate.

When Tpa reached 32°C, defibrillation attempts were initiated with external DC counter-shocks of 150 J, increased by 50 J for repeated shocks. If spontaneous circulation was restored, the CPB flow rate was reduced to 75 mL/kg/min at 60 min, to 50 mL/kg/min at 90 min, and was stopped at 120 min. Bleeding into the abdomen or chest was controlled with ligation of involved vessels and with electrocautery. The abdominal and thoracic incisions were closed in layers, with a left-sided chest tube (28 Fr) inserted through the 7^{th} intercostal space along the midaxillary

line. Donor blood was transfused, if necessary, to maintain hematocrit above 25%. Partial cross-match was accomplished before all transfusions by adding a drop of the donor blood to the recipient dog's blood at room temperature and observing for macroscopic agglutination.

Intensive Care

After weaning from CPB at 2 h, controlled ventilation and circulatory support was continued to at least 20 h. Neuromuscular blockade was maintained with intermittent doses of pancuronium bromide (0.1 mg/kg i.v.). Sedation and analgesia were provided with N_2O/O_2 (50/50%) plus i.v. boluses of morphine (0.1-0.3 mg/kg), and diazepam (0.1-0.2 mg/kg) to prevent signs of wakefulness, e.g., mydriasis. Severe hypertension (MAP >150 mmHg) despite adequate analgesia was controlled with i.v. boluses of labetalol (0.25 - 0.5 mg/kg) or hydralazine (0.1 - 0.2 mg/kg).

Hypotension (MAP <90 mmHg) was treated with normalization of filling pressures by fluid administration (blood or 5% albumin depending on the hematocrit value) and with titrated norepinephrine. Standard intensive care included airway suctioning, periodic deep lung inflations, and position change (rotation). The dogs received Cefazolin (250 mg i.v.) every 8 h for infection prophylaxis.

At 20 - 24 h, paralysis was reversed with neostigmine (50 μg/kg) plus atropine (25 μg/kg) and the dogs were weaned to spontaneous breathing via T-tube. The chest tube was removed in the trauma dogs after >30 min of spontaneous breathing if signs of air leaks or ongoing blood loss were absent and if PaO_2 was maintained >100 mmHg on air and $PaCO_2$ was 30-40 mmHg. The dogs were extubated when they met the above-mentioned criteria and after their upper airway reflexes had returned. If the dogs could not be weaned to spontaneous breathing or

required continued circulatory support they were kept ventilated for an additional 24 h before new attempts at weaning. After extubation, the catheters were removed under brief N_2O - halothane anesthesia by cone mask. The dogs were transferred to a step-down unit to 72 h, with O_2 by mask and continuous monitoring of pulse rate and arterial O_2 saturation. Suspected pain was controlled with titrated i.v. doses of morphine (0.1-0.2 mg/kg), distress with i.v. diazepam (0.1 - 0.3 mg/kg). The maintenance fluid was dextrose 5% in NaCl 0.45% until 24 h, and dextrose 10% in NaCl 0.45% thereafter, until the dog was able to eat and drink. The dogs were continually monitored by technicians, with critical care physicians immediately available.

Outcome evaluation

Performance was evaluated according to overall performance categories (OPC 1 = normal; 2 = moderate disability; 3 = severe disability; 4 = coma; and 5 = death) [14]. Neurologic function was evaluated as neurologic deficit scores (NDS 0 - 10% = normal; 100% = brain death) [3,14]. OPC and NDS were evaluated every 8 h after extubation. Attempts were made to discontinue any sedation at least 4 h prior to final evaluations. If necessary, sedation was reversed with naloxone hydrochloride (narcotic antagonist) 1.5-6.0 μg/kg or with flumazenil (benzodiazepine antagonist) 0.1 mg i.v., repeated if needed.

After final outcome evaluation, for morphologic studies, the dogs were re-anesthetized with ketamine 10 mg/kg intramuscularly, followed by halothane 0.5 to 1.5% in N_2O/O_2 (50/50%). A left thoracotomy was performed, and the proximal descending aorta was ligated. A large-bore cannula was inserted proximal to the ligature. The dogs were then euthanized by infusing paraformaldehyde (4%, pH 7.4) into the aortic arch using a roller pump at a pressure of approximately 100 mmHg, with the right atrium opened, until clear fluid returned. A complete

necropsy was performed with scoring of macroscopic damage to extracerebral organs (minimal, mild, moderate or severe), taking into account the pattern, appearance and anatomic distribution of the lesions. One hour after perfusion fixation, the brain was removed. After cutting 3 mm thick slices, the same six slices of each brain were paraffin-embedded, cut into sections 4 microns thick, and stained with hematoxylin-eosin-phloxine. Using light microscopy, the same pathologist, blinded for treatment assignments, scored 19 distinct anatomic brain regions for severity and extent of ischemic neuronal changes, infarcts, and edema, as described previously[3]. The total brain histologic damage score (HDS) was the sum of all area scores. An HDS of > 40 represents moderate damage, and > 100 represents severe damage.

Statistical analysis

Data are presented as mean and standard deviation (SD) unless otherwise stated. Repeated measures analyses of variance were performed followed by Bonferroni/Dunn post-hoc tests to identify differences in hemodynamic parameters and temperature data between groups over time. NDS and HDS scores were analyzed using Mann-Whitney U Test, and Fisher's exact test was used to assess differences in OPC proportions (OPC 1 and 2 good outcome versus OPC 3,4 or 5 bad outcome) between groups. Pearson correlation coefficient was computed between the OPC and the volume of transfused blood, followed by Fisher's r to z transformation of the correlation coefficient to calculate a probability level. A p-value <0.05 was considered statistically significant.

RESULTS

Pilot experiments

Suspended animation induced by direct aortic (cannulation of the descending thoracic aorta through a left thoracotomy) flush of cold saline in a model of traumatic (laparotomy, liver or spleen trauma) exsanguination cardiac arrest no-flow of 90 min consistently resulted in severe coagulopathy with flat TEG curves and rapid exsanguination from the vascular or soft tissue injuries, or multiple organ dysfunction (cardiovascular failure, respiratory failure, renal failure and neurologic failure [15,16]). In other pilot experiments with abdominal and thoracic trauma, the flush was initially cephalad through a balloon catheter (8 French, Cardeon Co.) placed in the mid-thoracic aorta via the femoral artery until the target Tty reached 10°C, and then in a caudad direction by deflating the balloon and compressing the proximal aorta manually (via thoracotomy). After 90 min cardiac arrest with trauma, all dogs died within 24 h of irreversible shock. In contrast, in experiments without trauma and the same exsanguination insult, 90 min no-flow cardiac arrest, and resuscitation, aortic flush via a catheter in the iliac artery resulted in good outcome[12]. With resuscitation from traumatic exsanguination cardiac arrest of 90 min not yet feasible in our model, an arrest duration of 60 min was chosen for the definitive study.

Resuscitation

All 14 dogs in the final series (both groups) were successfully resuscitated and survived to 72 h. Restoration of spontaneous circulation was achieved within 70 min of recirculation with CPB (Table 1). There were no differences between the groups in requirements of drug dosages during CPB, in the number of countershocks, or in the energy delivered to achieve restoration of spontaneous circulation. Three dogs in the trauma group could not be weaned from controlled

ventilation because of severe airway edema (resulting in upper airway obstruction) and spontaneous hypoventilation. Consequently, neurologic outcome was evaluated in these dogs at 72 h after reversing the neuromuscular blockade and analgesia with the orotracheal tube in place and, if necessary, with intermittent hand ventilation. They were then reanesthetized for perfusion fixation and morphologic evaluation.

Physiologic parameters

No significant differences were found in the baseline physiologic parameters between the two groups. Heart rate, MAP and cardiac output values were not different between the groups (Table 2). There were no group differences in arterial pH, PO_2, PCO_2 or base excess during the experiment (controlled parameters). An average flush volume of 620 mL/kg (range 360-800) was required to reach the target Tty of 10°C (Fig. 1). Lactate levels peaked in both groups 60 to 90 min after initiation of CPB without any group differences, and returned gradually back to baseline at approximately resuscitation time 6 h.

Coagulation and Blood loss

After initial exsanguination cardiac arrest there was minimal blood loss from skin incisions. To maintain hematocrit >25%, transfusion of donor blood was, however, required in 6 of 8 dogs in the trauma group and in no dog in the control group. Blood loss from the abdominal or thoracic injuries varied (Table 3). The transfusion volume varied between zero and 1500 mL and correlated with final neurologic deficit ($p = 0.039$). Both groups demonstrated coagulation abnormalities after the insult, with transient hypocoagulability by TEG (decreased alpha-angle and decreased maximum amplitude) at 1 h of recirculation (Table 4); TEG variables normalized

in both groups within 24 h, but indicated a hypercoagulable state at the end of the experiment (72 h), with an increased alpha-angle and large maximum amplitude.

Extracerebral outcome

At 72 h, in both groups, arterial pressure (Table 2) and blood gas values were normal and no dog required norepinephrine. At necropsy, moderate edema of subcutaneous tissue, airway mucosa and intestinal mucosa was observed in two trauma dogs and mild to moderate pleural effusions and ascites in 4 of the 8 trauma dogs (Table 5).

In the control group, no tissue edema and no other macroscopic extracerebral organ damage was observed at necropsy except for mild myocardial lesions (mainly focal subendocardial infarctions) in 3 of the 6 dogs. In 6 of 8 dogs in the trauma group, macroscopic cardiac damage was present, especially involving the anterolateral free wall of the right ventricle. In 2 of 8 dogs in this group, these lesions consisted of mild to moderate hemorrhagic infarctions mainly restricted to the subendocardium and subepicardium. In 4 trauma dogs, the heart surface lesions had coalesced and focally extended to transmural involvement. In the trauma group, total serum creatinine kinase (CK) significantly increased to 727 IU/L (range 447-1593 IU/L) but there was no significant increase in the CK-MB isoenzyme proportion and no increase in troponin-I levels, except for one dog with troponin-I of 8.8 ng/mL.

The lungs in both groups appeared normal, except hemorrhagic consolidation in one lower lobe in one trauma dog. The intestinal mucosa had mild to moderate hemorrhagic areas in 3 dogs in the trauma group. Anuria started in both groups with the onset of cardiac arrest and ended after 30-60 min of reperfusion, except in one trauma dog in which it persisted until 20 h; oliguria persisted in this dog as the creatinine level increased to 6.8 mg/dL and BUN to 66

mg/dL at 72 h. The kidneys had focal infarctions, edema or hemorrhage in 4 dogs in the trauma group. At 72 h, serum aspartate aminotransferase values were significantly increased in both groups (median 126, range 45-865 IU/L), whereas γ-glutamyl transpeptidase and bilirubin concentrations remained normal and serum albumin was below normal (median 2.3, range 2.1-2.5 g/dL).

Cerebral outcome

Final OPCs at 72 were better in the control group (Figure 2). All 6 control dogs were functionally normal (OPC 1). In the trauma group, 5 of 8 dogs were neurologically intact or had minor deficits (OPC 1 or 2). Three dogs in this group had poor neurologic outcome ($p = 0.208$): two remained comatose (OPC 4) and required controlled ventilation despite discontinuation of anesthesia, sedatives and analgesics and despite administration of naloxone and flumazenil; the third was re-intubated within an hour after extubation at 24 h due to stupor, general weakness and respiratory failure. The latter dog also remained on controlled ventilation until 72 h. Final NDS was normal in the control group (median 1, range 0-13) and abnormal in 4 of the 8 trauma dogs (median 12, range 0-87) ($p = 0.004$) (Fig. 2). Histologically, total brain HDS at 72 h was near normal in all dogs of both groups and averaged 12 (4-22) in the control group versus 0 (0-6) in the trauma group (NS) (Fig. 3). Regional brain HDS had the same distribution in both groups, with putamen and caudate nucleus being the most vulnerable regions. Histopathologic changes consisted mainly of scattered ischemic neurons in the vulnerable areas and, in 3 dogs, mild edema with no infarction.

DISCUSSION

In pilot experiments we found that exsanguination cardiac arrest of 90 min plus trauma is not reversible to intact survival, while without trauma full neurologic recovery could be achieved [12]. The cause of early post-arrest death in the trauma experiments with 90 min cardiac arrest, in spite of standard life support, was failure of multiple extracerebral organs, without significant brain damage. In the present definitive study, using a dog model of traumatic exsanguination cardiac arrest of 60 min, we found that rapid induction of profound hypothermia (suspended animation) can enable survival without brain damage, as we have shown without trauma before [12]. Although post-resuscitative extracerebral organ complications were worse in the trauma group, all the dogs survived to 72 h, 5 of 8 with good overall performance (OPC 1 or 2). Most importantly, no dog, with or without trauma, had any significant morphologic damage to the brain. This finding is important since, with conventional resuscitation techniques, the prognosis after traumatic exsanguination cardiac arrest is extremely poor [1,17,18]. The lack of histologic brain damage suggests that with longer intensive care life support (beyond 72 h), as is available clinically, all dogs might have achieved normal overall function in spite of trauma.

The concept of preserving the organism with suspended animation to buy time for transport and surgical repair with delayed resuscitation particularly applies to civilian or military trauma victims with truncal injuries who exsanguinate to cardiac arrest without concomitant brain injury. Such casualties are considered unresuscitable despite the fact that their injuries are technically repairable.

Systematic outcome studies in dogs have documented the feasibility of suspended animation for delayed resuscitation from cardiac arrest no-flow periods of up to 120 min [9-12]. The model used in these earlier studies with exsanguination through arterial and venous catheters

simulated isolated vascular injuries, without major tissue trauma. The majority of exsanguinating trauma victims, however, has concomitant injury to soft tissues and solid organs. Trauma may cause the systemic inflammatory response syndrome, including release of cytokines and soluble adhesion molecules, which is associated with the development of the multiple organ dysfunction syndrome (MODS) [19-21]. Moreover, coagulation disturbances associated with trauma, ischemia, hemodilution, hypothermia, cardiopulmonary bypass and reoxygenation injury may impact the outcome of operative intervention and may decrease the chance of achieving surgical hemostasis and long-term survival [22-25]. In the present model, all these pathophysiologic disturbances are associated with suspended animation, and may contribute to the development of severe coagulopathy and MODS. The extracerebral organ complications observed in the 3 dogs of the trauma group with poor outcome (OPC 3 and 4) are characteristic of MODS as defined by physiologic criteria [15,16]. Despite these dogs' poor overall and neurologic performance, however, no histologic damage was found in their brains. This discrepancy between histologic brain damage and clinical performance is in contrast with our results from previous cardiac arrest studies without trauma, in which a significant correlation has been seen between NDS and HDS [4,7-11,13,25-30]. Extracerebral organ dysfunction was, however, not present in the previous studies. Therefore, poor OPC and NDS scores in the trauma dogs of the present study may represent a metabolic encephalopathy, which is potentially reversible if the underlying derangement is corrected. These dogs continued to require ventilatory support. To tolerate this, they needed sedation and intermittent doses of a neuromuscular blockade. We cannot be certain that these effects were totally reversed before the 72 h evaluation of function.

The finding that the need for blood transfusion was associated with worse functional outcome suggests that common pathophysiologic mechanisms are involved in the initiation of

coagulation derangements and MODS. These derangements may include activation of coagulation cascades, an inflammatory response with the release of cytokines and an upregulation of adhesion molecule expression, as well as the oxidative stress caused by lipid or protein oxidation through intracellular free radical generation.

Limitations of this study include the small number of dogs used, which may not detect small differences in the analyzed parameters. Although our trauma model is clinically relevant, it does not represent the wide spectrum of tissue injury that may cause exsanguination cardiac arrest. In addition, intensive care was provided for a maximum of 72 hours while the three trauma dogs with poor outcome would have required intensive care beyond this period of time in the clinical practice. Accordingly, it is likely that prolonged intensive care would have led to good outcomes in these dogs.

Given evidence that suspended animation of one hour can be survived without evidence of histologic brain damage in spite of extracerebral trauma and MODS, clinical feasibility trials of suspended animation for victims of exsanguination cardiac arrest should be considered, starting in large trauma centers. Potential subjects would be trauma victims who have a mechanism of injury consistent with exsanguinating hemorrhage and lose a pulse just prior to, or after, arrival in the emergency department. These patients typically undergo a resuscitative thoracotomy. Rapid access to the descending aorta could be obtained directly and ice-cold saline could be flushed toward the heart and brain [9-12].

In conclusion, suspended animation in dogs, using aortic cold flush and delayed resuscitation with cardiopulmonary bypass, enables survival without brain damage after exsanguination cardiac arrest of 60 min no-flow, even in the presence of trauma. Extracerebral organ complications after resuscitation, however, are worsened by trauma.

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LEGENDS TO FIGURES

Figure 1. Tympanic membrane temperatures during exsanguination cardiac arrest of 60 min no-flow. Resuscitation was with cardiopulmonary bypass. Data are given as mean ± SD. No differences were observed between the groups.

Figure 2. Final overall performance categories (OPC 1-5, panel A) and neurologic deficit scores (NDS, panel B) at 72 h after exsanguination cardiac arrest with or without trauma. Each dot of OPC represents one dog. NDS is depicted in a box plot with the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles.

Figure 3. Regional and total brain histologic damage scores (HDS) at 72 h after exsanguination cardiac arrest with or without trauma. Box plots display the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles and outliers are plotted separately as circles (trauma group) or crosses (control group). Only scores above 0 are presented.

Table 1.
Resuscitation variables required for restoration of spontaneous circulation (ROSC)

Group	Trauma	Control
Countershocks, total number	1 (1-4)	1 (1-3)
Countershocks, total energy (J)	225 (150-700)	150 (150-450)
Time of ROSC*	43 (27-72)	47 (24-55)
Total Bicarbonate (mEq)	97 (56-210)	111 (50-258)
Total Epinephrine (mg)	0.9 (0.6-1.9)	1.5 (0.4-3.0)
Total Norepinephrine (mg)	1.9 (0-5.9)	2.7 (1.2-7.8)

Data are represented as median (range). *time after initiation of cardiopulmonary bypass. No differences were observed between the groups.

Table 2.
Physiologic variables in trauma and control groups during resuscitation from 60 min exsanguination cardiac arrest and suspended animation by aortic flush.

Time of Reperfusion	Mean Arterial Pressure (mmHg)		Heart Rate (beats/min)		Cardiac Output (L/min)	
	Trauma	Control	Trauma	Control	Trauma	Control
Baseline	110±16	116±16	118±13	121±13	3.1±1	2.6
5 min	77±20	65±19				
15 min	73±6	77±20				
30 min	83±26	93±16				
60 min	106±7	118±11	119±29	132±13		
90 min	123±14	120±18	124±28	136±30		
2h	115±19	118±16	143±16	139±5	3±1.1	3.7±1.1
3h	135±21	122±18	134±22	138±28	4.4±1.1	4.3±2.1
4h	133±13	135±16	134±16	128±23	3.8±1.2	3.9±1.3
6h	136±10	143±13	128±16	118±7	2.6±1	2.6±0.4
9h	128±16	127±16	124±26	115±25	1.7±0.9	2.4±0.4
12h	118±15	126±5	125±42	102±32	2.2±0.9	2.7±0.6
16h	107±11	123±12	138±43	113±37	3.1±0.4	2.7±0.3
20h	104±15	106±13	139±47	104±37	2.9±0.5	2.9±0.7
24h	98±11	93±11	138±41	90±28	3±0.7	

BL = baseline. Values are expressed as mean ± SD. No heart rate values available during cardiac arrest. No cardiac output values available during cardiopulmonary bypass. No differences were observed between groups.

Table 3.
Cumulative blood loss and transfusion volume (mL) in the trauma dogs.

Dog #	1		2		3		4		6		8	
Time of Reperfusion (h)	Blood loss	Transfusion	Blood loss	Transfusion	Blood loss	Transfusion	Blood loss	Transfusion	Blood loss	Transfusion	Blood loss	Transfusion
1											500	400
2									125		1150	1200
4									255	400	1250	
6	60		550		0		70			800		
9					350				570			
12			950	750			160		935			
18	115				750	550				1400		
24	176		1300		800	950			1275			
40	250					1400			1325	1500		
Major bleeding site			Chest		Abdomen				Chest		Abdomen	
OPC	1		3		4		2		4		1	

OPC=overall performance category. There was no significant bleeding in dogs 5 and 7, both of which had OPC 1 at 72h.

Table 4. Thromboelastography variables in trauma and control groups.

	Alpha-angle		Reaction time (min)		Coagulation time (min)		Maximum amplitude (mm)	
Time (h)	Trauma	Control	Trauma	Control	Trauma	Control	Trauma	Control
Baseline	60±13	60±9	6.3±2.0	6.3±1.2	10.7±7.8	8.9±2.1	54±12	60±9
1	*32±13	*42±19	*9.4±1.8	9.3±3.7	*20.0±11.1	*16.1±7.7	*37±11	*45±11
3	*49±16	*45±16	*8.1±2.2	9.9±6.0	*18.5±20.4	16.5±12.1	50±14	49±12
6	*42±15	*51±9	9.8±4.1	8.1±3.1	*21.8±18.6	*12.4±3.8	48±10	49±13
9	*42±18	*49±10	*9.3±4.2	8.4±4.4	13.1±3.9	12.7±6.4	*42±17	53±7
15	*45±9	*53±11	8.0±2.3	7.3±1.3	13.0±3.3	11.4±2.5	50±6	49±15
24	55±6	51±12	6.7±1	8.6±2.4	10.2±1.8	12.8±3.9	54±3	48±11
72	67±13	*71±3	5.9±3.2	7.0±1.4	8.0±4.3	8.8±1.8	68±7	70±3

*$p < 0.05$ versus baseline. No significant differences were observed between the groups. Values are expressed as mean ± SD.

Table 5. Gross extracerebral organ damage at necropsy (72 h) after 60 min exsanguination cardiac arrest and resuscitation.

Group	Dog number	Edema	Pleural effusion	Ascites	Heart	Lungs	GI	Kidney	Liver
Trauma	1	0	0	1	1	0	2	0	0
	2	0	0	0	2	0	1	0	0
	3	4	1	0	4	0	0	1	0
	4	0	0	0	0	0	0	0	0
	5	0	2	1	0	1	0	0	0
	6	0	0	0	4	0	0	3	0
	7	3	2	0	4	0	3	2	0
	8	0	3	0	0	0	0	2	0
Control	1	0	0	0	0	0	0	0	0
	2	0	0	0	1	0	2	0	0
	3	0	0	0	1	0	0	0	0
	4	0	0	0	0	0	1	0	0
	5	0	0	0	0	0	0	0	0
	6	0	0	0	2	0	0	0	0

Trauma group (n=8)	0 (0-4)	1 (0-3)	0 (0-1)	2 (0-4)	0 (0-1)	0 (0-3)	1 (0-3)	0

Control group (n=6)	0	0	0	0 (0-2)	0	0 (0-2)	0	0

1 = minimal, 2 = minor, 3 = moderate, and 4 = severe. Group values are expressed as median (range)

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APPENDIX 19

Novel Potentials for Emergency Hypothermia: Suspended Animation with Delayed Resuscitation from Exsanguination Cardiac Arrest

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Summary. Most combat fatalities result from rapid exsanguination in the field and resuscitation via fluid administration is generally unsuccessful. In a series of experiments over the past 5 years, we have developed a novel approach targeting the use of rapid induction of profound hypothermia by aortic flush to produce a state of suspended animation for delayed resuscitation after experimental exsanguination cardiac arrest in dogs. In over 200 experiments in dogs, exsanguination cardiac arrest was induced by rapid hemorrhage over ~5 min. After the 5-min hemorrhage and an additional 2 min of cardiac arrest, hypothermia (8°–34°C, tympanic temperature) was induced by aortic or femoral flush of ice-cold saline via a balloon catheter. Cardiac arrest was then continued for durations ranging between 15 and 120 min. The specific duration and temperature selected depended on the goals of the specific study. Delayed resuscitation after the predefined suspended animation interval was achieved using cardiopulmonary bypass (for 1–2 h), mild hypothermia (34°C to 12 h), and 72–90 h of continuous intensive care. In some studies, the insult also included laparotomy, splenectomy, and thoracotomy, to simulate trauma. In other studies, pharmacological agents were combined with hypothermia to test for therapeutic synergy. Final neurologic outcome was assessed at 72–96 h by overall performance category and neurological deficit scores. Brain histopathology was also evaluated. Normal neurologic outcome with minimal histopathologic damage was routinely achieved after a cardiac arrest of 90 min using this suspended animation approach. In some dogs, good neurologic outcome was achieved even after a cardiac arrest of 120 min. A delay of 5–8 min in the induction of suspended animation attenuated its preservative effect. Of 14 drugs tested, only the antioxidant tempol produced a synergistic effect with hypothermia. The addition of trauma worsened organ function without affecting brain histopathology. Suspended animation with delayed resuscitation represents a revolutionary approach to resuscitation of the trauma victim with otherwise lethal exsanguination cardiac arrest. Our studies suggest additional benefit from the combination of antioxidants with hypothermia, and challenge the previously posed limits of

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hypothermic protection and preservation of the brain. In ongoing studies we are testing suspended animation after prolonged shock, evaluating the mechanisms of hypothermic protection using proteomics, and probing beyond the 2-h theoretical limit for cardiac arrest duration with intact survival.

Key words. Hemorrhagic shock, Hypothermia, Suspended animation, Combat casualty, Neuroprotection

Introduction

Most deaths in combat occur in the field from rapid exsanguination, not from the development of postresuscitation disorders such as multiple organ failure or sepsis. Colonel Ronald Bellamy [1] in his treatise on the cause of death in conventional land warfare discussed the fact that about 44% of combat casualty deaths in the Vietnam conflict resulted from wounds that produced exsanguination (often internal) in the field. In this subgroup of battlefield victims, many reached a military medic within minutes and a substantial number of the casualties killed in action had potentially reparable injuries. It is also well known that administration of large volumes of intravenous fluids in the field or on transport can be futile in this setting of rapid exsanguination, and results in massive hemodilution and failure to prevent the development of exsanguination cardiopulmonary arrest [2]. These facts suggested the need for a novel approach to the resuscitation. In 1984, Dr. Peter Safar and Colonel Bellamy subsequently pioneered the concept of an alternative approach that might salvage some of these combat victims, namely, induction of a state of "suspended animation" in these victims at the time of arrest, to be followed (after transport to a field hospital) by surgical repair and delayed resuscitation using cardiopulmonary bypass [3].

Studies on this project have been underway in the Safar Center for Resuscitation Research at the University of Pittsburgh School of Medicine since 1988. Despite the seemingly daunting nature of this approach, i.e., how might one consider successfully inducing a state of suspended animation, to preserve the brain, heart, and other vital organs for a period of time and successfully follow this with delayed resuscitation, Safar and colleagues, in a series of studies using a canine model of exsanguination cardiopulmonary arrest, have outlined a putative approach to this otherwise lethal condition. This approach, which has been described in a series of reports [4–12], involves the rapid induction of profound hypothermia by aortic flush with ice-cold saline.

Exsanguination Cardiac Arrest Model

In these studies, a canine model of exsanguination cardiopulmonary arrest has been used. This model has been described in detail in multiple reports, and has included various minor modifications depending on the specific goals of the study [4–9]. Briefly, in studies approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh School of Medicine and the United States Department of Defense, a protocolized and controlled rapid exsanguination was induced in halothane-anesthetized male dogs (custom-bred hunting dogs, 20–25 kg body weight) using both femoral artery and right atrial catheters. Mean arterial blood pressure was 20 mmHg at 4 min. To ensure zero blood flow after 5 min of hemorrhage, ventricular fibrillation was induced with a transthoracic shock [5].

Aortic Flush to Induce Suspended Animation

In the initial studies of the induction of suspended animation for delayed resuscitation, after completion of the 5-min exsanguination period described above, dogs were allowed to remain in a state of cardiopulmonary arrest for 2 additional minutes without any intervention. After this 7-min insult, the aortic arch was flushed (through a balloon catheter) with ice-cold (~4°C) saline [or room temperature (~22°C) saline in control groups] to rapidly induce various degrees of hypothermia ranging from mild (34°C) to profound (10°C). Temperature was assessed using probes in multiple locations, but tympanic temperature was defined as the target, since this location is known to represent the best non-invasive means of approximating brain temperature [13]. The target tympanic temperature was varied, as described above, depending on the goals of the study. Obviously, the flush volume and rate determined the time necessary to achieve the desired target temperature. In some studies, we fixed both the flush volume and flush temperature and allowed modest variation between animals in the level of hypothermia that was achieved. The time to target temperature varied, depending on the depth of hypothermia that was desired. In the studies where only mild or moderate (28°–32°C) hypothermia was the goal, the target temperature was often reached in less than 5 min. Even with prolonged suspended animation at profound hypothermia, the time to target temperature was generally less than 15–20 min. The duration of suspended animation also varied in different experiments, again depending on the goal of the specific study. In early reports on the use of this approach, the duration of suspended animation was chosen to be either 20 or 30 min [4,5], while in more recent studies, we have been able to successfully extend the duration of "suspended animation" to as long as 120 min [9].

Delayed Resuscitation

After the desired interval of suspended animation, resuscitation was initiated by starting closed-chest cardiopulmonary bypass and the shed blood was reinfused. Mild hypertension was used during early reperfusion to promote cerebral blood flow [14] and rewarming was also achieved on bypass, but only to the level of mild hypothermia (34°C) that was maintained for the initial 12 h. After the initial 12 h, normothermia was maintained until 72 h. Cardiopulmonary bypass was gradually weaned during the initial 2 h of resuscitation. During the initial recovery period, dogs received protocolized and titrated care that mirrored contemporary clinical intensive care and included continuous monitoring, mechanical ventilation, pressor and inotropic support with norepinephrine as needed, intravenous fluids, and sedation. Dogs were weaned from mechanical ventilation and extubated, generally on days 2 or 3. Monitoring and care was then continued in a step-down unit until sacrifice by transcardiac perfusion with paraformaldehyde at 72 h. Details of the intensive care protocol are provided in a number of prior reports on this model [4–9].

Outcome Assessment

Functional outcome assessment included overall performance category (OPC; 1 = normal, 5 = brain death) and neurologic deficit scores (NDS; 0%–10% = normal, 100% = brain death). Daily, best, and final OPC were assessed. After paraformaldehyde perfusion, coronal brain sections were examined by a pathologist blinded to treatment group assignment. Nineteen brain regions were scored for damage to generate a histologic damage score (HDS, 0 = no damage, >100 = severe damage), as previously described by our group [5,9].

Individual Studies Assessing the Ability of Suspended Animation to Preserve the Organism After Exsanguination Cardiac Arrest

Suspended Animation of 20–30 min: Comparison of Ice-Cold vs Room-Temperature Flush

In the initial studies with this model we tested the effect of aortic flush of 500 ml of either room temperature (control) or iced (~4°C) saline [4]. A tympanic temperature of ~36°C vs ~34°C was achieved with this modest aortic flush volume. Despite the use of only mild hypothermia, suspended animation induced with ice-cold flush significantly improved outcome as defined by each of the parameters defined above. For example, median OPC was 4 in the control group vs 1 in the ice-cold saline group ($P < 0.05$). Mean (±SEM) HDS were 109 ± 39 vs 30 ± 24 in the control vs ice-cold saline groups, respectively ($P < 0.05$). Using an identical protocol, an ice-cold saline flush volume of 100 ml/kg facilitated intact recovery from suspended animation of a 30-min duration [5].

Pharamacologic Agents to Augment Ice-Cold Saline in the Induction of Suspended Animation

To determine whether drugs could enhance the beneficial effects of hypothermia in this suspended animation paradigm; and thereby reduce the volume of flush required, we tested the effect of 14 different mechanism-based pharmacologic strategies in the aforementioned 20-min model of suspended animation. These therapies included agents targeting energy failure (thiopental or fructose bisphosphate), excitotoxicity (MK 801, YM 872, or phenytoin), calcium accumulation (nimodipine, diltiazem, or W7), oxidative stress (tempol), apoptosis (cycloheximide), or mitochondrial permeability transition (cyclosporin), along with several other traditional agents (lidocaine and glucose/insulin). Overall, the effects of drugs were modest as compared to the powerful effect of profound hypothermia in our paradigm (see below). Some of the results of this work have already been published [6–8]. However, one drug, tempol, did significantly enhance the effect of hypothermia in this paradigm [8]. Tempol is a cell-permeable, stable, nitroxide antioxidant. It has direct radical scavenging effects, and also acts both as a superoxide dismutase mimetic and oxidizes Fe^{2+} to pre-empt the Fenton reaction [8]. Tempol given at a dose of 150 or 300 mg/kg was detected in the brain at 72 h after administration by electron paramagnetic spin resonance, and treatment improved functional outcome (OPC and NDS, $P < 0.05$ for tempol vs vehicle groups), but did not reduce histopathological damage (HDS). Although overall, our studies with pharmacologic approaches to augment hypothermia were generally disappointing, we recognize that it was not possible to carry out detailed studies of brain pharmacokinetics and pharmacodynamics of these agents in our dog suspended animation model. It was also not possible, given the limited tools available to study molecular mechanisms in dogs, for example, to demonstrate effects of therapies on key proteins in the apoptosis cascade, or on mitochondrial injury. In addition, we did not study the effect of drugs in combination with profound or ultraprofound hypothermia. Pharmacologic adjuncts and optimal cooling solutions may differ for different target temperatures. Thus, these studies with pharmacologic agents represent an initial screening approach to combination therapy (hypothermia plus drugs) in our model. Our work suggests that therapies targeting oxidative stress represent an important area for additional exploration.

Suspended Animation of 60–120 min

If suspended animation was induced in the field in the setting of exsanguination cardiac arrest, to be able to allow helicopter transport of an arrest victim to a field hospital (where both emergency surgery and cardiopulmonary bypass for delayed resuscitation would be available), a longer duration of suspended animation (longer than 20–30 min) was felt to be essential. In an initial investigation targeting the goal of extending the duration of suspended animation after exsanguination cardiac arrest that could achieve intact neurologic outcome, we tested the effect of cooling to profound or deep levels (10°–15°C) of hypothermia using larger aortic flush volumes [9]. This approach (use of profound or deep hypothermia) was taken because of the failure of drugs to dramatically improve the efficacy of moderate hypothermia, as described above. First, we compared large-volume aortic flush to induce either deep (20°C or 15°C) or profound (10°C) hypothermia in our suspended animation model studying a 60-min duration. A temperature of 20°C failed to achieve normal outcome, while either (15°C or 10°C) produced normal functional and histologic outcomes (OPC 1 and NDS 0%–3%, HDS 0–20) [9]. However, to achieve these temperatures (20°C, 15°C, or 10°C) required, on average, flush volumes of 160, 308, and 482 ml/kg, respectively. Normal outcome after 90 min of suspended animation in our exsanguination cardiac arrest model was achieved with a brain temperature of 10°C. This was produced with a flush volume of over 500 ml/kg. Using profound hypothermia (tympanic temperature of 10°C) and a flush volume of over 600 ml/kg, suspended animation of 120 min led to normal functional and histologic outcome in some, but not all, dogs [9]. In these studies of the application of suspended animation for prolonged durations (≥90 min), it became necessary to optimize whole-body cooling by initially cooling the brain to target (tympanic) temperature, followed by deflation of the aortic balloon, and withdrawal of the catheter to a position in the abdominal aorta and continued optimal cooling of the structures subserved by the distal aorta—particularly the spinal cord and gut [9]. These remarkable studies demonstrate the potent preservative and resuscitative effects of profound hypothermia in the setting of exsanguination cardiopulmonary arrest.

Reducing the Fluid Volume Required to Induce Suspended Animation

For the field application of a therapy such as suspended animation, unlimited quantities of ice-cold saline would not be available. Thus, we sought to develop a strategy that would reduce the flush volume required. To this end, venoarterial recirculation of the cold flush was instituted [10]. The venous drainage from the right atrium was recirculated, cooled, and reinfused into the aortic catheter. This approach dramatically reduced the flush volume necessary to achieve deep or profound hypothermia. In that study, we also determined that aortic flush could be successful whether it was initiated in the distal aorta (femoral catheter) or the aortic arch [10]. Clinically, the recirculation approach may be limited by disruption of major blood vessels.

Superimposing Trauma onto the Suspended Animation Paradigm

Recent work in our center has focused on maximizing the clinical relevance of this suspended animation approach, in an effort to refine and optimize this therapy for a potential clinical feasibility trial. Since exsanguination cardiopulmonary arrest is produced by initial injury (usually penetrating) tissue trauma

paradigm. To further maximize the clinical relevance of the experiments (mimicking field induction and prolonged transport), a 120-min interval of suspended animation (at 10°C) was used. This combined insult, however, was associated with the development of multiple organ failure, coagulopathy, and death or poor outcome [11]. To treat the coagulopathy and multiple organ failure that developed in this setting, we added plasma exchange therapy to the protocol (three single volume exchanges during the initial 24 h of the resuscitation phase) to achieve survival with good neurologic outcome. Details of this work were recently presented at the, 2004 Congress of the Society of Critical Care Medicine in the United States [12].

Future Directions

Current studies in our laboratory are investigating the impact of superimposing a prolonged period of hemorrhagic shock into the model before the induction of suspended animation—asking the question "If the patient who has been in shock deteriorates to pulselessness, is suspended animation still feasible?" This scenario mimics a soldier or civilian who develops hemorrhage-induced cardiopulmonary arrest over a more protracted period of time (1–2 h rather than 5 min) [15]. Additional laboratory work underway is also assessing the protein damage during the period of prolonged hypothermia, using proteomics [16]. We also plan to again address the issue of optimal use of drugs and fluids to develop a better suspended animation solution than normal saline. Finally, as discussed above, we hope to begin planning for the first application of suspended animation in the setting of civilian exsanguination cardiopulmonary arrest. We are also working with industrial partners to aid in the development of "smart catheters" necessary for rapid cannulation of the aorta and devices needed for rapid cooling in patients [17].

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APPENDIX 20

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Chapter #

FUTURE DIRECTIONS

Samuel A. Tisherman, MD, Fritz Sterz, MD, Wilhelm Behringer, MD, Patrick Kochanek, MD

Hypothermia research has come a long way over the past 50 years. We have asked many questions about how hypothermia works and in which situations is it beneficial. From a mechanistic standpoint, our understanding of the effects of hypothermia, both beneficial and detrimental, are much more complex than just direct effects on oxygen metabolism, as was first thought.

Laboratory studies have demonstrated benefit of therapeutic hypothermia in cardiac arrest caused by ventricular fibrillation, asphyxiation, or exsanguination, as well as traumatic brain injury, stroke, hemorrhagic shock, myocardial infarction, hepatic failure, and even pulmonary failure with sepsis. Additional studies are needed to more clearly define the optimal timing of hypothermia in terms of induction and duration, and the optimal depth. As we move forward in translating these findings to clinical studies, there may be appropriate indications to perform studies, if not done already, in animals that are high on the phylogenetic scale to hopefully better predict what will happen in humans.

The pathophysiologic mechanisms behind the molecular, cellular, organ, and organism level changes that occur after the various disease states addressed in this book are quite complex. So far, however, there has been little research into multifaceted therapeutic interventions that include hypothermia. Better understanding of the biochemical and molecular mechanisms behind the effects of hypothermia should allow us to develop synergistic pharmacologic approaches that perhaps could complement or potentate the beneficial affects of hypothermia, as well as decrease the detrimental effects. It is naive to think, however, that therapies aimed at one pathway will have an overall beneficial affect with such complex disease

processes in critically ill patients. It is not surprising that so many single drug clinical trials have failed to show benefit.

Hypothermia affects many pathways simultaneously, and thus may have more hope for benefit. The fact that two randomized controlled clinical trials demonstrated benefit of hypothermia in diverse groups of patients after cardiac arrest, even when induced relatively slowly, is encouraging, particularly since drug studies have been disappointing. This success should help the endeavors to proceed with clinical trials after other insults. By the same token, the overall negative results of the most recent trial of hypothermia after head injury should not discourage further studies in this area. We should learn lessons from this study regarding the potential for different outcomes with different subpopulations, the need for close attention to detail regarding protocolized patient care algorithms, and timing of hypothermia induction.

Even when positive studies are published, clinical research should not stop there. Additional studies are needed to improve the techniques for inducing hypothermia and to better define the optimal parameters, timing and depth. Ideally, we should develop key endpoints for resuscitation that help us decide when to cool, how deep, and when to rewarm. Patient selection should also be better defined.

Dissemination of research findings and development of clinical practice guidelines related to hypothermia become the next steps. It was impressive how quickly the American Heart Association and the International Liaison Committee on Resuscitation picked up on the studies showing benefit of hypothermia after cardiac arrest and published statements encouraging the use of hypothermia.

We've come a long way in laboratory and clinical research into the potential benefits of therapeutic hypothermia in a variety of situations. With this momentum, we should anticipate that hypothermia will be applied to even more disease states, perhaps ones that have not even been thought of yet. Rigorous research from the molecular level to the bedside needs to continue. Although hypothermia may not have the scientific appeal of the most recently described cytokine pathway, monoclonal antibody, or genetically engineered animal, funding agencies need to recognize the great potential for hypothermia to have impact upon complex disease states in acute care medicine. There is no doubt that hypothermia, when applied in the appropriate manner at the appropriate time, can help save lives.

Smart aortic arch catheter: Moving suspended animation from the laboratory to the field

Lyn Yaffe, MD; David Abbott, BS; Bruce Schulte, BS

The objective of the ongoing smart aortic arch catheter research and development program is to engineer "smart" catheter systems for enabling rapid vascular access and catheter placement, primarily within the aorta, for emergency hypothermia and suspended animation induction (1–6). The catheter systems are being designed and engineered to emphasize easy and rapid vascular access and catheter placement, in a compact and portable system, for use by civilian paramedics, military medics, or other trained first responders. The rapid vessel access devices will ultimately provide the necessary means for inducing suspended animation or preservative-resuscitative hypothermia, initially for use in hospital emergency rooms, then mobile intensive care unit ambulances or helicopters, and eventually for paramedics at the point of injury and in the field for combat medics.

The catheters will have the capability of delivering a large volume of cold (~2°C) saline flush into the aorta within several minutes. Immediate and targeted emergency hypothermia interventions may be able to isolate vital organs such as the heart, brain, spinal cord, and associated vasculatures and to impose a state of clinical preservation until transport can be provided to a facility for acute surgical care and delayed resuscitation. The smart catheter program encompasses stepwise design and development of smart catheter components for vascular imaging, trocar guidance and insertion, catheter placement, cold-flush connections, and monitoring of hypothermia by first responders in the field. Prototype catheter designs, aortic arch ultrasound imaging, three-dimensional position tracking of trocar and catheter tips, and system integration thus far have demonstrated the clear feasibility of rapidly accomplishing smart catheter placement for suspended animation induction. Specific catheter designs and guidance systems provide easy, rapid insertion and placement of catheters within the aorta and thereby facilitate the use of lifesaving emergency hypothermia for otherwise unresuscitable conditions. Initially, catheters are being designed and developed for 1) direct aortic insertion by the trauma surgeon in an emergency room via a thoracotomy site, 2) transthoracic aortic placement by a paramedic in the field using semiautomated ultrasound guidance and magnetic position tracking, and 3) aortic placement via femoral access by a paramedic in the field, initially by ultrasound guidance.

The successful design and development of a smart catheter and its guidance and placement system must provide easy-to-use, safe, and efficacious self-sealing, multiple-lumen, aortic balloon catheters, for both civilian and military trauma scenarios, with sufficient portability for field use at or near the point of injury. The aortic arch balloon catheter system will enable: 1) easy, semiautomated, foolproof insertion, sealing against the aortic wall via thoracotomy or transthoracic access, and guidance and confirmation of ascending, descending, or aortic arch placement; 2) rapid delivery of cold-flush solutions into the aorta from an external reservoir; 3) hypothermic preservation of the brain, heart, and spinal cord; 4) access for continued suspended animation and transition to cardiopulmonary bypass; and 5) access for optimal rewarming and transition to normothermic cardiac function.

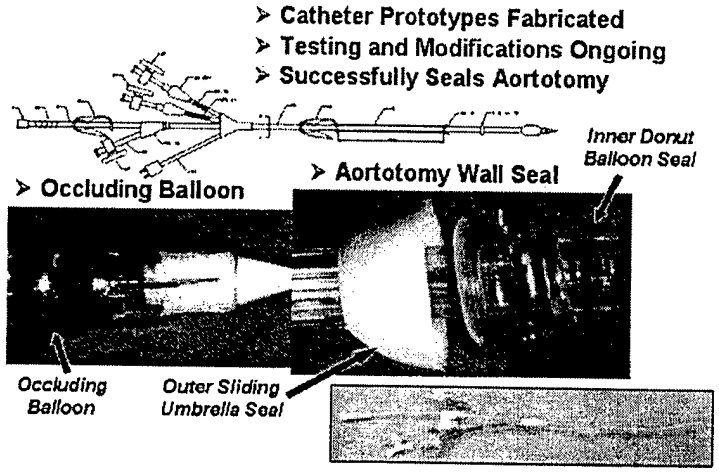

Figure 1. Thoracotomy catheter that has been designed and successfully tested in large animals. The catheter features include a mechanical seal for the aortotomy site consisting of an inner balloon seal and an outer sliding umbrella seal, which together compress the aortic wall to provide a tight seal. The aortic occluding balloon catheter provides aortic access for the delivery of cold-flush solutions.

From Alion Science and Technology, McLean, VA.
Key Words: suspended animation; hypothermia; delayed resuscitation; catheter; aorta; vessel access; portable ultrasound; magnetic position tracking
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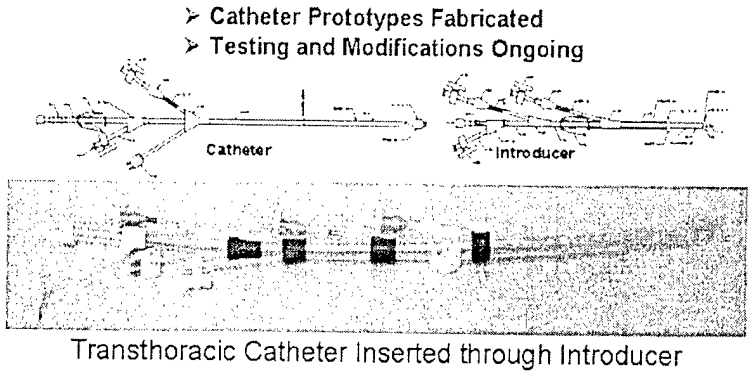

Figure 2. Similar to the thoracotomy catheter, the transthoracic catheter features include an introducer with a mechanical seal for the aortotomy site consisting of an inner balloon seal and an outer sliding umbrella balloon seal, which together compress the aortic wall to provide a tight seal. The transthoracic aortic occluding balloon catheter is then inserted through the introducer, as shown, to provide aortic access for cold-flush solutions.

Designs and Results

Catheters. Currently, the insertion of a catheter through the femoral artery into the aorta or directly into the aorta after left thoracotomy may be very quickly achieved. At trauma centers, surgeons are able to perform open chest heart massage in ≤1 min after confirming cardiac arrest and other options are exhausted. Similarly for closed chest scenarios, surgeons are able to cannulate the femoral vessels in humans within 3–4 mins during normovolemic cardiac arrest, while standard cardiopulmonary resuscitation is ongoing, well within the 4–5 mins before serious cerebral ischemic consequences. Ultimately, for exsanguinous no-flow, a direct femoral cutdown, left thoracotomy, or preferably, as proposed in this article, a smart catheter inserted transcutaneously is feasible and needed that quickly facilitates brain and heart cold flush. Rapid and easy vascular or aortic access is critical for the induction of emergency hypothermia and suspended animation at the point of injury to provide a brain and heart cold flush followed by continued fluid cooling. Even for experienced emergency room staff, identification and dissection of peripheral femoral vessels for insertion of arterial and venous catheters may take at least 15 mins in a pulseless patient, or even in a patient with low blood pressure. Typically, this emergency room intervention may be necessary to save the life of a victim using cardiopulmonary bypass for cardiopulmonary-cerebral resuscitation. The smart aortic arch catheter system is being designed for a fast, easy, and safe method to cannulate the aorta for targeted organ cooling. Catheter design and development has been ongoing and will continue by using approved materials for large-diameter balloon catheter and cannula designs. Both single and coaxial catheter designs have been explored. Simulation models have been constructed to produce breadboard configurations of the catheter and guidance systems working within closed-loop models of the aorta and phantoms for initial testing. Catheters and introducers have been fabricated with the assistance of Catheters and Disposables Technology (Minneapolis, MN).

For immediate interventional access, the smart catheter has been designed so that rapid access through the chest wall, from a parasternal approach, may be accomplished with subsequent direct insertion into the aortic arch. On insertion through the aortic wall, the catheter design includes the ability to provide a tight-sealing mechanism at the point of entry through the aortic wall to prevent fluid leaking from the aorta. Balloon-cuff concepts have been conceptualized and designed that may be adapted for this aortic catheter. An aortic arch catheter has been designed so that safe, easy, and rapid access to the aorta may be achieved through the chest wall from a transthoracic, percutaneous, or thoracotomy approach. Prototype, donut-shaped, balloon-cuff concepts have been designed and are used for this aortic catheter as one potential approach (Figs. 1 and 2). These designs maintain tight, leak-proof pressure on each side of the aortic wall. Ultimately, after delayed resuscitation, the point of aortic access would have to be closed surgically. Alternatively, access could be via the femoral artery, with a long catheter being extended to the appropriate position within the thoracic aorta or arch. The benefits of this approach include less potential damage to the aorta and the ability to have a lower placement of the catheter for increased cooling to the lower portions of the spinal cord and abdominal organs in the event of prolonged suspended animation, assuming the availability of adequate volumes of cold fluids.

Guidance and Placement System. For placement of the transthoracic introducer and catheter, portable ultrasound devices have demonstrated the ability to image the ascending aorta, the aortic arch, and the proximal descending aorta. Key images depend on suprasternal notch ultrasound probe placement. The ability to couple the image with access guidance and positioning of an introducer and catheter against the aortic wall was also demonstrated to be feasible using a bench-top prototype and ultrasound phantoms. Studies of the catheter placement challenge revealed the requirement for a location and placement capability based on ultrasound imaging integrated with three-dimensional position tracking. The initial details for integration of real-time ultrasound aortic arch images together with the trocar/catheter tip three-dimensional position have been developed. A software approach to provide this capability has been developed using ultrasound image and position data integration technology available through Cedara Software Corporation (Mississauga, Canada).

The smart catheter guidance, placement, and positioning system has been designed at this point to utilize three-dimensional ultrasound technology based on Cedara Software Corporation's Volume Explorer Framework technology. Position tracking has been successfully demonstrated using Ascension Technology's (Burlington, VT) miniBird magnetic tracking system. Although the smart catheter ultrasound system was initially configured to work with the Terason 2000 laptop-based portable ultrasound system (Terason, Burlington, MA), the current placement, positioning, and tracking system may be integrated with other portable or stationary ultrasound devices. The working prototype system is shown in Figure 3.

At this point in development, the demonstration prototype for the integrated

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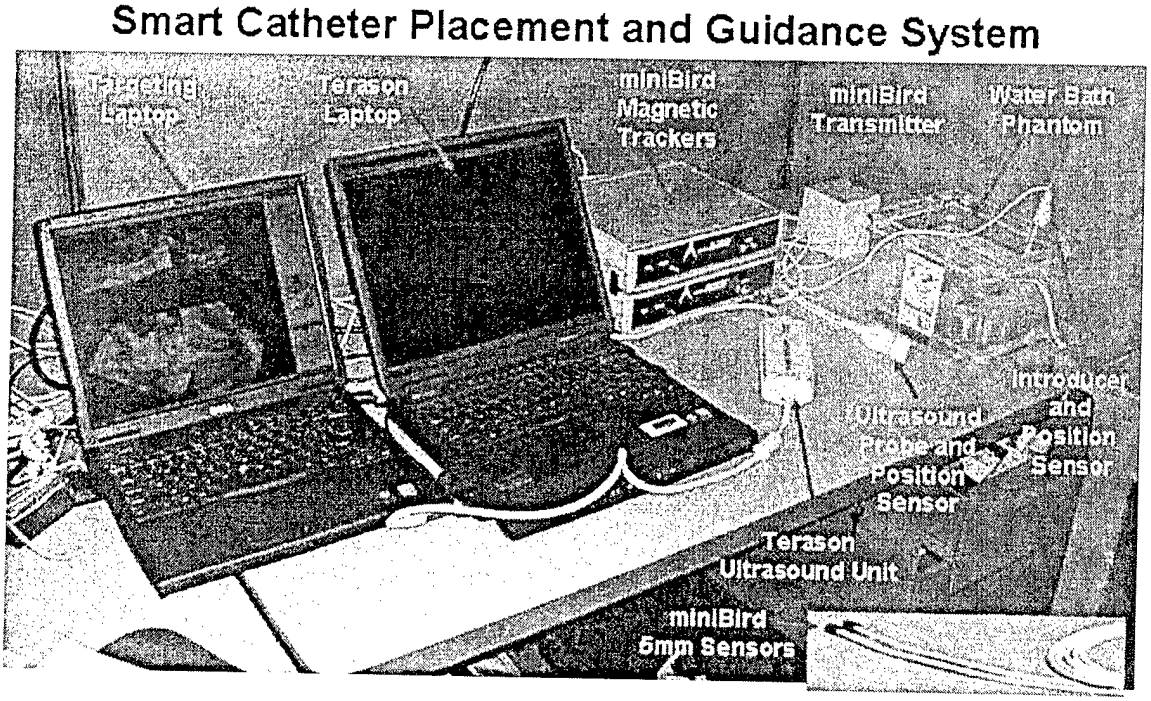

Figure 3. Current smart catheter guidance and placement demonstration prototype system, including the Terason 2000 portable ultrasound unit and ultrasound probe; the Ascension miniBird magnetic trackers, transmitter, and 5-mm position sensors; and ultrasound laptop and targeting laptop. Ultimately, all software and necessary interfaces will be integrated onto a single laptop or LCD for display.

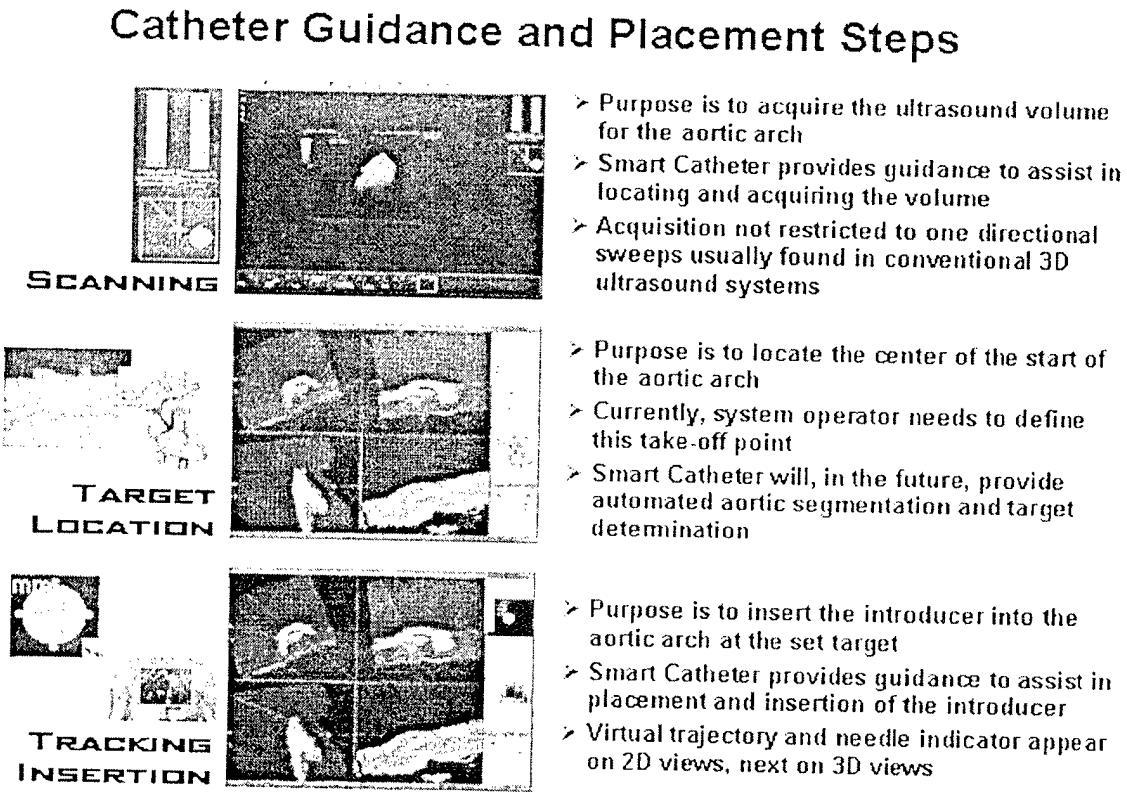

Figure 4. Three primary steps in the ultrasound-based guidance and placement system for the smart catheter into the aorta via a transthoracic approach include: scanning, target location, and tracking insertion. Ultimately, scanning will be continuous and in real time, target location will be fully automated based on aortic arch segmentation as is currently performed, and target insertion will be tracked in real time using a three-dimensional (*3D*) view and virtual trajectory for the introducer/catheter. *2D*, two dimensional.

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Moving suspended animation from the laboratory to the field is now fully feasible and achievable in the near future.

guidance and positioning system includes: 1) the Terason laptop ultrasound system and ultrasound probe; 2) the Ascension miniBird magnetic tracker, transmitter, and 5-mm position sensors; 3) Cedara smart catheter–specific software; and 4) smart catheter introducer and catheter. The smart catheter software system divides the catheter placement and positioning procedures into three phases, including acquisition, targeting, and insertion. These functions are detailed in Figure 4, including computer interfaces displayed during the procedures. The design includes automatic target determination of the aortic arch point for catheter insertion. The system currently provides two user interfaces, one relatively complex interface displayed on the laptop and a second simplified interface displayed on a small LCD. Ultimately, when adequate resolution is available, a heads-up display will be employed to provide the user with catheter placement and positioning information.

The current system prototype seeks to incorporate a semiautomated to fully automated aortic/vascular target identification capability with image visualization enhancements. This is being accomplished through automated segmentation of the target of aortic ultrasound image followed by automated location of the catheter insertion target point on the wall of the ascending aorta. Ongoing work will also include the display of the introducer's trajectory in a three-dimensional view. Ultimately, for the transthoracic approach, a smart catheter "bib" concept, as shown in Figure 5, has been designed for stepwise development and will be prototyped. This smart catheter system bib will be placed on the chest and positioned to specific anatomic landmarks to aid in the positioning of the ultrasound probe, the placement of the magnetic positioning reference point, and the entry point for the catheter introducer.

Conclusions

The smart aortic arch catheter project goal is to meet the development challenge for field induction of suspended animation. Catheter seals have been successfully developed and tested, and the feasibility of an ultrasound based guidance, placement, and tracking system for the smart catheter has been demonstrated using the Terason laptop ultrasound system integrated with Ascension's miniBird magnetic position trackers and Cedara's three-dimensional ultrasound imaging and navigation software specifically adapted for the smart catheter system. Based on these initial design developments and prototype demonstrations, moving suspended animation from the laboratory to the field is now fully feasible and achievable in the near future.

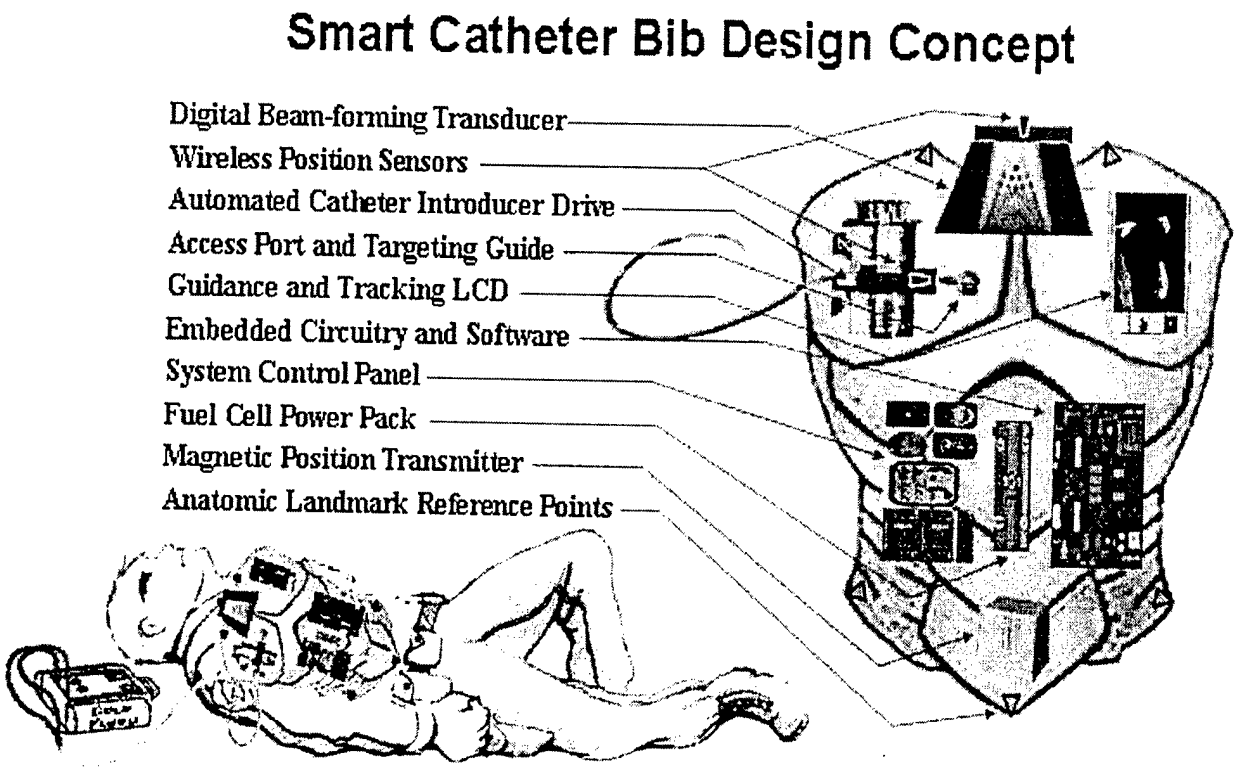

Figure 5. Smart catheter "bib" design concept that has been developed and will be prototyped in a stepwise fashion as key technologies become available. Initially, the bib will include only the ultrasound transducer, access port and targeting guide, guidance and tracking LCD, magnetic position transmitter, and anatomic landmark reference points.

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Therapeutic Hypothermia in Resuscitation: The Safar Vision

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Much has been written about the incredible life of Peter Safar, 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 Memorial Library, 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 felt were critical about this area of study, namely, accurate and consistent terminology concerning the depth of hypothermia and the situation surrounding its use. He felt that hypothermia should be categorized into mild (34-36°C), moderate (27-33°C), deep (15-26°C), profound (10-14°C) and ultra-profound (<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 1) 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 statements above, these would be resuscitative rather than protective or preservative therapies.

Peter Safar and resuscitative hypothermia in the 1960-1980s

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 re-instate it, if a secondary rise in intracranial hypertension occurred during re-warming. 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 of 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 ILCOR and the American Heart Association! The figure outlining Peter's ABCs from 1964 and the use of hypothermia is shown in figure 1.

In the laboratory, one of the earliest uses of therapeutic hypothermia in the collected works of Dr. Safar is an interesting report by Gisvold et al in 1984 (13) 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 7/10 vs 2/9 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 (14), 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 I am sure you are all 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 VF cardiopulmonary arrest in humans (15-17), and as described above, this has now been recommended for clinical use by the key endorsing societies worldwide (18,19).

On the day that the ILCOR and AHA guidelines were published, endorsing mild hypothermia after VF cardiac arrest in adults, I 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, ICU care, and that accurately modeled the clinical condition--Peter Safar believed that randomized clinical trials were only needed to show feasibility. Peter Safar was not convinced that 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, that 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, that 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 ICP monitoring and control. Peter's group published two such papers in 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 ACLS 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 felt were 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

Last year, Drs. Kochanek and Safar, wrote an editorial on the use of therapeutic hypothermia in traumatic brain injury that was published in JAMA (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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Figure Legend

Figure 1. 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 post-resuscitation induction of hypothermia (see arrow) in victims of cardiopulmonary arrest. This concept was recently endorsed into standard of care (see text for details).

Figure 1.

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HEART – LUNG RESUSCITATION

I FIRST AID: OXYGENATE THE BRAIN IMMEDIATELY

[redacted]

Airway – *TILT HEAD BACK*

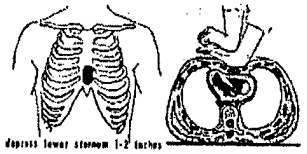
[redacted]

Breathe – *INFLATE LUNGS 3-5 TIMES, MAINTAIN HEAD TILT*

MOUTH-TO-MOUTH, MOUTH-TO-NOSE, mouth-to-adjunct, bag-mask

[redacted] LUNG INFLATIONS

Circulate – *COMPRESS HEART ONCE A SECOND. ALTERNATE 2-3 LUNG INFLATIONS WITH 15 STERNAL COMPRESSIONS UNTIL SPONTANEOUS PULSE RETURNS.*



for physicians only

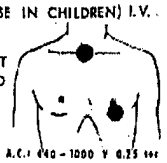
II START SPONTANEOUS CIRCULATION

Drugs – *EPINEPHRINE:* 1.0 mg (1.0 CC OF 1:1000) I.V. OR 0.5 mg INTRACARDIAC. REPEAT LARGER DOSE IF NECESSARY

SODIUM BICARBONATE: APPROXIMATELY 3.75 G/50 CC (1/2 DOSE IN CHILDREN) I.V. REPEAT EVERY 5 MINUTES IF NECESSARY

E. K. G. – • *FIBRILLATION:* EXTERNAL ELECTRIC DEFIBRILLATION. REPEAT SHOCK EVERY 1-3 MINUTES UNTIL FIBRILLATION REVERSED

• *IF ASYSTOLE OR WEAK BEATS:* EPINEPHRINE OR CALCIUM I.V.



Fluids – *I.V. PLASMA, DEXTRAN, SALINE*

Do not interrupt cardiac compressions and ventilation. Tracheal intubation only when necessary.

AFTER RETURN OF SPONTANEOUS CIRCULATION USE VASOPRESSORS AS NEEDED, e.g. NOREPINEPHRINE (Levophed) I.V. DRIP

III SUPPORT RECOVERY (physician-specialist)

Gauge *EVALUATE AND TREAT CAUSE OF ARREST*

Hypothermia *START WITHIN 30 MINUTES IF NO SIGN OF CNS RECOVERY*

Intensive Care *SUPPORT VENTILATION:* TRACHEOTOMY, PROLONGED CONTROLLED VENTILATION, GASTRIC TUBE AS NECESSARY

SUPPORT CIRCULATION
CONTROL CONVULSIONS
MONITOR

Figure 1. The A, B, C of emergency resuscitation. These instructions have been arranged for the front and back of a billfold card or for a poster which may be obtained from the Pennsylvania Heart Association or the Pennsylvania Department of Health, Harrisburg.

Suspended animation for resuscitation from exsanguinating hemorrhage

Samuel A. Tisherman, MD, FACS, FCCM

Cardiopulmonary resuscitation with artificial respirations and external chest compressions have enabled initiation of life-saving interventions by lay persons and medical personnel, anywhere, anytime (1, 2). During normovolemic cardiac arrest, external chest compressions have a physiologic basis for efficacy. Open-chest cardiopulmonary resuscitation is physiologically superior (3, 4), although clinical studies have been inconclusive (5, 6). During exsanguination cardiac arrest, however, external chest compressions are not physiologically effective. Clinically, trauma victims who suffer cardiac arrest from exsanguination have almost no chance for intact survival, even after emergency department thoracotomy and open-chest cardiopulmonary resuscitation (7). Rapid attempts at fluid resuscitation and hemostasis lose the race against the tolerance limits for complete ischemia of 5 mins for the brain (8) and about 20 mins for the heart (8, 9).

The majority of soldiers killed in action in Vietnam without brain trauma had penetrating truncal injuries (10). They exsanguinated internally within a few minutes. Such casualties are still considered unresuscitable, although many have technically repairable injuries on autopsy. In 1984, Bellamy, a U.S. Army surgeon, and Safar met and pondered recent military casualty data and agreed that a novel approach was necessary (i.e., suspended animation). Suspended animation is defined as treatment to preserve the viability of the entire organism during ischemia, such as no flow (cardiac arrest) or low flow (shock). The goal is to induce suspended animation with hypothermia, drugs, and fluids. If instantaneous preservation of the viability of brain and organism could be achieved, one could buy time for transport and major hemostasis during clinical death, to be followed by restoration of blood volume and resuscitation, using cardiopulmonary bypass (CPB).

Suspended Animation Animal Outcome Studies

Since the late 1980s, researchers at the Safar Center for Resuscitation Research of the University of Pittsburgh have been engaged in systematic outcome studies in dogs for the development of suspended animation (11). In the initial series of experiments, Tisherman et al. (12–16) and Capone et al. (17) explored hypothermic preservation at tympanic membrane temperatures (Tty) of 15°C (deep hypothermia) or 5–7°C (profound hypothermia) after 30 mins of hemorrhagic shock at a mean arterial pressure 40 mm Hg. Suspended animation was induced by closed-chest CPB with hemodilution by crystalloids. After circulatory arrest of 60–120 mins, CPB was used for reperfusion and rewarming. Tty of 34°C was maintained for 12 hrs, controlled ventilation to 24 hrs, and intensive care to 72 hrs. End points included functional outcome in terms of overall performance categories (OPC 1 = normal, 2 = moderate disability, 3 = severe disability, 4 = coma, 5 = death) and neurologic deficit scores (0–10% = normal, 100% = brain death). Standardized necropsy included perfusion fixation of the brain and histopathologic damage scoring of 19 brain regions.

Profound cerebral hypothermia (Tty 5–7°C) induced at the beginning of exsanguination cardiac arrest improved neurologic outcome compared with that with deep hypothermia (15°C) (12, 13). The University of Wisconsin organ-preservation solution in the microcirculation during circulatory arrest did not add cerebral benefit over that achieved with standard plasma substitutes (14). These initial studies had been performed with standard CPB systems and systemic anticoagulation, which would be contraindicated after trauma. In a separate study, use of a heparin-bonded CPB circuit without systemic anticoagulation did not offset the beneficial effect of profound hypothermia (15). The optimal hematocrit during no flow under profound hypothermia is unclear (16).

The last study of this series was the most important (17). Sixty minutes of normothermic hemorrhagic shock was followed by rapid cooling using CPB and 60 mins of cardiac arrest at Tty of <10°C. Complete functional recovery was achieved, and, documented for the first time, the brains were histologically normal.

Clinically, CPB cannot be initiated within the critical 5 mins of recognizable cardiac arrest. A different approach is needed. Rapid placement of an aortic catheter could allow targeting of the brain and heart with a flush of cold fluid. A double-balloon catheter could allow differential flushing of the heart and brain while assisting with hemostasis.

Hypothermia Strategies. Subsequent studies have utilized a single-balloon catheter (Cardeon, Saratoga, CA) for flushing the aorta with isotonic saline, at a rate of 1–2 L/min, starting at 2 mins of no flow. Catheter design seemed to influence outcome; with the opening at the tip, the straight flush resulted in better outcome than that achieved using a catheter with the tip closed and the flush

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Key Words: hemorrhage; cardiac arrest; suspended animation; induced hypothermia; delayed resuscitation; dog

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through multiple lateral openings. This flush at 0–4°C could lower Tty by 3°C per minute. The outcome model used included rapid, controlled hemorrhage from aorta and vena cava over 5 mins to cardiac arrest (which was ensured by inducing ventricular fibrillation), and aortic cold saline flush started at 2 mins of arrest, with drainage via the vena cava catheter (Fig. 1). The period of circulatory arrest was varied from 15 to 120 mins (18–21) under preservative Tty levels decreasing from 34°C to 6–10°C. Reperfusion and rewarming were accomplished with closed-chest CPB, primed with Ringer's and dextra 40 in saline.

With cardiac arrest of 15 mins of no flow, saline flush volume of 25 mL/kg (a clinically feasible, portable volume) at 24°C (room temperature) achieved Tty of 36°C and, at 72 hrs, functional normality with histologic damage, whereas the same protocol with saline at 0–4°C achieved Tty of 34°C, and two of six brains were histologically normal (18). With cardiac arrest of 20 mins (19), aortic arch flush rapidly lowered Tty to 34°C and achieved survival to 72 hrs with functional normality and minimal histologic brain damage.

For cardiac arrest of 15 or 20 mins, the catheter balloon was inflated in the descending thoracic aorta for aortic arch perfusion. With longer arrest times, ischemia of the spinal cord, gut, and liver became apparent. Hind leg weakness was observed. The authors found that the most reliable flush method might be the simplest: flush via a large-bore cannula in the femoral or iliac artery to include the entire organism. For circulatory arrest periods of >30 mins, very large volumes of cold flush solution would be required. For example, for a 70-kg adult human, this would translate to 7 L of iced saline, which is feasible for ambulances or emergency departments but not for field medics. For cardiac arrest of 30 mins (20), the flush volume of saline at 0–4°C was increased to 100 mL/kg via the femoral artery to achieve a Tty of 28°C; this achieved functionally normal brains (in some dogs, even histologically normal brains).

Cooling to a Tty of 20°C, 15°C, or 10°C preserved the brain and organism to achieve intact survival (OPC 1) after 60, 90, and in some dogs, even 120 mins of no flow (21) (Fig. 2). All six dogs with cardiac arrest of 90 mins and a Tty of 10°C were functionally normal, with no or minimal histopathologic damage. One dog, after cardiac arrest of 90 mins, one after cardiac arrest of 60 mins, and one normal dog without cardiac arrest had normal cognitive function based on a battery of tests 3 months later. Of concern clinically, however, was that delaying the start of flush to 8 mins of arrest in the 30-min cardiac arrest model negated the preservation achieved with flush starting at cardiac arrest of 2 or 5 mins (22).

To achieve a Tty of 10°C in an adult human with the flush strategy above would require enormous amounts of ice-cold fluid, which would be impractical in the hospital and impossible prehospital. Another approach would be to start with a single, small flush to achieve mild cerebral hypothermia and then to recirculate diluted venous drainage blood, with or without an oxygenator, through a cooler-heat exchanger, to reduce Tty to profound hypothermia (11). Nozari et al. (unpublished observations) found that the recirculation strategy enabled intact survival with full neurologic recovery after 90 mins of cardiac arrest at least as reliably as the initially used one-way flush but with one tenth the volume.

Pharmacologic Strategies. Pharmacologic approaches with novel drugs and solutions would be advantageous for induction of suspended animation by synergizing with hypothermia and, perhaps, decreasing the volume of flush that is needed (23–27). Even if the aorta could be accessed and cold flush initiated within the first 5 mins of normothermic no flow and a drainage catheter inserted into the vena cava, the 10- to 20-L cold solution (0–4°C) estimated to be required for a 70-kg adult human to lower Tty to 10°C (and core temperature to about 20°C) would not be feasible in the field. Although difficult in the ambulance or hospital emergency department, such large amounts of solutions could be stored in a refrigerator.

The same Pittsburgh team conducted

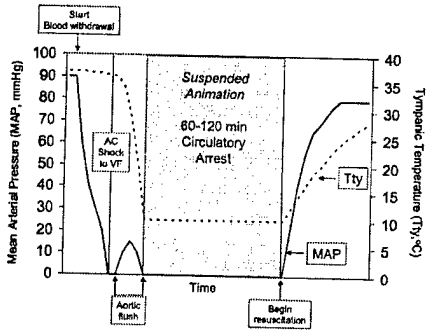

Figure 1. Model of exsanguination cardiac arrest, preservation via aortic flush, circulatory arrest for 15–120 mins, and resuscitation using cardiopulmonary bypass. *AC*, alternating current; *VF*, ventricular fibrillation.

	Overall Performance Category				
Arrest time	**1 Normal**	**2 Moderate Disability**	**3 Severe Disability**	**4 Coma**	**5 Dead**
15 min Tty 34°C	●●● ●●●	●			
20 min Tty 34°C	●●●●	●	●		
30 min Tty 28°C	●●●●	●●●●●*			
60 min Tty 10°C	●●●●				
90 min Tty 10°C	●●● ●●				
120 min Tty 10°C	●●	●	●	●	

Figure 2. Overall performance categories after exsanguination cardiac arrest of 15–120 mins with preservation via hypothermic aortic arch flush. *Tty*, tympanic membrane temperature. *Hind leg weakness.

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the first systematic exploration of pharmacologic cerebral preservation potentials of 14 different drugs in 73 dogs (Fig. 3). The model used was 20 mins of exsanguination cardiac arrest with a potentially portable volume of flush solution (25 mL/kg) at ambient temperature, which achieved only mild cerebral hypothermia. In controls, saline flush started at 2 mins of cardiac arrest achieved survival with brain damage (19). In groups of three to six experiments per drug, various doses were flushed into the aortic arch via a balloon catheter, and in some experiments, additional intravenous medication was given during reperfusion with CPB. The drugs were selected and grouped according to six mechanistic strategies (26): 1) delaying energy failure, 2) protecting membrane integrity, 3) preventing structural degradation, 4) regulating protein synthesis, 5) preventing reoxygenation injury, and 6) preserving mitochondria. Selection of drugs and doses was influenced by published beneficial results (mostly in rodents) and guidance by expert consultants. Pharmacologic properties that would allow blood–brain barrier penetration were also considered. The goal was to identify a breakthrough effect (i.e., the majority of dogs in the miniseries to achieve OPC 1 at 72 hrs). None of the 14 drug treatments resulted in a breakthrough effect (23–25) (Fig. 3). Only an occasional dog achieved OPC 1 (but with some histologic damage) after thiopental plus phenytoin or glucose plus insulin. The antioxidant tempol, however, gave a suggestion of benefit (26). Tempol is available and inexpensive and penetrates the blood–brain barrier, but it is not approved by the U.S. Food and Drug Administration. All eight dogs that received 150–300 mg/kg tempol in the aortic arch flush at the start of cardiac arrest achieved OPC 1 or 2 (good outcome), whereas none of the eight control animals achieved good outcome (p = .03). Of concern, however, is that histologic damage was not significantly mitigated by tempol. Various explanations for this have been discussed (26). The only negative side effect of tempol, minimal transient methemoglobinemia, was clinically not significant.

One may criticize this exploratory approach because it is not possible to rule out some benefit possibly revealed by larger sample sizes and randomized concurrent controls. The cost and time involvement needed to conduct such studies in large animals would be prohibitive.

Solutions. In the studies described above, isotonic saline solution was used for flush and dextran 40/Ringer's solution for reperfusion via CPB. Solutions designed specifically for profound hypothermia have been explored (27–30). Using the 30-min cardiac arrest model with Tty of 28°C (20), polynitroxylated albumin plus tempol (Synzyme, Irvine, CA) slightly improved neurologic deficit scores and histopathologic damage scores compared with saline, whereas 5% or 25% albumin did not (27). Using the 120-min cardiac arrest model with Tty of 10°C (21), Normosol (a pH-normalized Ringer's solution) was used for cold flush and "Unisol" (two solutions: an "intracellular fluid" with composition designed for stasis and an "extracellular fluid" designed for reperfusion), designed by Taylor et al. (29, 30) (Organ Recovery Systems, Charleston, SC), was used. With these "optimized" solutions, OPC 1 and only minimal to moderate histologic damage was achieved in five of six dogs. Additional studies to optimize the solutions are needed.

Trauma. Exsanguinating hemorrhage in trauma patients does not occur without significant tissue trauma. Nozari et al. (31) explored the above suspended animation approach with trauma added in the form of thoracotomy, laparotomy, and splenic transection. Splenectomy was performed during arrest. The coagulopathy due to hemodilution, hypothermia, and ischemia was greatly worsened by trauma, even with use of fresh donor blood during resuscitation. Nevertheless, exsanguination cardiac arrest of 60 mins plus severe trauma could be reversed to intact survival, but multiple organ failure occurred in several animals. The encouraging finding was that brain histopathology was normal. This suggests that, with prolonged intensive care and rehabilita-

	Overall Performance Category				
Drug	1 Normal	2 Moderate Disability	3 Severe Disability	4 Coma	5 Dead
Control	•	•••	••••••	••••	
Adenosine			••		
Thiopental	••		••	•••••	
Thiopental Phenytoin	•		••	••••	
Fructose Biphosphate			••	•••	
MK801			••	•••	
YM872			•	••	
Nimodipine			•	•	
Diltiazem			•	•	
Lidocaine			••	•	
Insulin Glucose	•		••	•	
W7			•	•	
Cycloheximide			•••		
Tempol	•••••	•••	•	•	
Cyclosporine A			•	•	

Figure 3. Overall performance categories after exsanguination cardiac arrest of 20 mins with preservation via aortic arch flush and novel pharmacologic potentials.

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tion (as could be utilized clinically), long-term intact survival would be expected.

Plasma exchange can decrease the microangiopathy seen in some patients with sepsis and multiple organ system dysfunction. Nozari et al. (unpublished observations), found that plasma exchange not only decreased the organ system dysfunction seen after trauma and suspended animation, but may also have improved neurologic outcomes.

Other Approaches. In addition to the Pittsburgh group, two other groups have explored the concept of suspended animation, although from somewhat different perspectives. Taylor et al. (29) and Bailes et al. (32) were interested in developing a method for protecting the brain during otherwise infeasible neurosurgical procedures. They showed that asanguinous low-flow perfusion of the organism with CPB of >3 hrs, under ultraprofound hypothermia (<5°C), could be survived with normal neurologic function. Specialized fluids were used during cooling, stasis, and resuscitation/rewarming. Long periods of total circulatory arrest were not explored, however. From a clinical perspective, in the exsanguinated trauma patient, intermittent low flow during suspended animation may be helpful for finding bleeding sites and, perhaps, improving preservation, although this remains to be explored.

Rhee et al. (33) have also explored suspended animation in a clinically relevant exsanguination model in pigs. Using readily available equipment, they induced profound hypothermia by aortic flush, both proximally and distally, via a thoracotomy and direct aortic cannulation. Repair of the aortotomy was accomplished during no flow. After total circulatory arrest of up to 40 mins, normal neurologic recovery could be achieved (33). The same group under Alam et al. (34) found normal cognitive function after exsanguinating hemorrhage from a vessel injury and prolonged asanguinous low flow (by CPB) at 10°C.

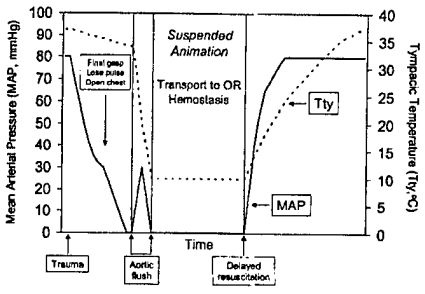

Figure 4. Possible clinical scenario for suspended animation in trauma victims with exsanguination cardiac arrest. As the patient becomes profoundly hypotensive, a last gasp and loss of pulse would be indications for rapid thoracotomy. If cardiac arrest is not rapidly reversed, the aorta can be cannulated and suspended animation can be induced via hypothermic flush to buy time for transportation to the operating room for control of major bleeding and delayed resuscitation using cardiopulmonary bypass. *OR*, operating room.

Cryobiology. Attempts at further extending the so far maximal duration of reversible cardiac arrest of 90–120 mins with hypothermia alone would take suspended animation research into cryobiology. Could one further extend the preservation time by going below 5°C? Profound hypothermia (5–15°C) has been shown in itself not to damage brain tissue (34, 35), but going below 5°C can cause denaturation of proteins and permanent cell damage, irrespective of the damage caused by ischemic anoxia (36). Ultraprofound cerebral hypothermia (<5°C) with special acellular synthetic solutions as blood substitutes, however, has been shown to preserve viability of rat hippocampus (36) and to achieve good outcome in dogs with low-flow CPB (32).

Future Directions

Potential Clinical Trials of Suspended Animation. For traumatic exsanguination cardiac arrest, clinical feasibility trials for the initiation of suspended animation are indicated, at least in emergency departments of major trauma centers (Fig. 4). Later, when appropriate devices become available for initiation of suspended animation outside the hospital, such feasibility trials could become part of emergency medical services research.

During severe hemorrhage without anesthesia, patients become unconscious when mean perfusion pressure decreases to <40 mm Hg, which is also about the point at which pulses are not palpable in large arteries. When apnea then ensues and pulsations are no longer palpable, one can assume cardiac arrest. Frequently, if the patient has had signs of life not long before this, emergency department thoracotomy is performed, particularly for victims of penetrating trauma. If a pulse cannot be rapidly restored, this could be a signal for accessing the aorta and administering the cold flush (i.e., inducing suspended animation). Drainage could be achieved rapidly by opening the right atrial appendage. The other potential approach for access would be cannulation of the femoral artery and vein via cutdown.

Given that the mortality rate for trauma patients who become pulseless from exsanguination and undergo emergency department thoracotomy is near 100% (7), clinical trials cannot be randomized. A reasonable approach would be to induce suspended animation after a brief period of unsuccessful resuscitation attempts, including thoracotomy and open-chest cardiopulmonary resuscitation. As clinical studies begin and experience grows, there are important questions that should be addressed. Who may benefit from expensive and labor-intensive suspended animation? What logistic problems need to be overcome to initiate suspended animation?

Device Development. To take suspended animation outside the hospital, devices for implementation will need to be developed. These devices should include a "smart catheter" to facilitate rapid percutaneous access to the aorta and vena cava, without thoracotomy and a miniaturized cooling-pumping device. Ideally, for portability in the field, the maximally miniaturized cooling source with pump could be developed for dual use: 1) for venovenous extracorporeal cooling for rapid induction of mild systemic or cerebral hypothermia in conditions with circulation (after normovolemic cardiac arrest, hemorrhagic shock, traumatic brain injury, stroke) and 2) for profound hypothermic aortic flush in conditions without circulation (i.e., suspended animation for cardiac arrest).

Other Applications. The main goal of suspended animation development has been to save some of the presently unresuscitable victims of traumatic cardiac arrest. It is worth keeping in mind that the suspended animation approach could also be useful when surgeons and anesthesiologists are unexpectedly losing ground with unmanageable hemorrhage during various surgical operations and for performing otherwise infeasible cardiovascular or neurosurgical procedures.

Summary

In dogs, isotonic saline at 0–4°C, flushed into the aorta at a rate of 1–2 L/min, with drainage of the vena cava, can achieve deep to profound hypothermia of vital organs at a cooling rate of up to 3°C per minute. This achieves preservation of viability of the organism during predictable durations of no flow: cardiac

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arrest of 15–20 mins at Tty of 30–35°C, cardiac arrest of 30 mins at Tty of 25°C, cardiac arrest of 60 mins at Tty of 15°C, and cardiac arrest of 90 mins at Tty of 10°C. So far, pharmacologic approaches have not resulted in any breakthrough effect on outcome above that achieved with hypothermia, except perhaps the antioxidant tempol. Additional studies of novel drugs and, perhaps, combination therapies remain warranted. The optimal fluids to have in the circulation during circulatory arrest and reperfusions need to be determined. As laboratory studies to optimize suspended animation proceed, clinical trials should be initiated. In addition, devices should be developed to facilitate induction of suspended animation, eventually in the field.

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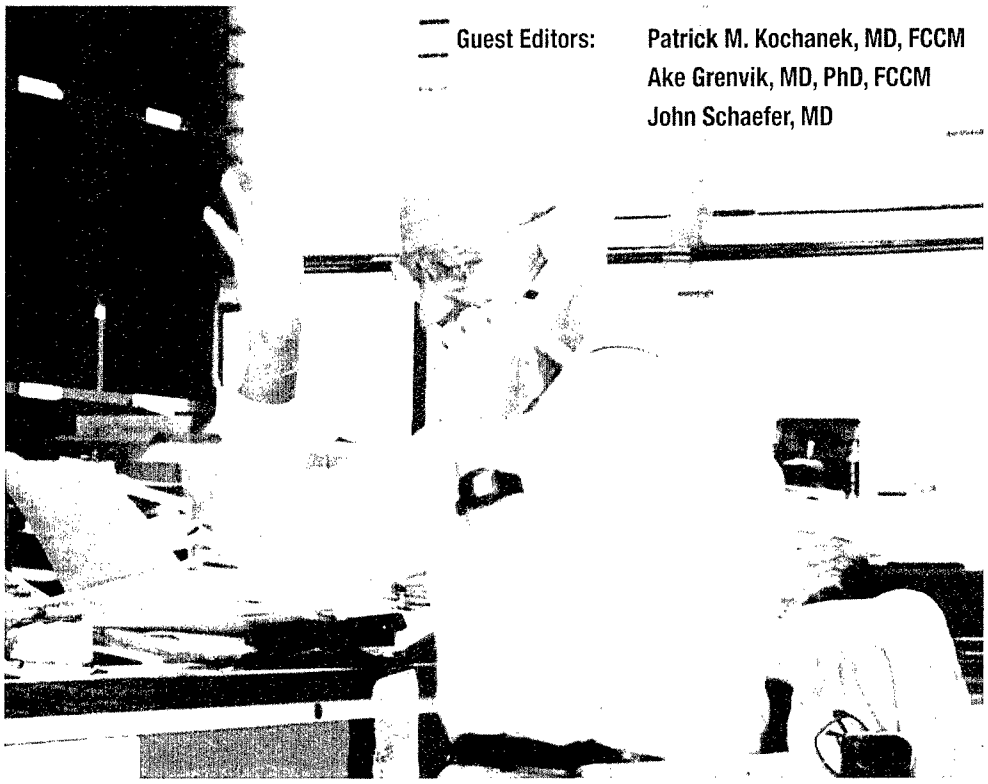

Guest Editors: Patrick M. Kochanek, MD, FCCM
Ake Grenvik, MD, PhD, FCCM
John Schaefer, MD

A Celebration of the Life of

Peter J. Safar, MD

and Proceedings of the
Second Annual Safar Symposium

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AKE GRENVIK, MD, PHD, FCCM
JOHN SCHAEFER, MD

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A Celebration of the Life of

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A special supplement for a very special man: A celebration of the life of Peter J. Safar, MD

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This special supplement to *Critical Care Medicine* honors Peter J. Safar, MD—a very special man in the fields of critical care, anesthesiology, emergency medicine, and disaster reanimatology, the collective fields that he called acute medicine. This supplement celebrates his incredible life through a number of articles, testimonials, memorials, letters, and historical photographs. We took great care to try to convey to you the remarkable scope of the creative genius of Peter Safar. The supplement also includes quotes from many colleagues and friends of Peter. Dr. Safar positively influenced an amazing number of people—and the stories that they tell provide us a glimpse of the genius, strength, passion, elegance, and humanism that he imparted. In addition, this supplement includes, in part, proceedings of the Second Annual Safar Symposium, which was held on October 30, 2003, at the University of Pittsburgh School of Medicine—part of what has become "Peter Safar Day" each year at the University of Pittsburgh.

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We are honored to be able to assemble this tribute to our colleague, mentor, and dear friend.

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The incredible career of Peter J. Safar, MD: The Michelangelo of acute medicine

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Peter Safar was born April 12, 1924, in Vienna, Austria. He graduated from Piaristen Gymnasium in Vienna in 1942 at the height of the Second World War. After this, he was drafted into the German army by the Nazis, who were occupying Austria at the time. Threatened by deployment to the war zone against Russia, through manipulative ingenuity, Peter succeeded in acting up a mild eczema to a degree that made him unsuitable to serve on the war front. Thus, he had the opportunity to become a medical student at the University of Vienna in 1943. He graduated 5 yrs later. Choosing education in medicine was a natural decision for Peter, the son of two prominent Viennese physicians (1).

Peter Safar moved to the United States for further training. He first completed a year of surgical internship at Yale University and returned to Vienna during the summer of 1950. This is when he proposed to Eva Kyzivat, who became his lifetime partner and tireless supporter throughout their 53 yrs of eventful marriage. Peter started his anesthesia residency in 1950 in Robert Dripp's department at the Hospital of the University of Pennsylvania in Philadelphia. With James Eckenhoff, LeRoy VanDam, and John Severinghaus in Dripp's department, Peter had excellent influence by these prominent anesthesiologists in all areas of academic anesthesiology, including research. In addition, the renowned Julius Comroe served as chairman of the University of Pennsylvania Department of Physiology at that time.

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After his anesthesia residency, Peter and Eva were obliged by law to leave the United States for a couple of years to be permitted to apply for immigration status on return to the United States. They chose to go to Lima, Peru, where Peter started an anesthesia department at the National Oncology Hospital. In February 1954, he joined the anesthesia department at Johns Hopkins Hospital, and the next year moved to Baltimore City Hospital as Chief of Anesthesia. He served in this capacity for 6 yrs. It was here that Peter performed his daring studies on mouth-to-mouth ventilation of unconscious, paralyzed volunteers, mostly physician residents and nurses, who all trusted him to perform these risky investigations without any untoward consequences. These studies convincingly demonstrated the overwhelming superiority of mouth-to-mouth ventilation over the current arm-lift/chest-pressure techniques, which he showed not to move any air in and out of the lungs at all (2, 3).

Peter learned about the efficiency of exhaled-air ventilation in maintaining normal blood gases in nonbreathing, anesthetized patients during surgery from his friend James Elam (4). Peter called the technique, A for airway and B for breathing. He had previously learned to keep the airway open through backward tilt of the head, while pulling on the chin to move the obstructing tongue away from the posterior pharynx in unconscious patients (5). When Kouwenhoven's group at Hopkins, including Knickerbocker and Jude, described the efficiency of external cardiac compression in producing blood flow in patients with a nonbeating heart (6, 7), Peter quickly added this technique and thus established the ABC of cardiopulmonary resuscitation, with C standing for circulation (8).

Presentation of the new mouth-to-mouth ventilation technique at an international resuscitation congress in Norway in 1958 led to Peter's life-long friendship and collaboration with Bjorn Lind, then chief anesthesiologist in Stavanger, and Asmund Laerdal, an entrepreneur in Stavanger. These two Norwegians started work on a full-size mannequin for training of mouth-to-mouth resuscitation *ad modem* Peter Safar. Asmund Laerdal brought the prototype to Pittsburgh, and Peter recommended modifications, most importantly, a spring attachment inside the mannequin's chest to also permit external cardiac compression simulation. This mannequin became the world-conquering Resusci-Anne. The Stavanger-Pittsburgh association became a most fruitful collaboration, currently well into its second generation. The late Asmund Laerdal's son, Tore, assumed responsibility for their successful family business two decades ago. He has continued the traditional Laerdal generosity toward resuscitation research. Similarly, the leadership at what is now the Safar Center for Resuscitation Research was assumed by Patrick Kochanek in 1994.

Pittsburgh

In 1961, Peter was invited to Pittsburgh to consider the position as chief of anesthesiology at Presbyterian University Hospital. Although told that this was an impossible position, he accepted the challenge and so started Peter's Pittsburgh career that came to include so many important aspects of medicine. At the young age of 37, he began to develop what later became the largest academic department of anesthesiology in the United States from a very small start, with only three board-certified anesthesiologists on the faculty, including himself. In addition to Presbyterian University Hospital, Peter incorporated the anesthesiology services of Montefiore Hospital, The Eye and Ear Institute, Magee-Womens Hospital, Children's Hospital, and Veterans Administra-

tion Medical Center, all of which were located on the University campus. When Peter Safar, after 17 yrs, resigned as chairman of this huge department, the service covered approximately 60,000 surgical procedures per year, with >50 staff anesthesiologists and a large number of nurse anesthetists. The diversity of surgical cases and anesthetic procedures provided an excellent training program for the many anesthesiology residents in Peter's department.

In 1958, Peter Safar had already established a 16-bed general intensive care unit (ICU) in Baltimore, which probably was the first in the world to have 24-hr coverage by residents of different disciplines in house and staff physicians on backup call from home (9). He brought these experiences to Pittsburgh, where he initiated another general ICU with similar organization at Presbyterian University Hospital. In 1963, he introduced the first subspecialty training program for physicians in what was to become critical care medicine (10). Critical care medicine was then a division within the department of anesthesiology. Peter had concluded that every anesthesiologist who is skilled in managing operating-room patients in poor physical status should also be a reanimatologist and intensivist, for which purpose special training should be available in anesthesiology residencies. Although the first few trainees in the ICU at Presbyterian University Hospital were anesthesiologists, other physicians with different training backgrounds joined his program, such as Jan Smith of South Africa with training in internal medicine and pulmonology and Ake Grenvik from Sweden with his primary background in general surgery and cardiothoracic surgery. However, both of them also had additional training in anesthesiology.

Resuscitation Research

A very tragic event in the Safar family occurred in 1966 when Peter's and Eva's daughter Elizabeth developed a status asthmaticus, resulting in cardiac arrest. Cardiac function was restored, but she remained comatose and did not recover. This and other events in Peter's medical career increasingly made him realize that cardiopulmonary resuscitation must also include the brain. He coined the expression "cardiopulmonary cerebral resuscitation," with the acronym CPCR, which he championed. Increasingly, he concentrated his resuscitation research activities on methods to improve brain recovery after different forms of cardiac arrest. In the small research facilities within the anesthesia department at Presbyterian University Hospital, he established a research program that attracted both advanced and young anesthesiologists. Among the first to serve in Peter's laboratory were Drs. Bjorn Lind of Norway, James Snyder of Pittsburgh, who later became the chief of critical care medicine when Ake Grenvik stepped down in 1990, and Edwin Nemoto, who directed this laboratory for many years (11–13).

Resuscitation research activities were funded first locally and then through the Laerdal Foundation, National Institutes of Health, and eventually various branches of the Armed Forces of the United States. In 1978, Peter resigned from the chair of anesthesiology and founded his International Resuscitation Research Center (IRRC), located on the university campus in what previously was a casket factory (the A. F. Hill Casket Company). Peter jokingly referred to the transition from resurrection to resuscitation in that facility. Under his leadership, a myriad of resuscitation methods were scrutinized, initially testing a large number of promising brain-protective drugs.

Four different areas of activities were represented at IRRC for which Peter assigned the following associate directors: Nicholas Bircher (cardiac arrest laboratories), Norman Abramson (cardiac arrest clinical studies), Samuel Tisherman (shock/trauma), and Ernesto Pretto (disaster reanimatology). Research fellows from all over the world were attracted to the IRRC. Under Peter Safar's leadership, >60 such fellows served for ≥1 yr in research training at his facility. This resulted in hundreds of peer review publications and some 500 abstracts, with presentations at various national and international congresses. In 1988, Safar and Bircher published the textbook *Cardiopulmonary Cerebral Resuscitation*, which set the standard for the discipline and was translated into some 20 different languages (14).

In 1994, Peter Safar resigned from his directorship at IRRC. Peter Winter, chairman of the department of anesthesiology since 1979, appointed Patrick Kochanek, a pediatric critical care medicine faculty member at Children's Hospital and dedicated to brain research, as the new director of IRRC. Pat Kochanek immediately renamed IRRC to the Safar Center for Resuscitation Research. Peter Safar, together with Samuel Tisherman and others, continued their promising research to improve brain survival. Much of Peter's work focused on the use of hypothermia. Safar was one of a few key individuals involved in bringing renewed interest in hypothermia in the 1980s—spearheading the use of mild (rather than moderate) hypothermia in resuscitation from cardiopulmonary arrest. One of his former students, Fritz Sterz of Vienna, recently played an instrumental role in bringing this to clinical use by leading a successful European multiple center trial of this therapy, the results of which were published in the *New England Journal of Medicine* (15). More recently, Peter Safar and Sam Tisherman—along with a group of talented trainees—performed exciting studies on the use of profound hypothermia, induced by aortic flush of iced saline, to preserve and then resuscitate the heart and brain after cardiac arrest periods of 60–120 mins, previously unheard of. It was through Peter's collaboration with Ronald Bellamy in the Armed Forces, a noted authority on combat casualties in the Vietnam War (16), that this technique became an approach worthy of further investigation to study the military problem of combat victims bleeding to death in the battle field from injuries, which *per se* would be repairable and survivable if the victim could reach a surgical trauma facility in time for this intervention. Being able to keep heart, lungs, and brain alive for delayed resuscitation became known as "suspended animation." Some of the most important work on this exciting research has been recently published in *The Journal of Trauma* (17, 18) and *Critical Care Medicine* (19). Samuel Tisherman and his associates, who are continuing this promising research work, at the time of Peter Safar's death were planning to test the technique in civilian traumatology on victims arriving in hospital emergency departments in or close to cardiac arrest after extensive bleeding from various forms of trauma. Thus, Peter Safar brought this "science-fiction" technique to the doorstep of clinical trial but, unfortunately, was not given the opportunity himself to witness the expected first success of this modern approach to traumatic/hemorrhagic shock leading to cardiac arrest. To use Peter's own expression, these victims often represent unfortunate young individuals with "hearts and brains too good to die"—the

target of his life's work in the field of reanimatology.

Critical Care Medicine and Related Fields

Clara Jean Ersoz was one of the earliest anesthesiology trainees in the critical care medicine program. She temporarily served as medical director of the general ICU at Presbyterian University Hospital in 1968, but she then moved to a prominent administrative position at St. Clair Hospital in southern Pittsburgh. Peter Safar took a sabbatical leave in academic year 1969–1970, joining Severinghaus and Comroe in research at their Cardiovascular Institute in San Francisco. During that time, he appointed Ake Grenvik as director of the ICU to later make him chief of the critical care medicine division in the department of anesthesiology. After returning to Pittsburgh, Peter initiated the second pediatric ICU in the nation at Children's Hospital. Stephan Kampschulte, a German anesthesiologist trained in Peter Safar's program, who had special interest in pediatrics, was appointed the first director of this ICU. He later returned to his native country after marrying another of our German critical care medicine fellows, anesthesiologist Marie Louise Lembke. Unfortunately, Stephan Kampschulte died of a massive stroke in 1994. During his early years in Pittsburgh, Peter Safar also initiated a respiratory therapy service with Bela Eross as the director.

In the 1970s, Peter Safar started a unique community emergency medical service, hiring unemployed African Americans and training them in basic resuscitation. The Freedom House Enterprise ambulance program was born and, most prominently, run by Nancy Caroline, an internist trained in Peter's critical care medicine program. She left in 1976 for Israel and became the medical director of Magen David Adom, the Israeli Red Cross. Nancy Caroline was an excellent writer and authored the first and widely spread Emergency Medical Services textbook, published in three editions (20). Dr. Caroline is frequently referred to as the "mother of Emergency Medical Services" in Israel.

Peter Safar was also heavily involved in ethical problems and, together with Ake Grenvik, served on a committee chaired by Pittsburgh Coroner Cyril Wecht to develop the first hospital guidelines in the nation on brain death evaluation and certification (21). This was of great importance when transplantation surgery flourished after recruitment to the University of Pittsburgh Medical Center of the widely known transplantation pioneer, Thomas Starzl. Furthermore, Safar and Grenvik, together with the ethicist and lawyer Alan Meisel, designed hospital guidelines, which also were among the very first in the nation, for foregoing life-sustaining therapy in futile cases (22–24).

International Involvement

Among Peter Safar's numerous international connections, his collaboration with Vladimir Negovsky's group in Moscow was unique. Already in 1937, Negovsky initiated a resuscitation research laboratory, studying the process of dying in search of new methods for "reanimation," such as intra-arterial administration of blood in lethal hemorrhagic shock. Peter visited Negovsky repeatedly, beginning in 1963, and Negovsky, in turn, visited Pittsburgh four times during their long-standing scientific friendship. After 50 yrs, Negovsky's Reanimatology Institute grew into the Laboratory of General Reanimatology of the USSR Academy of Medical Sciences as it moved from October Street near the Red Square to the outskirts of Moscow. This institution served as a model for Peter's establishment of his own IRRC. Incredibly, Dr. Negovsky preceded Peter Safar in death by 1 day.

During 15 yrs, from 1979 to 1994, most closely together with Norman Abramson, Peter conducted an international brain resuscitation clinical trial (BRCT), involving 20 medical centers in seven different countries. Promising drugs and techniques studied on animals in the IRRC laboratory were tested clinically (25–27). However, there was no obvious breakthrough, and Peter gradually turned to the greater potentials of hypothermia from simple mild hypothermia to the more complex profound hypothermia, as discussed above. Limitations on deferred consent, at the time, prevented Peter from carrying out the hypothermia trials in the United States.

Professional Honors

Peter Safar's curriculum vitae encompasses approximately 1,400 publications, including almost 400 peer-review articles, >600 abstracts, 20 books, and numerous book chapters and other publications such as invited reviews, guidelines, commentaries, and editorials. In 1968, during a Federation of the American Societies of Experimental Biology Meeting in Atlantic City, three "musketeers" with a common interest in management of the critically ill and injured patients, Max Harry Weil (internist/cardiologist), Peter Safar (anesthesiologist/intensivist), and William Shoemaker (trauma surgeon), jointly decided that it was time to start an association of professionals involved in intensive care. At a subsequent meeting in Los Angeles of 28 founding physicians of various specialties, the Society of Critical Care Medicine was established (28). Peter served as the Society's second president and initiated the Society of Critical Care Medicine journal, *Critical Care Medicine* (29). In the mid-1970s together with the late Rudolf Frey of Mainz, Germany, Peter started the Club of Mainz (30). This was later to become the World Association for Disaster and Emergency Medicine. During his presidency of the World Association for Disaster and Emergency Medicine, Peter initiated its journal, currently known as *Prehospital and Disaster Medicine*.

Over the years, Peter Safar received several honorary doctorate degrees from various universities, including the Johannes Gutenberg University of Mainz, Germany, in 1972; the University of Campinas in Brazil in 1996, and the Otto von Guericke University of Magdeburg in Germany in 1997. In 2003, he was to receive a Doctor Honoris Causa degree at Charles University in Prague of the Czech Republic, but his illness prevented him from receiving this honor in person. However, the University of Pittsburgh provided him with its Honorary Doctor of Science degree in February 2003, when he also served as the convocation speaker. In the mid-1970s, Peter Safar was an invited member of the White House Interagency Committee on Emergency Medical Services. In 1999, he received the Austrian Cross of Honor (first class) for Science and Art. The list of honors goes on and on. Three times he was nominated for the Nobel prize in medicine and physiology.

Elegance, Humanism, and Talent

Early during Peter Safar's incredible career in Pittsburgh, the expression about him was coined, "today anesthesia, tomor-

Despite the frenzy of 21st century medicine and the incredible purpose driving his important scientific missions, Peter accomplished all of his life's work with remarkable elegance.

row the world." Indeed, Peter Safar became heavily involved in a large number of different areas throughout the world. Typical for Peter Safar, he was not only active in various medical societies but also in the World Federalist Association and in the International Physicians for the Prevention of Nuclear War. His passion for what he called peace medicine—doing good for mankind—was intimately linked to everything in his life, including his work on resuscitation. He believed that developments in the collective fields of acute medicine must be propagated universally. This was clearly reflected in this seminal work on the worldwide dissemination of cardiopulmonary resuscitation and was a theme to which he was always faithful during his illustrious career. "Simple, inexpensive, and effective," he would proudly say about a potential therapy that showed promise.

Despite the frenzy of 21st century medicine and the incredible purpose driving his important scientific missions, Peter accomplished all of his life's work with remarkable elegance, from sipping merlot for creativity at laboratory meetings, to making sure that visiting professors were treated like family members, and to religiously remembering everyone's birthday. While we were all trying to keep up with his science, he was writing letters to the current U.S. president, talking with the *Pittsburgh Post Gazette*, or working with physicians for social responsibility. One of the components of "Peter's Laws" was, "It is up to us to save the world" (1, p. 343). He led this quest by example.

Like most successful world leaders, Peter Safar was multitalented. He was a great family man and friend who was always available to listen to others and help them in any situation, such as escapees from post–World War II Europe seeking a new future in the United States. He was an athlete, mountaineer, excellent snow and water skier, and above all, a superb musician who loved to play classic Viennese compositions on his grand piano at home.

Peter Safar's Legacy

The future of all of Peter Safar's implementations looks extremely bright. The anesthesiology department is in the able hands of John Williams, occupying the endowed chair as the Peter and Eva Safar Professor in Anesthesiology and Critical Care Medicine. The Safar Center for Resuscitation Research continues its world prominence under Patrick Kochanek's leadership. Critical care medicine in 2000 was declared the first separate academic department in the United States, with Mitchell Fink as the founding chairman. The emergency medicine department, including the Center for Emergency Medicine, enjoys a worldwide reputation, with Paul Paris at the helm. A recent spin-off in the anesthesia department the Peter M. Winter Institute for Simulation, Education, and Research, which, with John Schaefer as its medical director, has become the largest and most active medical simulation center in the nation, building on Laerdal's modern simulation systems, which are a contemporary development of Resusci-Anne. Hundreds of other talented clinicians, scientists, and educators both in Pittsburgh and around the world will proudly carry on the Safar legacy, each feeling truly honored to have known him.

We feel enormously fortunate to have been able to witness and partake in the ingenuity and elegance of the life of Peter Safar. We will never forget the lessons he taught and the remarkable nuances that defined this special man—from the six rubber bands on his wrist to help him immediately organize the manuscripts and papers that constantly pelted him to the camera and tape recorder in his pocket ready to go to ensure that history would not be cheated. Although deeply saddened by the loss, we will move forward as colleagues and friends with renewed purpose—elevated to new heights and charged by the spark of genius.

A thousand thanks, Peter.

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Pioneering contributions of Peter Safar to intensive care and the founding of the Society of Critical Care Medicine

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During the Crimean War, Florence Nightingale, the parent of professional nursing, segregated the most severely injured soldiers and bedded them in close proximity to the nursing station. This perhaps represented the beginning of intensive care. During the poliomyelitis epidemics in Scandinavia of 1949 and 1952 and, subsequently, during the polio epidemic of 1948 and 1949 in Los Angeles, special respiratory units were organized for bag ventilation of patients with bulbar polio. Excepting postanesthesia recovery units first implemented by Dandy in 1923 at the Johns Hopkins Hospital, which evolved more fully during the Second World War, there were no intensive care units as we know them today until 1958 (1).

Almost concurrently, although with somewhat differing emphasis, Weil and Shubin at the University of Southern California School of Medicine and the Los Angeles County General Hospital and Safar at the Baltimore City Hospital developed the first physician-staffed medical and surgical units for management of patients with immediately life-threatening conditions (2, 3). The Los Angeles team was co-headed by two cardiologists, Weil and his life-long collaborator, the late Dr. Herbert Shubin, and Chief Surgeon Leonard Rosoff. It was initially named the Shock Ward because its initial emphasis was on acute circulatory failure. Peter Safar's unit was identified as an "intensive care" unit, with major emphasis on management of the airway and on breathing, following the tradition of Dandy (4). Both in the Los Angeles and in the Baltimore units, there was 24-hr/day, 7-day/wk physician commitment to the care of the most seriously ill and injured by a multidisciplinary team representing both medical and surgical specialties. The goal of both units was fuller commitment to lifesaving care for the most seriously ill and injured, with primary emphasis on breathing, circulation, neurologic recovery, and control of infection. Both were committed to clinical and laboratory research, although the focus of the research of the Eastern and the Western centers was quite different. The Los Angeles team focused on an understanding of mechanisms of acute life-threatening illnesses and injuries (5–7). Accordingly, it pioneered the development of monitoring and measuring devices. Equipment, including recorders, transducers, cuvettes, and thermocouples were taken from the physiology laboratory to the bedside. Central venous and arterial catheterization for pressure and cardiac output measurements by dye dilution techniques, measurements of central and peripheral body temperatures, detection and quantitation of life-threatening cardiac arrhythmias based on electrocardiographic heart rate and pulse rate, and respiratory frequency were implemented. The University of Southern California unit was a joint project of the departments of medicine and surgery and included isotopic methods for measurements of plasma and red cell volumes, especially for detection of hypovolemic shock. The "STAT Laboratory" concept was born in Los Angeles for rapid, "point of care" measurements of blood gases, electrolytes, and arterial blood lactate (8). As early as 1960, the University of Southern California unit began to implement, primitive, digital computer methods for data management and bedside display (9).

Peter Safar's unit maintained early emphasis on the airway and ventilation, in part an extension of the Safar-initiated priorities in 1957 of the A and B of cardiopulmonary resuscitation, including Peter's singular commitment to that of saving lives by demonstrating options for better management of the airway and breathing and for pharmacologic interventions (10, 11). Peter was an early proponent of titrated therapy. He and his associates maintained early emphasis on ventilation, cardiopulmonary resuscitation, and neurologic outcomes in addition to the other priorities of the modern anesthesiologist. The University of Southern California group emphasized circulation, including acute myocardial infarction, sepsis, and drug overdoses. In the years that followed, however, interest in circulation gained momentum in Pittsburgh and ventilation in Los Angeles.

In 1961, both units began the first fellowship programs in what emerged as critical care medicine. The initial leaders of the field came from these programs, and our graduates literally populated new centers all over the globe and constitute a new generation of critical care leaders.

In 1962, surgeon William Shoemaker began what became one of the first trauma units in the United States at the Cook County Hospital in Chicago (12). Shoemaker had been trained in surgical physiology at the Peter Bent Hospital in Boston by the famed Dr. Francis Moore and in biochemistry by Baird Hastings, the Harvard University giant of the field. In that setting, Shoemaker's interest included hemorrhagic shock and its complications and the hemodynamic and metabolic consequences of injury (13).

It was at a meeting of the Federated Societies in Atlantic City and during a casual walk on the famed boardwalk that Safar, Shoemaker, and Weil first shared concepts and aspirations on the care of patients with life-threatening conditions. Cardiologist/physiologist Weil, anesthesiologist/resuscitation-leader Safar, and surgeon/physiologist Shoemaker found a

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commonality of concepts and goals. Peter was already well armed and, in fact, experienced in identifying the need for a more appropriate system, beginning with out-of-hospital emergency care. He promoted triage and stabilization of patients at the site, competent management during prehospital transport, preparedness for direct admission to the hospital emergency area, and orderly passage through preanesthesia, operation, and postoperative recovery. To Peter, the rational extension of this system was that of intensive postoperative care in either or both postoperative recovery and intensive care units. Peter also had a keen appreciation for the diversity of disease states that were not exclusively in the domain of the anesthesiologist, including drowning, life-threatening bronchoconstriction, coma and vegetative states, and out-of-hospital cardiopulmonary resuscitation. Weil and Shubin both had a background in cardiorespiratory physiology. Weil had his residency and fellowship training at the University of Minnesota in the laboratories of the famed physiologist Maurice Visscher and infectious disease expert Wesley Spink. At the Mayo Clinic, Weil was under the tutelage of clinical physiologists Earl Wood and Ward Fowler and the famed cardiologist Howard Burchell. On the boardwalk in Atlantic City, the appropriateness of the multidisciplinary commitment to patient care by three academic doctors from diverse specialties became a bond. This multidisciplinary commitment to acute care emphasized the patient but also recognized the huge implications for acute care education and research.

Like comrades in arms, Safar, Shoemaker, and Weil maintained continuing dialog over the ensuing months, and their discussions culminated in meetings initially in Los Angeles in February 1970 in conjunction with the Eighth Annual Course on Critical Care Medicine and Shock, sponsored by the University of Southern California School of Medicine and its division of critical care medicine chaired by Weil. In July of 1970, the three initiators and their associates expanded to a group of 28 invited American medical leaders from diverse specialties. The intent was to propose an organization that became the Society of Critical Care Medicine. At the Ninth Annual Course on Critical Care Medicine and Shock in Los Angeles in February and later that year in May of 1971 at a course directed by Peter and the Department of Anesthesiology of the University of Pittsburgh, the Society was formally inaugurated with 100 members. Dr. Aki Grenvik, Peter's student and colleague, was a major contributor to the initial success of Society of Critical Care Medicine as chairman of the membership committee. Weil was elected as the first president and began the tradition of what became annual presidential addresses (14). Safar was the second president and Shoemaker was the third president. In January of 1973, strongly supported by Safar and Weil, Shoemaker became the founding editor of *Critical Care Medicine*, now the leading journal in the field, worldwide, in critical and intensive care.

We defer to our colleagues who contributed to this special issue of *Critical Care Medicine* to cite the remarkable achievements of Peter Safar, our friend, colleague, and leader. They will appropriately speak about Peter's extraordinary breadth of interest and involvement. The innovative and pioneering contributions of Peter started with resuscitation. The A, B, and subsequently, A, B, and C of cardiopulmonary resuscitation were Peter's. They will speak of the extraordinary humanism of Peter that complemented and reinforced his contributions to education, science, and practice. Peter Safar's home discipline was clinical anesthesia and its day-to-day practice. However, it was always in the context of saving lives. His involvement in prehospital emergency care of patients extended all the way from the site of intake to discharge from intensive care. He helped pioneer disaster care. His humanism was exemplary and courageous. He would risk his reputation to foster even politically unpopular proposals that would save lives—always respecting lives, but also the need for gently guiding patients out of life when there was no longer capability to maintain meaningful life. A workaholic by his own description, he was a beloved mentor and an academic parent to so many, including medical students, residents, fellows, and professional nurses. To his colleagues, he was a compassionate friend, a collaborator, and respectful combatant and, ultimately, a conciliatory compromiser.

Peter had visualized a comprehensive system of acute care that, as cited above, would start at the prehospital site of injury, illness, or disaster, provide for initial stabilization before transport and entry into the hospital, triage and emergency management on arrival, orderly transfer to the operating room or intensive care unit, and all of these under the umbrella of "resuscitation" or the French model of "reanimation." Stimulated by the extraordinary respect he had for the contributions of his Russian colleague and friend, Professor Negovsky, Peter regarded himself as a resuscitation physician (15, 16). Peter most persuasively sought to combine emergency medicine, intensive care, and disaster and rescue medicine as one discipline. The name critical care medicine, synonymous with intensive care medicine, was in part from the title of a 1966 monograph authored by Dr. Stephen Ayres, entitled "The Care of the Critically Ill" (17), and from the name of the 42-bed Center for the Critically Ill, which was the 1967 successor unit of the Los Angeles University of Southern California Shock Ward (18). Peter, during the years that followed, remained committed to the ultimate unification of emergency, disaster, and critical care medicine under a single multidisciplinary specialty umbrella. However, critical care medicine became a subspecialty, and emergency medicine ultimately became a separate primary specialty (19).

Peter Safar's autographic memoir speaks beautifully of the unique achievements of this great man (14). Of the two remaining of the trio of critical care initiators, we were blessed by admiration and professional friendships that existed among the three of us during our professional lifetimes. We shared destinies for >35 yrs. As we mourn Peter's passing, we perceive it as a painful and personal loss. However, his wondrous hold on life, always moving forward against odds and in so many spheres, fortified us all. The extraordinary qualities of this giant are best described in his own words: "The impossible is simply a greater challenge." One of us (M. H. Weil) had the privilege of maintaining close contact with him in the last year when, with the compassionate closeness and support of his wife, Eva, overwhelming cancer and infection would not dampen Peter's spirit. His extraordinary commitment to life and unrelenting spirit to move forward against impossible physical odds of pain and disability were with vigor, decorum, and even charm and, most remarkably, without even a complaint. We will do well to commit ourselves to keep our eye on the horizon projected by Peter, for it extends beyond our individual identities as physicians and even beyond the Society which he served so well.

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Memorial Service Honoring Dr. Peter Safar, Heinz Chapel, Pittsburgh, PA, October 29, 2003: Remarks of Chancellor Mark A. Nordenberg

Good afternoon. Let me welcome each of you as we gather to remember the life of Dr. Peter Safar and to honor his memory. On behalf of the entire university community, I want to extend an especially warm welcome to Eva Safar, to Philip Safar, and to Paul Safar. We are pleased to be with you today, we are grateful to you for sharing your husband and father with us for so many years, and we recognize that your encouragement and support were essential to all of Peter's many important accomplishments.

Over the course of its proud, 216-yr history, this university has been the home to many high-achieving professionals who also were wonderful people. However, few have had the kind of impact, here and at a distance, that Peter Safar did.

Peter was not just a pioneer within his discipline. Instead, he could be viewed as the creator of several disciplines. And his work within them not only enriched lives, it saved them, and in very large numbers. As distinguished and influential as Peter was within his field, he was never confined to it. Instead, his curiosity was almost boundless, and he seemed interested in virtually any cause that might improve the human condition. And Peter's interest in the human condition was not abstract but was, instead, reflected in his everyday dealings with others. Peter was not just a friendly and courteous person, he took kindness and grace to new levels—or, perhaps, it was back to old levels. Certainly, in this modern and, too often, impersonal world, his courtly demeanor stood out, almost as some type of personal art form.

I always felt privileged to be a part of a university that included Peter Safar. And I always felt blessed that he considered me to be a friend. And I always felt lucky that I had the chance to benefit from his thinking on a range of important issues.

More than two centuries ago, Voltaire wrote: "I know of no great men except those who have rendered great services to the human race." Certainly, Peter met that test, and he did it from within our midst. But for so many of us, Peter also was a great man because of the many smaller services he rendered to us individually, as his colleagues and friends.

Peter was a great and gracious person, and he will be missed. We all are very lucky to have known him, and we also are fortunate to have the enduring benefit of his unique and inspiring example.

From the University of Pittsburgh School of Medicine, Pittsburgh, PA.

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Memorial Service Honoring Dr. Peter Safar, Heinz Chapel, Pittsburgh, PA, October 29, 2003: Remarks of Senior Vice Chancellor Arthur S. Levine, MD

Dr. Peter Safar once told an interviewer that our first calling is to use the gifts we are given and to make the world a better place. It seems to me that Peter was someone who followed his own advice quite well. It's no doubt that the gifts he displayed as a physician, an educator, a researcher, and a gentleman were remarkable, but all the more remarkable was what he did with those gifts, especially to aid people in their most fragile and vulnerable moments of life.

Dr. Safar's revolutionary body of work in resuscitation, emergency medicine, and critical care made him an icon in the world of medicine. His influence was most certainly felt here at the University of Pittsburgh, which had the wonderfully good fortune to be his scientific home for 42 yrs. He was, in fact, one of the key figures who helped launch the School of Medicine to the prominence it now enjoys. Quite literally, he helped put us on the map, but his influence on the global scale cannot be discounted.

The innovations he developed have changed the face of medicine and the way it is practiced around the world, especially critical care medicine, which, until Dr. Safar came along, was not considered the specialty it is today. The multidisciplinary fellowship training program in critical care medicine that he established here at Pitt has trained hundreds of intensivists—doctors who specialize in treating critically ill patients in intensive care units—and because of our leading role in this field, the School of Medicine last year became the first in the nation to establish a department of critical care medicine.

Dr. Safar's legacy will live on through the important work of the Safar Center for Resuscitation Research, which so appropriately bears his name, as do the new annual Safar Symposium and the long-standing Peter and Eva Safar Annual Lectureship in Medical Sciences and Humanities. His legacy will also live on in the minds and hearts of those who knew him and his charm, his ready smile, his diligence, his dedication, and his enthusiasm. In a very real way, his legacy will even live on through the millions of people who never knew him but whose lives he touched because of the extraordinary medical accomplishments he left behind.

I would like to reflect briefly on just one of those accomplishments: cardiopulmonary resuscitation. As one of the pioneers of this life-saving technique, Dr. Safar pushed for acceptance of CPR in the medical community. Now, many years later, it is widely recognized as an essential response to life-threatening cardiopulmonary emergencies. As such, it is taught to millions of people each year and is credited with saving thousands of lives.

As anyone in medicine will tell you, being able to save even a single life is one of the most rewarding experiences anyone can imagine. However, the vast majority of cardiac arrests take place outside of hospitals—in people's homes or in public places with no trained medical personnel around. Peter labored diligently and passionately to put CPR into the hands of ordinary people by training them how to use it anywhere, anytime, so they might be able to sustain patients through the critically important minutes until medical care arrives, and sometimes to even save a person's life.

It happens all the time. Three buddies were playing golf at a country club in Bulltown, PA, one day when one of them suddenly collapsed on the 13th hole; the other two performed CPR until help arrived. In Sheboygan, WI, a young man who knew CPR likewise helped save his 51-yr-old father who went into cardiac arrest while cutting grass at home. And just the other day here in Pittsburgh, an everyday hero who is certified in CPR resuscitated an elderly man who collapsed on a Port Authority bus.

Dr. Peter Safar empowered people to make a real difference in the lives of others, just as he himself made a difference. And so, every time someone new learns or uses CPR, his legacy will live on as well. We come here today to celebrate that legacy, which will be with us for a long, long time. There's no doubt that Peter Safar used his gifts well to make the world a better place. He once said quite simply: "I made use of the opportunities that life offered to do some good." And for that, Peter, we thank you.

From Health Sciences, School of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.
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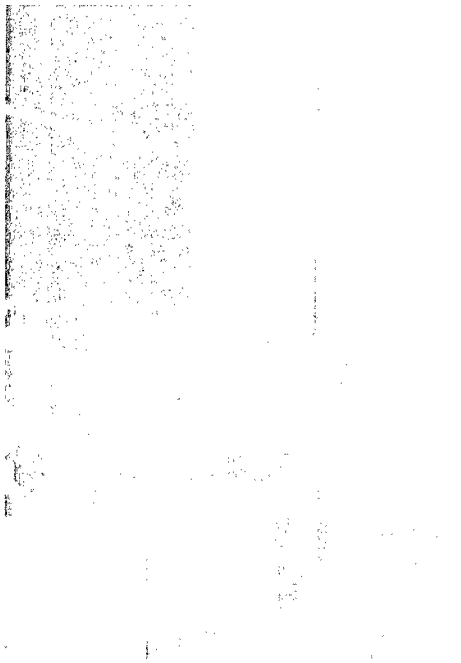
Quotes From Colleagues and Friends in Celebration of the Incredible Life of Peter J. Safar, MD



Dr. Peter Safar in action at the International Resuscitation Research Center during the heyday of the Brain Resuscitation Clinical Trials (BRCT) conducted out of the center, circa 1985.

Peter Safar and I have been friends for nearly forty years. When I was still a wet-behind-the-ears anesthesiologist/scientist and he was the founder of his third anesthesiology department, he and I had research interests in common having to do with pulmonary pathophysiology. We also had first names and a Viennese background in common. To my intense astonishment, he treated me as an equal and a colleague. Ever since, I have observed his career with awe, affection, and respect.

In addition to being the founder of the department, which I was privileged to chair, Peter was a hugely productive investigator whose work had impact far beyond anesthesiology. His development of resuscitation made a profound impact on medicine as a whole and on the lay public as it has saved countless lives. Not content with scientific impact, Peter went on to become, perhaps uniquely, a creator of fields and professions. He was an instrumental leader in the development of the fields of critical care medicine, respiratory therapy, emergency medicine, disaster medicine, and resuscitation medicine, helping found societies and journals that came to define these now independent disciplines. For his numerous and important contributions to the world he was three times nominated for the Nobel Prize.

He accomplished all of this with endless, intense hard work and with charm and charisma, often over the doubts and impediments of bureaucrats who could not understand his vision. He was also a world citizen and a peace advocate who befriended and encouraged everyone with whom he came in contact, from young children to academic physicians in the Soviet Union at the height of the Cold War. Of the many things he taught me, the most memorable was, "It is up to us to save the world."

In later years he was, for me, the ideal "former chairman." He was always available to help and advise when sought and never interfered unless asked. Clearly, one of my responsibilities as chairman was to champion, aid, and abet his activities and to help to promote his many triumphs. It was a privilege beyond measure. I, and all who had the honor of knowing him, miss him deeply.

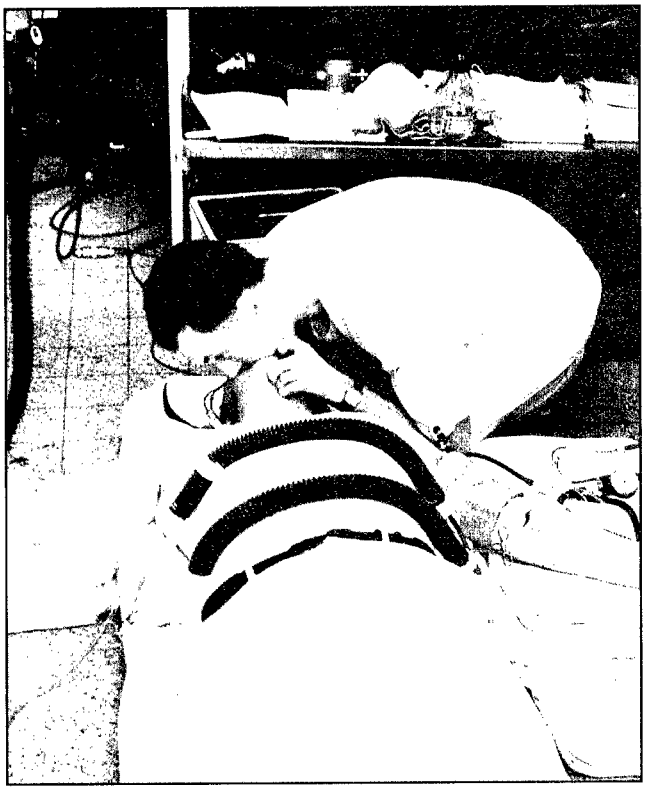
Peter M. Winter, MD
Professor and Chairman, Emeritus
Department of Anesthesiology
University of Pittsburgh

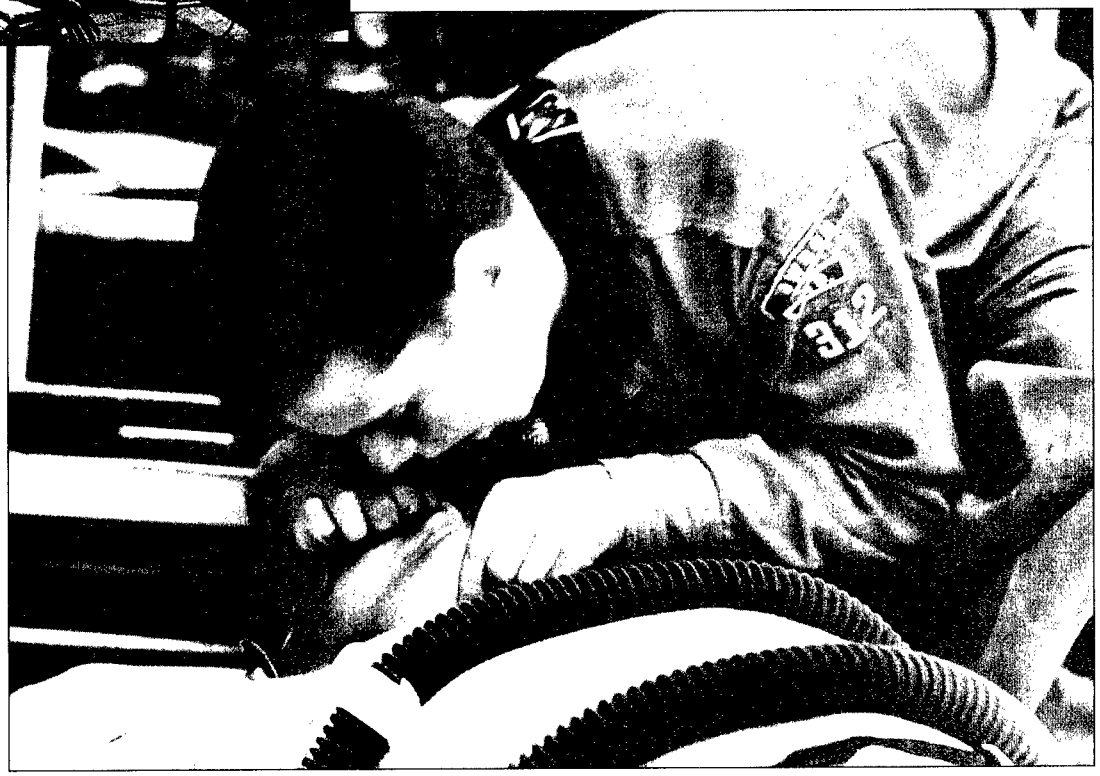
Historic photos from the birth of CPR, circa 1957. Baltimore City Hospital was the site of remarkable human studies in which volunteers were administered curare-induced blockade and the efficacy of mouth-to-mouth resuscitation was documented.

[right] Dr. Safar and volunteer Dr. Peter Safar document the head-tilt jaw-thrust and mouth-to-mouth resuscitation.

[below] Dr. Safar stands behind the anesthesiology machine and demonstrates the new method to the lay public.

[below right] One on one demonstration of the method to a boy scout.





The wonder of Peter Safar's professional life is not in the remarkable accomplishments recorded in his CV, and they were too numerous to recount, nor even in the fact that during his life he affected so many other lives. Certainly, Peter's untiring efforts affected survival and quality of life for patients throughout the world and are accomplishment enough for history to judge a man great. And one could look at the number of colleagues with whom he inspired and the impressive numbers of grants they have obtained or papers they have published. Again, accomplishment enough for any great man.

But to my thinking these are not the only, nor indeed the most important, metrics by which to measure the greatness of this man. Peter's truly unique accomplishment is the emotional connection he inspired among his friends (as he would call them) — not only toward himself, but toward each other. These "friends of Peter" have grown into a vast network of colleagues, all committed to continuing inquiry and research inspired by Peter's visions.

Peter's immortality is assured. For those of us fortunate enough to have known him will continue in his footsteps and will continue to affect others, who in turn will affect others. And this cycle will continue as long as man's battle against premature death continues. And so will continue the memory and impact of a great man.

Norman S. Abramson, MD for the BRCT Investigators

As one of the true clinician-scientists, Peter challenged poorly reasoned and substantiated dogma. His work literally saved tens of thousands of productive lives. He led by example, teaching us the lessons of diligence and tenacity. Peter was a consummate artist in everything he did, seeing clearly how things ought to be. Peter not only developed the techniques for resuscitation, but laid the intellectual foundations for their study and improvement.

Nicholas G. Bircher, MD
Associate Professor
Department of Anesthesiology
University of Pittsburgh

I was privileged to observe him enlighten, educate, and kindle the true spirit of humanitarianism in fellow professionals and laypersons alike. Simply stated, his unique gift provided medical professionals and laypersons worldwide with a basic sense of confidence and competence that enabled them to come forward, kneel down, and use their hands and breath to save a human life. Could there ever be anything more beautiful and precious?

Allan Braslow, PhD
Education Researcher & Developer
President, Braslow & Associates
Greenwich, CT

Dr. Peter Safar (front row, 3rd from left) and his Anesthesiology faculty at the Baltimore City Hospital, circa 1969.

For more than four decades, the U.S. Army Medical Department has had a long history of support for the work of Dr. Peter Safar. We have been partners from the early days of his groundbreaking work in the development of cardiopulmonary (cerebral) resuscitation and the establishment of the first intensive care units to his more recent creation of a resuscitation research center and his work in controlled hypothermia for cerebral protection following hemorrhagic shock.

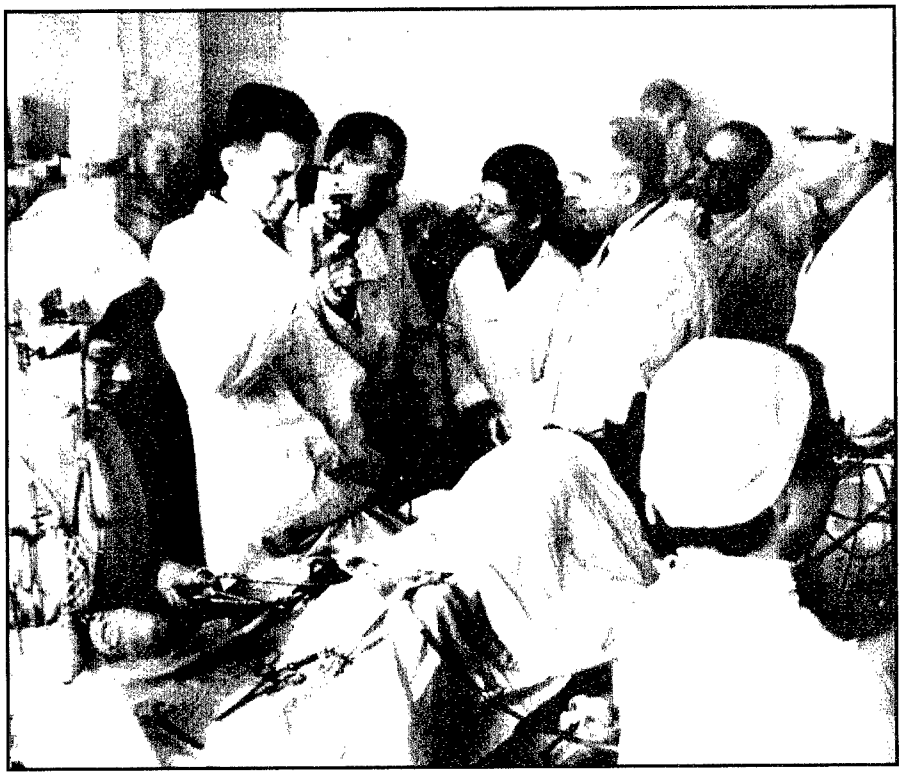
The Army owes Peter Safar a great debt of gratitude for all of his work to radically improve the care and survival for all severely injured people.

His dedication, energy, vision and compassion will continue to be an inspiration.

COL Dean E. Calcagni, MC
Deputy Director
Telemedicine and Advanced Technology Research Center
U.S. Army Medical Research and Materiel Command

During a cocktail party that was given for me by the medical school of the University of Pittsburgh during the course of one of my recruitment visits in the spring of 1972, Peter Safar, who was then the chairman of the Department of Anesthesiology, walked up to me and said, "I want you to come. If you are willing to deal with their minds, I will be happy to try keeping them alive." Since I am Hungarian by origin, his Viennese accent and mine was the source of some amusement to those who witnessed our conversations.

Thomas Detre, MD
Medical Director
International Programs
University of Pittsburgh Medical Center
Distinguished Service Professor of Health Sciences
University of Pittsburgh



Dr. Peter Safar (standing at left taking photograph) at the Negovsky Institute in Moscow in 1963. Political barriers were unable to prevent Dr. Safar from carrying out his mission in the worldwide dissemination of CPR; not a trivial feat in light of the state of the world in 1963. Dr. Safar had great respect for the innovative work of Dr. Vladimir Negovsky and his resuscitation center in Moscow. Dr. Negovsky is the third to the right of Dr. Safar.

Just before I knew he was sick, I asked him to join the proposed Association for Humanitarian Medicine, but his open mind and universal spirit responded saying, "Is not all medicine humanitarian?" "Of course," I said, in disagreement, "while all medical intervention to reduce suffering is in essence humanitarian, Humanitarian Medicine goes far beyond." He then magnanimously revised his initial reaction, saying, "You are right, count me in." You are in, Peter, the humanitarian doctor and the scientist without borders.

S. William A. Gunn, MD
With Peter Safar and friends, a cofounder of the World Association for Disaster and Emergency Medicine
Founder, International Association for Humanitarian Medicine

"Humanitarian Medicine – as defined in The Dictionary of Disaster Medicine and Humanitarian Action, 2nd edition: While all medical intervention to reduce a person's sickness and suffering is in essence humanitarian, Humanitarian Medicine goes beyond the usual therapeutic act and promotes, provides, teaches, supports, and delivers people's health as a human right, in conformity with the ethics of Hippocratic teaching, the principles of the World Health Organization, the Charter of the United Nations, the Universal Declaration of Human Rights, the Red Cross Conventions, and other covenants and practices that ensure the most humane and best possible level of care, without any discrimination or consideration of material gain."

On May 21, 1997, Dr. Peter Safar, originally of Austria, received the Golden Rathausmann Award (a miniature of the statue atop the Rathaus (City Hall), and the equivalent of the "key to the city") from the mayor of Vienna. We were honored to be included among the invited guests and thus had the opportunity to witness this expression of the country's pride in one of its native sons.

Later that evening, we met Peter at a Weinstube in Vienna for a quiet dinner among old friends. We had a copy of that day's city newspaper, Der Standard, which featured a front-page picture of the award ceremony along with a description of Peter's illustrious career. A waiter took a photograph of the three of us sitting together that evening, Peter in the middle holding a copy of the newspaper under his chin - our "proof of life" picture. Copies of that photo sit in our offices today as a cherished memento of that treasured event.

Christopher M. Grande, MD, MPH
Executive Director, International Trauma Anesthesia and Critical Care Society (ITACCS)
Anesthesiologist and Intensivist

Walter Mauritz, MD, PhD
Director, International Trauma Anesthesia and Critical Care Society (ITACCS)
Chair
Department of Anesthesiology
Lorenz Bohler Trauma Center
Vienna, Austria

Dr. Peter Safar (3rd row, 1st on left) and the participants in the Freedom House Ambulance project in Pittsburgh in 1975. This project was instrumental to the development of Emergency Medical Services (EMS) in Pittsburgh. Project leader Dr. Nancy Caroline (1st row, center) was an early follow of Dr. Safar's who went on to become the Mother of EMS and Director of the Red Cross in Israel.

I was traveling back from an out of town meeting on the same plane with Dr. Safar in the Fall of 2002. He had known we would be on the same flight, and because he was in between chemotherapy sessions and had recently undergone a major surgery, he asked if I could "look out for him." After an uneventful flight, we gathered our luggage from baggage claim and I prepared to accompany him to the parking lot. We were both parked in Extended Parking, more than a mile from the terminal. Dr. Safar, pulling his luggage with one arm and carrying a stack of papers under the other, began heading towards the corridor leading to the long walkway that extends all the way to the parking area. I pointed out to him that he was heading in the wrong direction. If we wanted to catch the shuttle bus to the parking area, we had to take only a short walk in the opposite direction. He paused only long enough to look down at my knees and ask, "Is there something wrong with your legs?" I had to sprint a few yards to catch up with him!

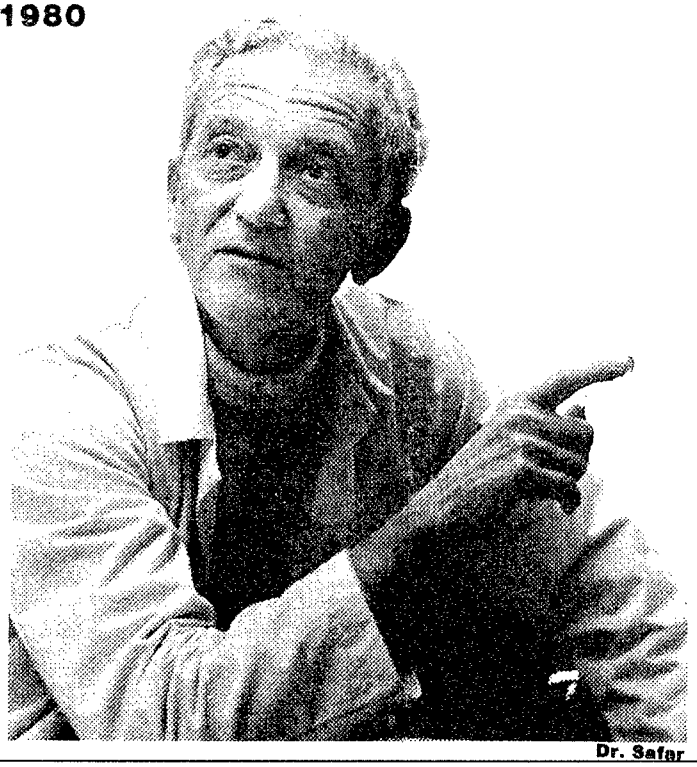
Robert Hickey, MD
Children's Hospital of Pittsburgh
Division of Pediatric Emergency Medicine
Pittsburgh, PA 15213

CPR pioneer Dr. Peter Safar (left) and Laerdal Medical founder Mr. Asmund Laerdal in 1990. Asmund Laerdal, with input from Drs. Bjørn Lind and Peter Safar, spearheaded the development of CPR mannequin Resusci-Anne. Peter Safar often said that business decisions related to the development of Resusci-Anne in the early 1960s were made with a handshake rather than a contract. Dr. Safar and Laerdal legacies will forever be intertwined.

Dr. Peter Safar (2nd from right on right side of table) at the historic meeting of the Wolf Creek Conference in 1975. Dr. Joseph Redding, another pioneer in the field of resuscitation medicine, is seated to the right of Dr. Safar. Drs. Max Harry Weil and James Elam were among the esteemed faculty at this meeting in recognition of the development of resuscitation guidelines.

AUGUST/1980

Resuscitation Research Center Opens

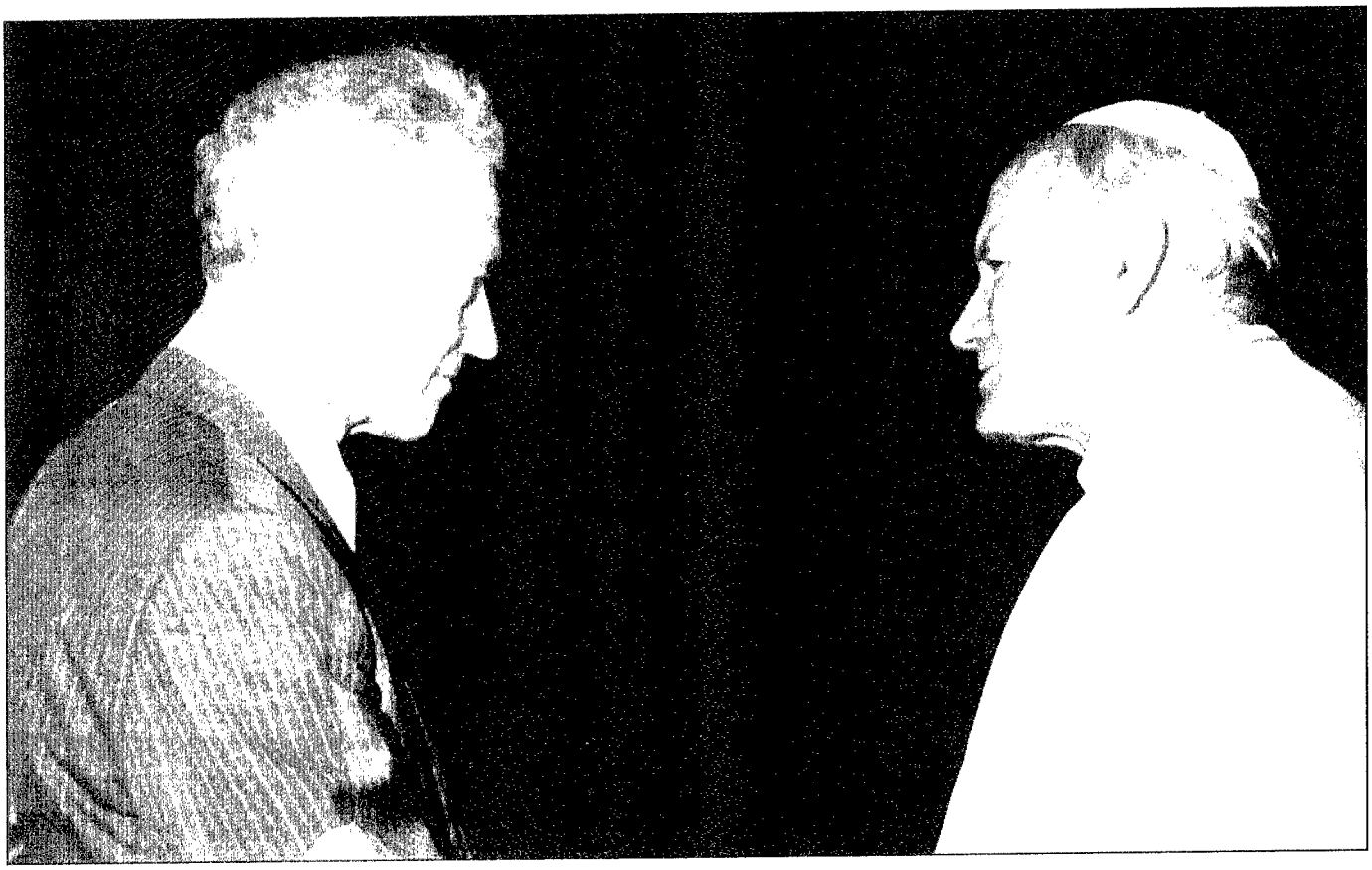


Dr. Safar

Dr. Peter Safar in 1980 at the opening of the Resuscitation Research Center at the University of Pittsburgh. The Center later became the Safar Center for Resuscitation Research at the University of Pittsburgh.

Peter Safar was dedicated to the values of human life and human rights in the most thoughtful and passionate ways. His own life was fulfilled by his service to these values in medicine, in the academy, and in the World Federalist Movement. He was a World Federalist through and through, intensely committed to promoting the global rule of law to achieve peace in the world. He was not a pacifist: he knew that there was real evil in the world that had to be fought steadfastly. But he always had the cause of peace and justice in his mind. Peter Safar was a man of global vision and of service in the cause of humanity.

Burkart Holzner, PhD
Distinguished Service Professor
International Studies Emeritus
University of Pittsburgh



Our time in life is brief. Most accomplish little that benefits those to come. Everyone should leave a legacy, no matter how small. Some, however, like Peter Safar have far exceeded this minimum. Peter has left something that benefits all humanity. His work on respiratory and brain resuscitation has earned him this neverending legacy. Combined with cardiac resuscitation as CPR, this work has become widely accepted and applied. The name of Peter Safar may, in the recesses of time, be lost in the association with his work, but the work will remain and continue without a knowing end. We owe much to Peter, his associates, and all those who continue to spread and educate from his achievements. On a personal note, my memory of Peter will always revolve around his accent and his "very large" briefcase.

James R. Jude, MD
Coral Gables, Florida

[illegible] Dr. Safar's work was [illegible] to the [illegible] with the [illegible] Safar served as the President [illegible] Association of Departments of Emergency Medicine from 1981–85. Above [illegible] Dr. John Dodd II.

[illegible] Dr. Safar with [illegible] Jimmy and Rosalynn Carter at the Carter Foundation.

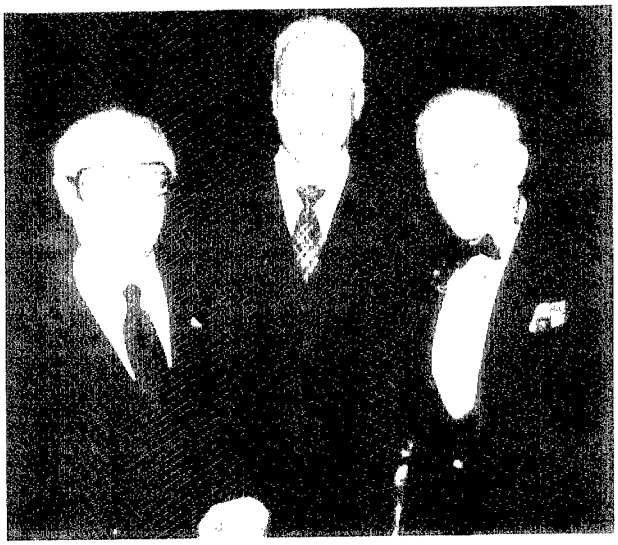
[illegible] Dr. Safar receiving the Award of Merit of Honor [illegible] Harold Hillman at the Annual Conference of Anesthesiologists in [illegible] Safar's highest professional honor.

I went to the University of Pittsburgh Medical School because Peter Safar was there, intending to meet him, which I did. He was well-known in ambulance driver circles in which I was active before medical school.

I chose anesthesia and critical care because he was an enormously positive role model and counsel. I study the brain because of his influence early in my career. I try to pass on to medical students and residents the same enthusiasm and dedication he showed me.

Although he is missed now, his impact will continue for generations.

W. Andrew Kofke, MD, MBA, FCCM
Professor, Anesthesia and Neurosurgery
Director of Neuroanesthesia
University of Pennsylvania



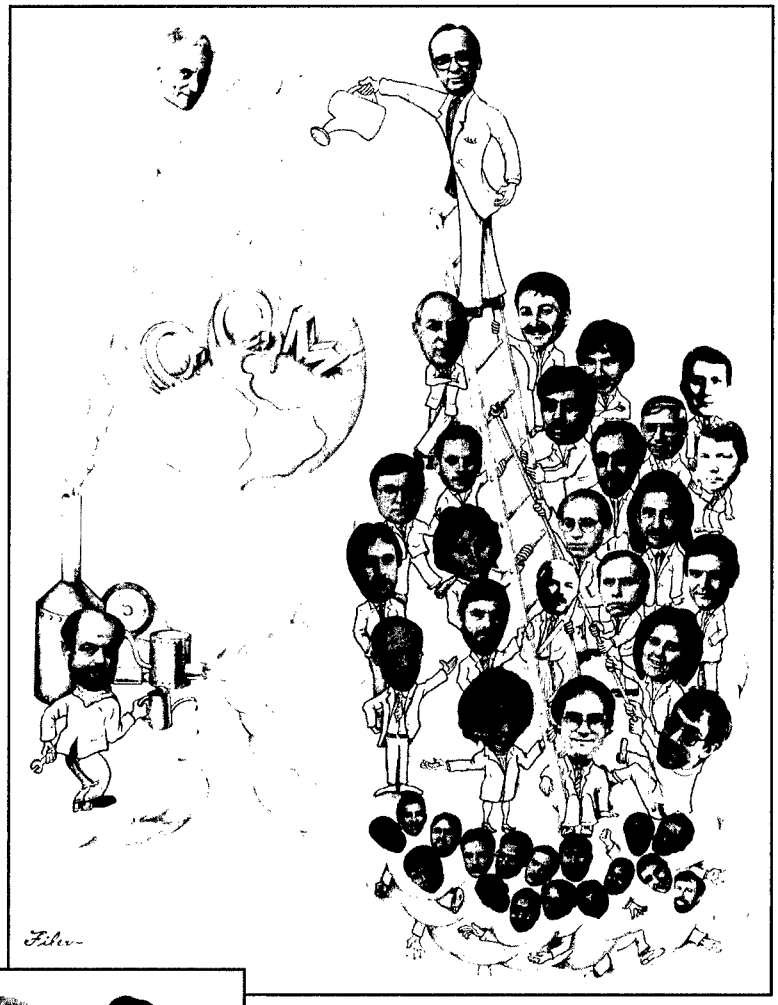
Dr. Max Harry Weil (center) with Drs. Laurence Katz (left) and Peter Safar (right) at the Second International Conference on Resuscitation in the Ischemic Setting, 1977, Pittsburgh, PA. (Critical Care Medicine, 1977).

In 1982 I was an undergraduate student in college and curious about how resuscitation research was performed on dying patients. I wrote letters of inquiry and sent a copy of my senior thesis (Hypothermic resuscitation) to a number of investigators including Dr. Safar, whose name I found in a popular press magazine. Dr. Safar was the only person to write back and I was surprised when he invited me to Pittsburgh to see how to "properly conduct" research. I took a bus from New Jersey to Pittsburgh a couple of weeks later and thanks to the support and guidance from his assistants, Fran Mistrick and Nancy Moran, I was able to stay in student housing for a week while Dr. Safar gave me a grand tour of the International Resuscitation Research Center (IRRC). Upon completion of my visit, I expressed my desire to continue work in the field of medicine and Dr. Safar invited me to return as a "premedical research fellow" at the IRRC. His only condition was that I maintain his philosophy that research must be shared with others and never be performed in secrecy. He encouraged me to be open to ideas from the younger generation and promote their enthusiasm and curiosity. He provided me with these wonderful words of wisdom while we sat at a back table and drank plum wine in the Chinese restaurant around the corner from the Safar Center for Resuscitation Research (formerly IRRC).

Laurence Katz, MD
Associate Professor
Department of Emergency Medicine
University of North Carolina at Chapel Hill

The American Society of Anesthesiologists is saddened at the passing of Dr. Peter Safar. We have lost a giant. Dr Safar's commitment to the care and safety of patients will be missed. Yet, each day, patients continue to benefit from his commitment to them. His legacy lives on.

Roger W. Litwiller, MD
President, The American Society of Anesthesiologists

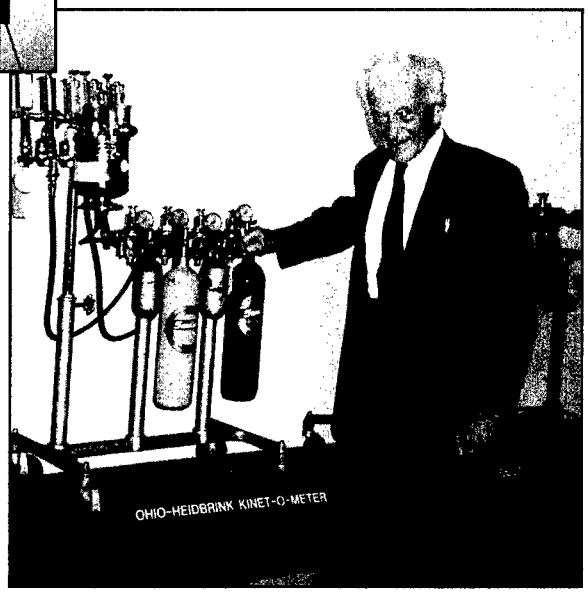


Cartoon (circa 1989) of the Critical Care Medicine (CCM) Division within the Department of Anesthesiology and CCM that Dr. Peter Safar spawned at the University of Pittsburgh. The Anesthesiology and CCM departments are now separate and currently comprised of 133 and 47 faculty, respectively. Dr. Safar is in the upper left in the clouds, Dr. Ake Grenvik is watering the CCM Division, while Dr. Peter Winter (left) as department chairman is oiling the furnace that was the Department of Anesthesiology and CCM.

When I had the privilege of meeting Dr. Peter J. Safar a few years ago, I was immediately fascinated by his joie de vivre. His was an inquisitive, energetic mind that produced major innovations in the critical areas of cardiopulmonary and cerebral resuscitation. Yet he understood with every fiber of his being that medicine is a unique and vital mix of art and science. I was impressed by his love of the humanities, especially music and literature. His eyes would sparkle even more than usual when he discussed the musical contributions of Gustav Mahler and Anton Bruckner! Peter Safar touched people in a very special way, whether as a teacher, scientist, humanist, or friend, and he and his infectious passion for life and for excellence will be profoundly missed.

Kathryn E. McGoldrick, MD
President, Wood Library-Museum of Anesthesiology

Dr. Peter Safar received the Lifetime Achievement Award for SCCM surrounded by former Critical Care Medicine Chief, Dr. James Snyder, and Distinguished Service Professor of Critical Care Medicine, Dr. Ake Grenvik, at the University of Pittsburgh, circa 2002.



Dr. Peter Safar at the Wood Library-Museum on the occasion of the entry of his autobiography into that prestigious library. In addition to his incredible accomplishments in Critical Care Medicine and Emergency Medical Services, Dr. Safar's core specialty was Anesthesiology, and he is considered one of the foremost figures in the history of that field.

Medicine has been blessed by the presence and contributions of this scholarly, yet down to earth, physician in the fields of anesthesia, critical care medicine, and especially resuscitation. Peter, the "Father of Modern CPR," accomplished over his lifetime what few have ever done. I will always remember the friendly smile, the twinkle in his eye, and his compassion and service for all mankind. He was an outstanding teacher, scholar, writer, researcher, prognosticator, and a true friend. I will greatly miss his wit, humor, and most of all the man, a man for all ages and a "giant" amongst us all.

William H. Montgomery, MD
Founder and Immediate Past President, Citizen CPR Foundation
Straub Clinic and Hospital
Honolulu, Hawaii

Photos depicting the personal side of Peter Safar, including his love of music, mountain climbing, and skiing.

[top] Peter Safar (right) mountain climbing on White Mountain, circa 1981.

[center] Drs. Peter Safar and Charles Brindis play a classical piece for four-hands. Anton Bruckner and Gustav Mahler were two of Peter's favorite composers.

[bottom] Former Safar Center fellow, Dr. Sven-Erik Gisvold (left) and Dr. Peter Safar (right) on the slopes at the Seven Springs Ski Resort just east of the city of Pittsburgh, circa 1980. Dr. Gisvold is currently Editor-in-Chief of Acta Anaesthesiologica Scandinavica.

The meetings with Peter Safar left a deep trace in my life. He was self-disciplined, purposeful, incredibly hard working, good-natured, and always in love with the cause to which he devoted all his life. He was highly educated, a real connoisseur of art and music. An amazing party at his place where he played beautifully Mozart and Chopin charmed me. His playing had what some professionals lack — inspiration.

Peter Safar was friendly with Vladimir Negovsky and we know only perfectly well how much Peter did to make the world treat Russia and Russian scientists with respect. His behavior and mode of thinking during the last months of his life from his frequent letters impressed me:

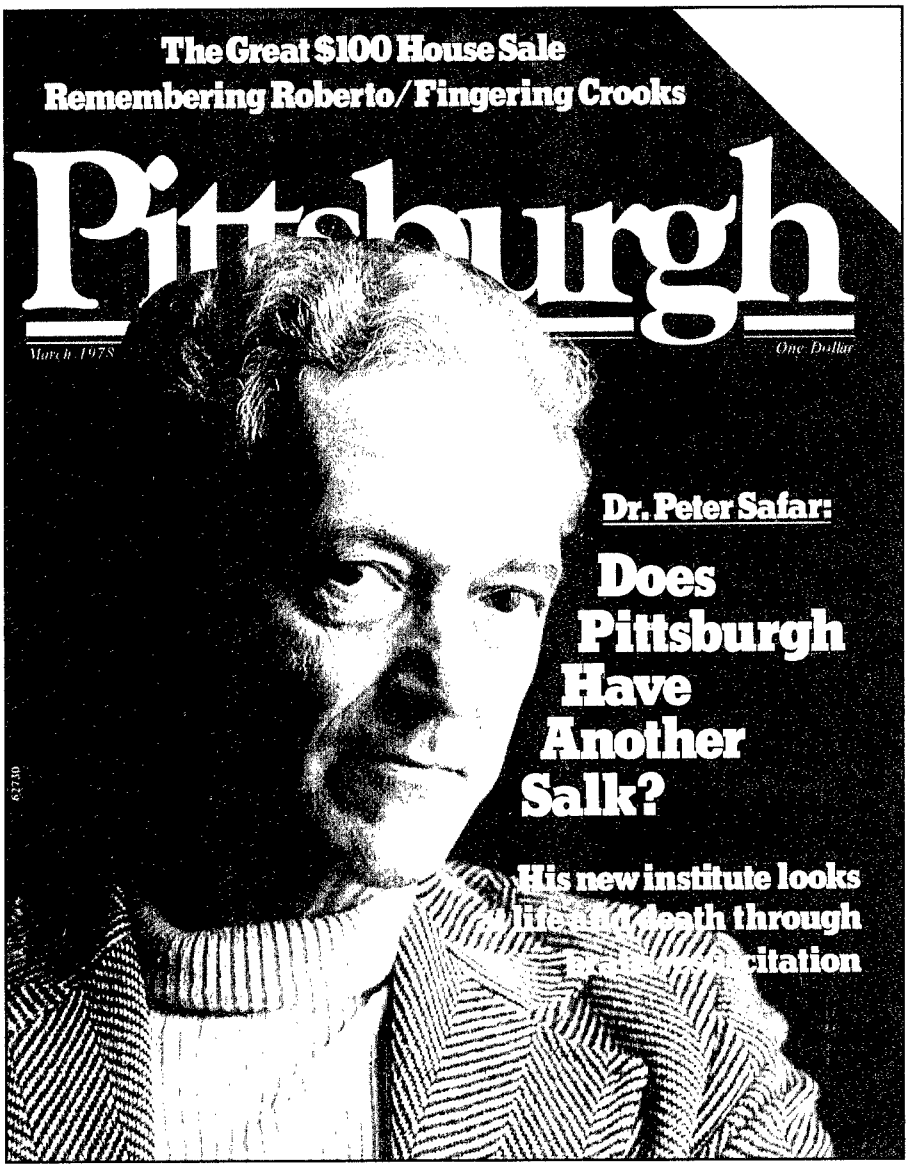
"February 10: Music evening at Dr. Brindis' home. I played two romantic slow movements by Mozart. Both hands now move and feel almost as before the weakness and numbness of October.

It all looked good. He (the reaper), trying to get me because for half a century our work has deprived him of many victims, did not succeed with disease #1 (paralysis), disease #2 (kidney tumor) and disease #3 (gut problems, narcotics, weaning attempts). Philosophically, although April 22 was a death sentence, quality survival time is now my primary consideration. If I survive the operation on May 8, I will fight for every day with a functional brain.

I am in dialogue with the grim reaper. I told him that I am fighting for survival time with quality, and that my associates and former students will continue to resuscitate and to deprive him of his potential victims. My physicians and I are optimistic about shrinkage of my metastases will be accomplished. Ideally, death should come not from the killer of fit young people, but from the angel of death when one's time to depart has come."

I loved him as a person, his humor, and love for life. In my heart he will be forever.

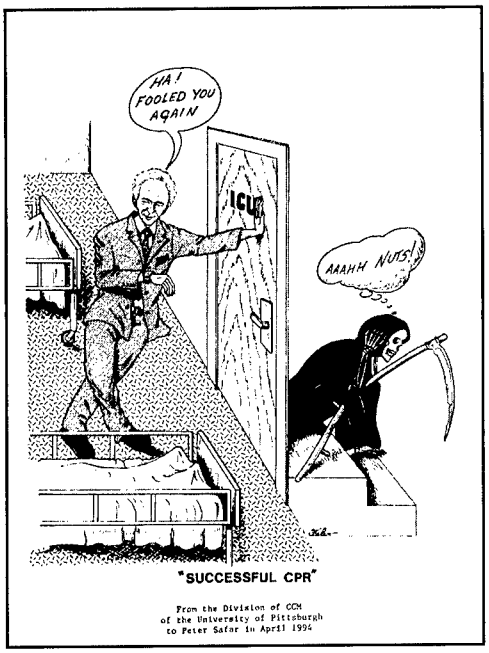
Professor Victor Moroz
Director, Institute for General Reanimatology
Moscow, Russia

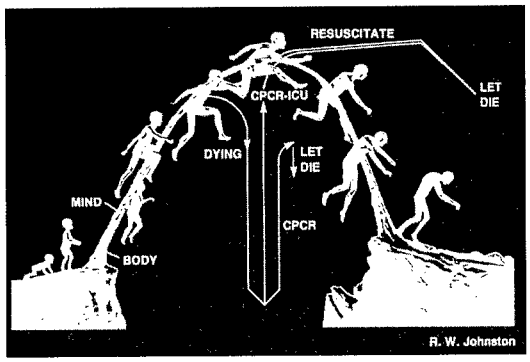


Dr. Safar's international success in the field of resuscitation became legendary in Pittsburgh as shown by the March 1978 cover of Pittsburgh Magazine.

Peter Safar was a man of indomitable resolution who was always completely involved in the task at hand. I remember an all-night imaging experiment where Peter not only was in attendance but personally bought and peeled fruit for the fellows to eat during the long night. His staff and fellows worked hard to meet his expectations because he inspired them by his example and was able to communicate his enthusiasm. It was wonderful that his total commitment and enthusiasm extended to all aspects of his life.

Ann Radovsky, DVM, PhD
WIL Research Laboratories
Ashland, Ohio





[left] Cartoon entitled "Successful CPR" dedicated to Dr. Safar in 1994.

[right] Sculpture entitled "The Nine Ages of Man" by R.W. Johnston, in the University of Pittsburgh School of Medicine. Dr. Peter Safar was constantly striving to facilitate the natural course of this arc of life by preventing sudden cardiac death in people with "hearts and brains too good to die."

I first met Dr. Safar long ago when I was new to the world of CPR and EMS. Although I was just starting out, he believed in me and encouraged me time and time again. He often would review my writing and challenge me to think big, to question conventional wisdom, and to consider things from a global, humanitarian perspective. His guidance to do the right thing, even when it is politically incorrect, is a lesson learned that will always be a part of me.

Like so many others, I have been incredibly honored that Peter took such a sincere interest in my work and life. His philosophy on the need for universal training in life-supporting-first-aid that is simple, straightforward and easily accessible to the public has had a fundamental influence on my career.

More than this, though, Peter influenced my life. Over the years, he met most of my children and made a lasting impact on them, too. It wasn't so long ago that my daughters and I visited with him in his office over the customary espresso and biscotti (with a bottle of red wine handy, of course). He seemed to drop everything, though stacks upon stacks of projects were calling him, so he could give us his full attention. He proceeded to encourage my older daughter in her pursuit of a career in medicine and subsequently emailed back and forth with my younger daughter to help her with a school project.

How did someone as brilliant and prominent as Dr. Safar always find the time for everyone he met, no matter his or her stature? I think it was because he believed so passionately in the goodness of mankind and its potential for even greater goodness.

Thank you, Dr. Safar, for making the world a better place.

Mary Newman
Executive Director
National Center for Early Defibrillation
University of Pittsburgh Schools of Medicine

On our trip to Denver he was suffering from his spinal pain. His pain was so intense that any "normal" individual would need hospitalization to cope with. But he was still determined to attend the meeting.

All through the trip he continued to read, prepare his talk, and review my experiments. His talk was amazing, very detailed, accurate, and incredibly advanced and updated. He was without doubt the star of that entire session. He received, of course, considerable admiration from his peers and attendees.

After a well-done job, I thought that he would just relax and take care of his now advanced disease and pain, but not. He continued to meet colleagues, discuss research projects, and plan for future experiments.

On our way back, we were waiting for the next flight to Pittsburgh. He continued to ask details about our last experiments. I realized that he was in great pain and was trying to find a place where he could lie down so the cervical pain would be relieved. I suddenly found him lying down on the floor, as we did not find a better place. I was going to ask him how I could help, when he just opened his eyes, looked at me with a smile, and asked, "So tell me why do you think that the bleeding is more severe when trauma is added to ischemia in your experiments?"

Ala Nozari, MD, PhD
Former Research Fellow, 2001-2003
Massachusetts General Hospital
Boston, Massachusetts

Mr. Tore Laerdal, son of Asmund Laerdal, Resusci-Anne pioneer, and Dr. Peter Safar at the 20th anniversary celebration of the Safar Center for Resuscitation Research in 2000. Mr. Laerdal is President of Laerdal Medical and developer of Sim Man, which has heightened the Resusci-Anne concept for teaching resuscitation skills to a new level of sophistication.

Dr. Peter and Mrs. Eva Safar at the University of Pittsburgh Honors Convocation, February 2003. Dr. Safar was the keynote speaker and received an honorary Doctorate degree from the University of Pittsburgh, the fourth of his career.

I'm saddened to hear of the death of Dr. Safar. Although I wasn't in his presence much, it was enough to know that, in words I carefully reserve, he was truly one of "God's great creations." There are many people in the world that do good things; however, the number of people at Peter Safar's "level" is much fewer. He truly was a great man and will be sorely missed.

Robert C. Read
Lieutenant Colonel (Retired)
Project Manager, Clinical Applications Division
Telemedicine and Advanced Technology Research Center
Fort Detrick, MD 21702

From left to right, Mr. Robert Read, Mrs. Eva Safar and Colonel Dean Calcagni at the presentation of special recognition to Mrs. Safar by the United States Army Medical Research and Materiel Command for Dr. Safar's important contribution to the treatment of combat casualties. The presentation was held on October 30, 2003, immediately prior to the 24th Annual Peter and Eva Safar Annual Lectureship in Medical Sciences and Humanities. [A photo of this remarkable award appears on the first page of the tribute section.]

There is a lot to be thankful for and a lot of things to say about Peter Safar. He was a pioneer in anesthesia and intensive care medicine and dedicated his life to science. He educated many to become established researchers and was very eager to keep his international contacts, especially the bridge between Europe and the USA. I will also always remember Peter for the discussions about life and science at the local Chinese restaurant while drinking plum wine.

Sten Rubertsson, MD, PhD, EDIC
Associate Professor, Clinical Reader
Department of Surgical Sciences/Anesthesiology & Intensive Care
Uppsala University Hospital

My first meeting with Peter Safar took place in the lobby of the Sheraton Hotel in Boston on a cold February day in 1966. I was in the last months of my anesthesiology residency and as I was interested in the new field of "Acute Medicine," my mentor, Leroy Vandam, suggested that I contact the new up-and-coming star in this area - Peter Safar. As suggested, we met in the lobby of the hotel, where Peter was sitting with the now familiar files on his lap and countless rubber bands on his wrist. Attached to one of his files was my photo, and I was greeted with "Dr. Smith, pleased to meet you. So you want to be an Intensivist?"

Jan Smith, MB, ChB, MRCP
Professor & Vice Chairman
Department of Anesthesiology
Professor of Internal Medicine
University of Pittsburgh

In the late winter of 1952, the anesthesia department received its first supply of the new neuromuscular blocker succinyl choline. We had read about its rapid onset and offset and its paralyzing dose of about 100 mg for an adult. Before using it on patients, Peter Safar and I agreed to test it on each other. I was the first subject. In an anesthesia induction room, I lay on a stretcher with an anesthesia machine beside me. Peter injected a small dose, 20 mg, IV, which we assumed would only partially paralyze me. Within 20 seconds I discovered that I could not breathe or talk but could still use my arm. I reached for the anesthesia mask and tubing hanging beside me as if to alert Peter that I needed oxygen. Then my arm collapsed. He didn't get the message. But within a minute he noted my total paralysis and then put the mask on and gave me oxygen. In less than two minutes I was able to breathe, to sit up, then to stand up, then to jump up and down to prove that my strength had come back. However, the drug had given me intense lumbar back and thigh pain with the muscular fasciculations that occur as it depolarizes the neuromuscular junction, and that pain lasted many days. We cancelled doing the same thing to Peter.

John Severinghaus, MD
Ross, CA

From left to right: Drs. Lyn Yaffe, Patrick Kochanek, Florence Rollwagen and Peter Safar. Dr. Safar and Dr. Yaffe, former Director of Research and Development at the Naval Medical Research and Development Command and Combat Casualty Care Research area manager, at one of many meetings related to combat casualty care research. Dr. Safar's work in combat casualty care involved important interactions with both the U.S. Army and the U.S. Navy.

From left to right, Denise Kochanek, Dr. Peter Safar, Eva Safar and Dr. Patrick Kochanek celebrating the turning over of leadership of the Safar Center for Resuscitation Research to the younger generation in 1994. This photo was taken from the top of Mt. Washington, which boasts a great view of the city of Pittsburgh and was used by Dr. Safar during his career to recruit over 100 faculty members to the University of Pittsburgh.

When Mistress Medicine called nothing else seemed to matter to Peter or to any of us bound to him. A patient in crisis could not be denied, nor a trainee like me, who could ignore the Do Not Disturb sign on his office door, knock twice, and walk in to discuss a vital patient issue. He didn't mind and I knew he didn't mind, being disturbed. We were, after all, on the same mission.

His ideas appealed to my own desire to rescue patients at the edge of the abyss. His call for action was so clear that there was no sensible alternative: we can and we must. Peter's ideal physician would meet the patient in the field and escort him personally through the crisis. Effective restoration of breath in the service of life was his most obvious focus, and the quality of life as mediated through effective resuscitation of the brain was his larger concern. Peter also taught me what should happen when Death is inevitable. He railed vehemently against the stupidity or naiveté of those who refused to acknowledge when Death had won and demanded that palliative care receive as careful an effort as had rescue therapy.

What Peter the Idealist accomplished and taught was transformative. That his views eventually held sway, that the entire ICU team, led by the intensivist, should work together and treat the whole patient, is a tribute not just to his tenacity and powers of persuasion, but to the views themselves.

Thirty-five years after my life-changing encounter with Peter, his compelling personality, ability to inspire, and moral compass still resonate. What halcyon days to be so led!

James V. Snyder, MD
Professor, Department of Critical Care Medicine
University of Pittsburgh

In 1993 Peter prompted me to carry his life supporting first aid (LSFA) message to the masses and in turn became my mentor, confidante, and friend while carrying on this mission. His humanitarian efforts and research, along with his genuine charisma, will forever be remembered and cherished. As he was responsible for cradling so many souls back to life, he will always be remembered for his endeavors towards giving all human kind a "second chance."

Carol Spizzirri, RN
Founder, Save A Life Foundation
Chicago, IL

Lessons from Dr. Peter Safar:

- First and foremost, our role in life is to do something worthy of being written about or to write something worthy of others to read.
- All of us need to be devoted to the profession and strive to seek excellence daily in our efforts.
- Altruism is the essence for mankind. In one of his last letters to me he said, "Keep up your good missionary work." This truly was his mission in life for himself. He strived to instill this in all that he touched.
- Work hard, play hard, and live life to its fullest.
- Get to work early and stay late.
- Work with every individual and organization that is in position to make a difference.
- Find a purpose and devote your life's work to it.

Walt Stoy, PhD, EMT-P, CCEMT-PE
Professor and Director, Emergency Medicine Program
School of Health and Rehabilitation Sciences
University of Pittsburgh

Dr. Peter Safar at his 79th birthday celebration at the Safar Center for Resuscitation Research, April 12, 2003. Despite extensive metastatic cancer, Dr. Safar made important contributions to the mission of the Safar Center until two weeks before his death on August 3, 2003.

Peter Safar touched countless lives through his many contributions to resuscitation, critical care, and anesthesiology. In the history of medicine, very few physicians and scientists have had such an impact. Like the ripple on the pond that spreads in waves in all directions, Peter's legacy will continue to spread through those of us who had the great fortune of knowing him, working with him, or training with him (not "under" him, for he treated everyone as equal colleagues).

As we celebrate Peter's unique academic achievements, let us not forget his clinical side. He was an outstanding anesthesiologist. In the operating room, he devoted the same energy to patient care that, outside the OR, he devoted to research; always putting the patient first. His exploits were legendary. He was renowned for turning off the monitors and telling the residents, "(Pointing to the carotid pulsation.) Here is your EKG and blood pressure monitor. (Pointing to the tongue.) Here is your pulse oximeter. (Pointing to the pupils.) Here is how you monitor the depth of anesthesia." He was able to push trainees to their limits, safe in the knowledge that he could handle anything that might arise.

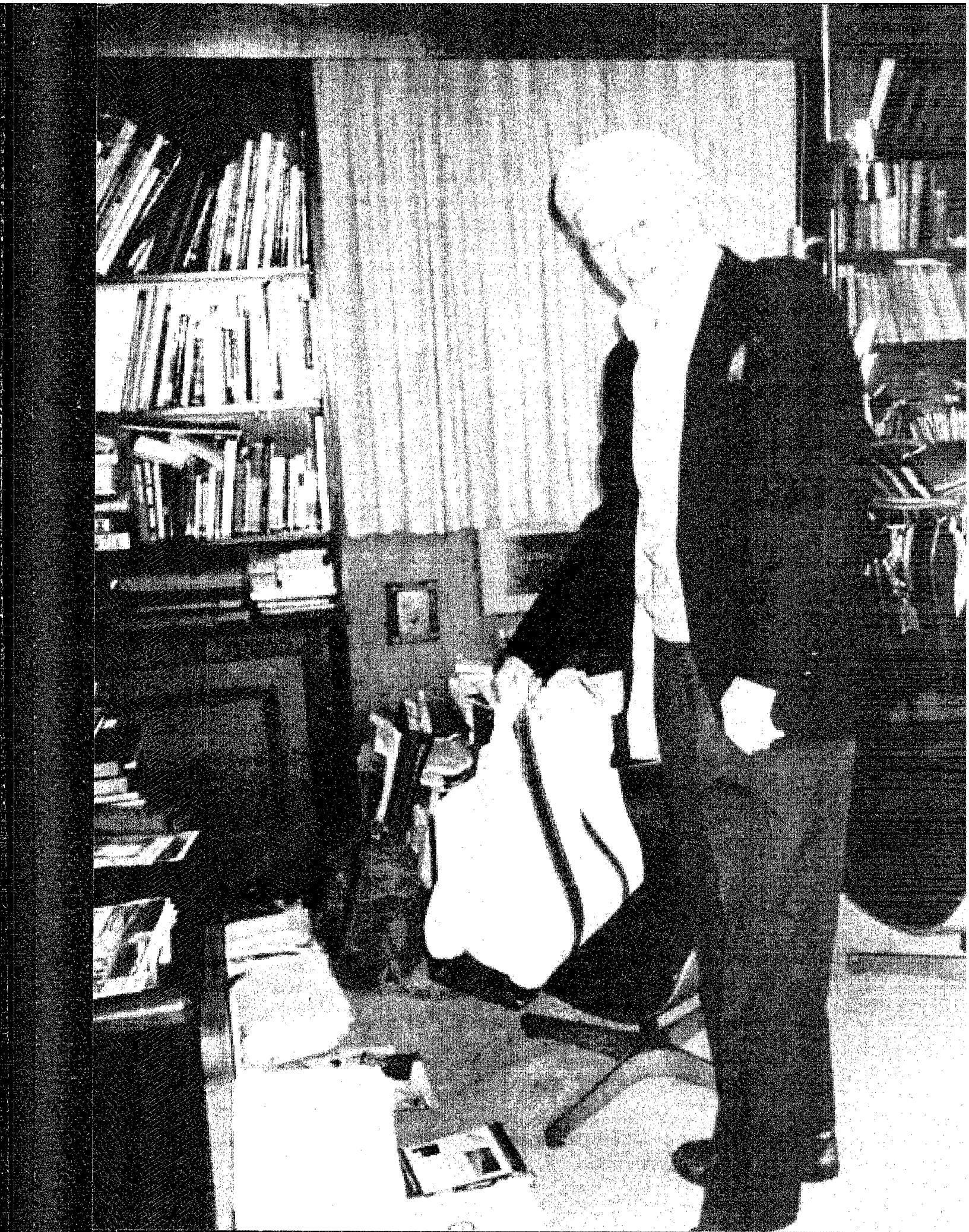
Peter's artistic, specifically musical, side was evident as he would describe an operation as "chamber music" in which all participants know their parts and no single leader is needed "to make beautiful music together." This was perhaps to the chagrin of surgical colleagues who think of operations more as symphonies, with the surgeon as conductor. Peter easily gained the respect and admiration of those of us on the other side of the ether curtain.

Peter Safar, our leader, teacher, mentor, and friend, will sorely be missed, but he has left his indelible mark on each of us and all of humanity.

Samuel A. Tisherman, MD
Associate Professor, Surgery and Critical Care Medicine
University of Pittsburgh

My most memorable time with Peter was when he was interviewing me for the Chair. He asked me, "What do you want to do with your life?" I told him I wanted to build a department that was world-renowned. He replied, "Yes of course, but what are you going to do to change the world?" That in one question is the way that Peter looked at the world. It was simply part of what one does in their life. One is expected to change the world no matter who you are or what you do. He was one of the most impressive men I have ever had or hope to have the chance to meet. Thanks for letting me get to know him.

John P. Williams, MD
Peter and Eva Safar Professor
Anesthesiology Chair
University of Pittsburgh
Pittsburgh, PA 15261



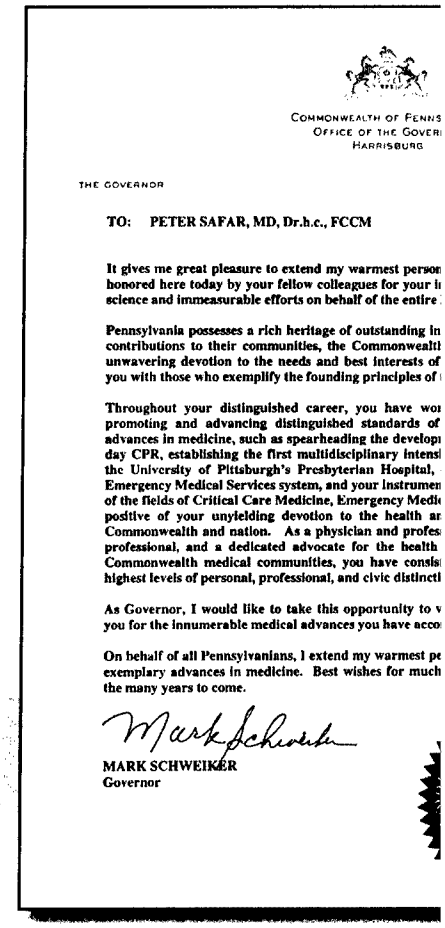
Dr. Safar was a key influence in our society, beginning with our predecessor organization, the University Association for Emergency Medicine, through today's Society for Academic Emergency Medicine. He shared his work and encouraged his trainees, many of whom are research and thought leaders in our field and our society, to join, to participate, and to improve the knowledge that has altered the care of the sickest patients. Much of our current success is due to Dr. Safar and his efforts; that legacy will endure.

Donald M. Yealy, MD
President, Society for Academic Emergency Medicine

Peter Safar in his home office, spring 1995.

Dr. Peter Safar had an enormous impact on so many individuals through his academic career, scientific leadership, personal warmth, and generosity. With certainty, he will never be forgotten, not only through the Center, lecture and symposia that bear the Safar name, but through the ongoing work of his students and associates who have learned the importance of deep caring and commitment to each person's well-being. I had the lasting pleasure of being a friend since the mid-1990's beginning at a "Lazarus meeting" to explore novel research topics for resuscitation of combat casualties. That friendship and dedication to advanced resuscitation techniques, particularly therapeutic hypothermia and suspended animation, has been a lasting inspiration to me. The vision of Dr. Safar will continue to inspire, and the dedication to his goals will remain strong. He leaves a lasting legacy, particularly through those countless individuals who never knew his name, but live and benefit because of his research and achievements in resuscitation and critical care medicine.

Lyn Yaffe, MD
Medical Director, Yaffe LLC
Former Director, Research & Development
Naval Medical Research & Development Command



COMMONWEALTH OF PENNS
OFFICE OF THE GOVERI
HARRISBURG

THE GOVERNOR

TO: PETER SAFAR, MD, Dr.h.c., FCCM

It gives me great pleasure to extend my warmest person honored here today by your fellow colleagues for your li science and immeasurable efforts on behalf of the entire

Pennsylvania possesses a rich heritage of outstanding in contributions to their communities, the Commonwealt unwavering devotion to the needs and best interests of you with those who exemplify the founding principles of

Throughout your distinguished career, you have wor promoting and advancing distinguished standards of advances in medicine, such as spearheading the develop day CPR, establishing the first multidisciplinary intens the University of Pittsburgh's Presbyterian Hospital, Emergency Medical Services system, and your instrumen of the fields of Critical Care Medicine, Emergency Medi positive of your unyielding devotion to the health ar Commonwealth and nation. As a physician and profes professional, and a dedicated advocate for the health Commonwealth medical communities, you have consis highest levels of personal, professional, and civic distinct

As Governor, I would like to take this opportunity to v you for the innumerable medical advances you have acco

On behalf of all Pennsylvanians, I extend my warmest pe exemplary advances in medicine. Best wishes for much the many years to come.

Mark Schweiker

MARK SCHWEIKER
Governor

University of Pittsburgh

Safar Center for Resuscitation Research

Office of the Director

3434 Fifth Avenue
Pittsburgh, Pennsylvania 15260 USA
412-624-6735
Fax: 412-624-0943

July 1, 1994

Dr. Peter Safar
International Resuscitation Research Center
University of Pittsburgh

Dear Dr. Safar,

I write this letter to you as my first official act as the newly appointed Director of the International Resuscitation Research Center. Unless you object, I would very much like to rename the Center in your honor. The most logical choice for the new name of the IRRC, is the **"Safar Center for Resuscitation Research."** Although this stationary is not finalized, I present you with this first letter as a memento of this event. It is my hope that the title "Safar Center" catches on as the new name for the institute. Clearly it is a name synonymous with resuscitation medicine.

I look forward to this exciting new challenge and thank you for this opportunity.

Best,

Patrick M. Kochanek, M.D.
Director, Safar Center

Commanding General
US Army Medical Research and Materiel Command
and Fort Detrick
Fort Detrick, Maryland 21702-5012

October 29, 2003

Dear Mrs. Safar:

On behalf of the entire US Army Medical Research and Materiel Command and Fort Detrick, I want to express my deepest sympathy to you and your family upon the death of your husband, Dr. Peter Safar.

Although I did not personally know your husband, I want to recognize his remarkable contributions to resuscitation medicine which have had an enormous impact on combat casualty victims in the United States military. His accomplishments included fundamental contributions to the development of cardio-pulmonary resuscitation, the establishment of the first intensive care units, and the creation of the Safar Resuscitation Center.

The Army owes Peter Safar a great debt of gratitude for all of his ground breaking work to radically improve the care and survival for severely injured people. You can be very proud of your husband's accomplishments. Please accept the thanks of a grateful Nation.

Sincerely,

Lester Martinez-Lopez, MD, MPH
Major General, Medical Corps
Commanding

City of Pittsburgh Office of the Mayor

A Proclamation

By virtue of the authority vested in me as Mayor of the City of Pittsburgh, I do hereby issue this proclamation honoring

PETER SAFAR

WHEREAS, Peter Safar was born on April 12, 1924, in Vienna, the son of Karl and Vinca and;

WHEREAS, after high school Peter was sent to a labor camp, where he dug ditches, and;

WHEREAS, in the fall of 1943, Safar was able to enter medical school and went on to become, in later years, the Chairman of Anesthesiology and Professor of Anesthesiology at the University of Pittsburgh as well as founder of and prior director of the International Resuscitation Research Institute at Pitt and;

WHEREAS, Dr. Safar basically invented cardiopulmonary resuscitation (CPR), along with another investigator and has spent his life improving methods of resuscitation.

NOW THEREFORE BE IT RESOLVED that I, Tom Murphy, Mayor of the City of Pittsburgh, do hereby commend Dr. Peter Safar for his dedication to improving the health and well-being of, not only the citizens of Pittsburgh, but citizens world-wide.

IN WITNESS WHEREOF, I have hereunto set my hand and caused the Seal of the City of Pittsburgh to be affixed.

Tom Murphy — Mayor

August 19, 2002 — Date

Peter Safar was a "giant" in the field of resuscitation. He was a founding father of this field and because of his insight, enthusiasm, and hard work, scores and scores of young and old scientists and clinicians have entered this area over the years. Peter was an engaging man with a quick-witted sense of humor and always knew what to say and how to say it in order to make someone feel special. I remember meeting him at one of the many resuscitation meetings we frequented and as we were discussing cardiac arrest/CPR at a poster session, he was continuously taking copious notes in a little notebook. In fact, he was writing so fast and furiously that it was a true distraction to me. I said, "Peter, why are you taking all these notes? Come on, it's me, Dick. You don't have to take notes. Let's just talk and argue." His response was classic Peter Safar: "I'm writing everything down because I don't want to forget the many important things you have to say here."

Richard J. Traystman, PhD
Associate Vice President for Research Planning and Development
Professor, Anesthesiology and Peri-Operative Medicine
Oregon Health and Science University
Portland, Oregon

Introduction to the Proceedings of the Second Annual Safar Symposium

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In the winter of 2002, the idea that an annual Safar Symposium be held at the University of Pittsburgh School of Medicine was put forth by John Williams, MD, chairman of the department of anesthesiology, University of Pittsburgh School of Medicine. Fortunately, Dr. Safar was able to take part in the first Safar Symposium in November of 2002. After an initial success in 2002, the second Safar Symposium was held—in conjunction with a memorial service to him—on October 30, 2003, in the Bioscience Tower at the University of Pittsburgh School of Medicine. The conference attracted about 150 clinicians and scientists from around the world and was sponsored by the U.S. Army Medical Research and Materiel Command. Selected portions of the proceedings of the Second Annual Safar Symposium are published as short articles on the pages that follow.

The proceedings highlighted two important aspects of Peter Safar's illustrious career, namely, resuscitation and education, and two important links that Peter Safar very much desired to see carried on in perpetuity—the link between the Safar and Laerdal legacies at the University of Pittsburgh and the strong relationship between the Safar Center for Resuscitation Research at the University of Pittsburgh, directed by Dr. Patrick Kochanek, department of critical care medicine, and the Winter Institute for Simulation, Education, and Research at the University of Pittsburgh, directed by Dr. John Schaefer, department of anesthesiology. The latter of these honors Dr. Peter Winter, former chairman of the department of anesthesiology, who followed Peter Safar in that role at the University of Pittsburgh. To that end, the Safar Symposium this year was composed of a morning session entitled "Breakthroughs in Resuscitation" and an afternoon session entitled "Advances in Human Simulation Education."

In 2003, the morning session focused on the use of hypothermia in resuscitation and neurointensive care. It featured six lectures by experts in the use of hypothermia in experimental and clinical brain injury. The topic of protective mechanisms of hibernation was addressed by Dr. John Hallenbeck, chief of the stroke branch at the National Institute of Neurologic Disorders and Stroke. The deleterious effects of rapid rewarming were discussed by Dr. John Povlishock, chairman of the department of anatomy at the Medical College of Virginia. The use of controlled normothermia to prevent secondary damage in neurointensive care was covered by Dr. Donald Marion, chairman of the department of neurologic surgery at the Boston University School of Medicine. A novel concept of using hypothermia-induced "suspended animation with delayed resuscitation" for otherwise unresuscitable combat casualties was the topic of Dr. Samuel Tisherman, associate director of the Safar Center and associate professor of surgery and critical care medicine at the University of Pittsburgh School of Medicine, and "smart catheter" strategies for rapid central cannulation in the field were addressed by former United States Naval Medical Research Institute director Dr. Lyn Yaffe of Alion Sciences.

The use of hypothermia in cerebral protection and resuscitation was a topic of great interest to Peter Safar because it was the therapy that had the greatest effect in all of the experimental models of cardiac arrest and shock that he studied during his career. Indeed, Dr. Safar recommended therapeutic hypothermia as part of an expanded ABC (airway, breathing, and cardiac compression) in a paradigm for Emergency Medical Services systems in the treatment of cardiopulmonary arrest as early as 1964 (1). The recent level I recommendation by the International Liaison Committee on Resuscitation, including the American Heart Association, supporting the use of mild hypothermia after cardiopulmonary arrest in adults has produced a tremendous surge in the interest and use of this promising therapy across the collective fields of acute medicine (2). The speakers addressed topics of great relevance to both our understanding of this therapy and its potential for novel future applications throughout acute medicine. The session was moderated by Dr. Clifton Callaway, associate professor in the University of Pittsburgh Center for Emergency Medicine, and Colonel Dean Calcagni, Deputy Director, Telemedicine and Advanced Technology Research Center, United States Army Medical Research and Materiel Command.

The afternoon session, "Advances in Human Simulation and Education," included six lectures. Dr. Doris Ostergaard, director of the Danish Institute of Medical Simulation, spoke on the renowned national simulation medical training program in Denmark. Dr. Michael DeVita, associate professor of internal medicine and critical care medicine at the University of Pittsburgh, spoke on the use of simulation in code team training to prevent medical errors. Dr. William Mc Ivor, assistant professor of anesthesiology at

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the University of Pittsburgh, discussed the use of simulation training for medical students during their anesthesiology clerkship. Dr. Paul Rogers, professor of critical care medicine at the University of Pittsburgh and respected expert in resident, fellow, and medical student education at the University of Pittsburgh, focused on the use of simulation in critical thinking by medical students. Finally, Mr. Tore Laerdal, president of Laerdal Medical, and Dr. Melinda Fiedor, clinical instructor and National Institute of Child Health and Human Development research fellow at the Safar Center and Winter Institute, addressed the topic of new areas for the use of simulation in medical education—including the hot topic of the potential applications of medical simulation in pediatric resuscitation and critical care medicine. Drs. Ake Grenvik, distinguished service professor of critical care medicine, and Peter M. Winter, professor and emeritus chairman of the department of anesthesiology, University of Pittsburgh School of Medicine, moderated this session on human simulation.

We would like to personally thank the United Sates Army Medical Research and Materiel Command, including the efforts of Colonel Dean Calcagni and Mr. Robert Read, for generous support of the symposium. We also thank Drs. John Williams, chairman of the department of anesthesiology, and Mitchell Fink, chairman of the department of critical care medicine, for additional support of this symposium. We thank Linda Amick, Fran Mistrick, Marci Provins, Valerie Sabo, and Christopher Edwards for their administrative and technical efforts on the symposium. Finally, we are very grateful to the authors of the articles in this supplement, both for coming to Pittsburgh to honor Dr. Safar and for their prompt delivery of their manuscripts, despite the hectic schedules we all face in 21st century academic medicine.

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Controlled normothermia in neurologic intensive care

Donald W. Marion, MD

Preclinical and clinical studies of therapeutic hypothermia completed during the last 15 yrs have dramatically expanded our understanding of this treatment for a variety of neurologic diseases, especially traumatic brain injury (TBI), stroke, and cardiac arrest. With few exceptions, the preclinical studies have shown that cooling of the brain to 32–33°C after trauma or ischemia leads to reduced levels of excitotoxic amino acids, reduced inflammation, a reduction in the volume of tissue damaged, and improved functional outcomes. Recently, two clinical trials studied the use of this treatment for patients with cardiac arrest and found improved outcomes for those cooled to 32–33°C for 12 or 24 hrs after the arrest (1, 2).

However, the efficacy of hypothermia for patients with severe TBI is not as clear. Although small clinical trials completed during the 1990s found benefit for subgroups of TBI patients treated with hypothermia (3, 4), Clifton et al. (5) did not find any benefit in a large, multiple-center trial of 392 patients completed in 2001. The results of this trial were surprising given the strong preclinical evidence in support of the efficacy of hypothermia for TBI and given the results of the smaller, single-center studies. Clifton et al. (5) also found that hypothermia was effective in reducing intracranial pressure. However, elevated intracranial pressure is closely associated with poor outcomes, so the results of the study by Clifton et al. (5) raise confusion about the link between intracranial pressure and outcomes. Based on the results of this trial, Safar et al. (6) have raised serious questions about the ability to conduct multiple-center clinical trials sufficiently controlled to allow for meaningful results. A subsequent analysis (7) of the consistency with which patients were medically managed in the study by Clifton et al. (5) seems to confirm some of the suspicions of Safar et al (6).

It also is possible, however, that therapeutic hypothermia is not as important in preventing secondary injury as is the prevention of fever. In the study by Clifton et al. (5), the temperature in the normothermia patients was tightly controlled to 37–38°C, and fever was aggressively treated. Such close attention to the prevention of fever in the control group may have reduced the expected morbidity and mortality in that group, resulting in outcomes that were similar to the hypothermia group. Several retrospective studies of patients with stroke, spontaneous intracranial hemorrhage, and subarachnoid hemorrhage have found an association between fever and poor outcomes. In this article, I will review studies that describe potential deleterious effects of fever and the incidence of fever in a typical neurologic intensive care unit (ICU), and I will conclude with results of a clinical trial that used an invasive temperature-modulation device to prevent fever in the ICU.

Laboratory Evidence of the Effects of Fever

In animal models of ischemia and of percussive or contusive brain injury, brain temperatures of >39°C are associated with an increase in the extracellular levels of excitatory amino acids and free radicals and with more extensive breakdown of the blood–brain barrier, increased enzymatic inhibition of protein kinases, and worsened cytoskeletal proteolysis (8). In a rodent ischemia model, hyperthermia (39°C) superimposed on transient ischemia led to a ten-fold increase in ischemic neurons and a significant increase in calpain activation and spectrin degradation (9). Others have found that the deleterious effects of hyperthermia are not confined to the time immediately after the insult. In their rodent ischemia model, Baena et al. (10) showed that even at 24 hrs after the insult, brain temperatures of >39°C led to a significant increase in the number of ischemic neurons in selectively vulnerable brain regions.

Clinical Evidence of Adverse Effects of Fever

Several retrospective studies have found a significant association between fever and outcomes after intracerebral hemorrhage, subarachnoid hemorrhage, and stroke. In their study of 196 patients with spontaneous intracerebral hemorrhage, Schwarz et al. (11) found significantly worse outcomes for those who had rectal temperatures of >37.5°C than those who did not. Oliveira-Filho et al. (12) reviewed the outcomes of 92 patients with subarachnoid hemorrhage, and found that 38 of these patients had rectal temperatures of >38.3°C for ≥2 days during the first week after hemorrhage. The odds ratio for poor outcomes (death, vegetative survival, or severe disability) in the subgroup with fever was 1.4 (95% confidence interval, 1.1–1.88) when compared with the patients who had no fever. Several studies have shown a similar effect of fever on poor outcomes for patients with stroke (13–15). In a meta-analysis of those studies by Hajat et al. (16), fever after stroke was found to be associated with a significant increase in neurologic morbidity ($p < .0001$) and with a highly significant increase in death ($p < .000001$).

Fever in the Neurologic ICU

Those who treat critically ill patients with neurologic disease are well aware that fever is a common problem during

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the first several weeks after the insult. The most common cause is nosocomial infection, and endotracheal intubation is a well-known independent predictor of pneumonia. These patients usually require intravenous and intra-arterial catheterization for the administration of fluids and for continuous monitoring of blood pressure and central venous pressure, but such catheterization also increases the risk for infection and sepsis. Other causes of fever are atelectasis, particularly in postsurgical patients who are not intubated. Fever is a common side effect of phenytoin, an anticonvulsant frequently used for trauma patients and patients with intracranial hemorrhage. The presence of blood in the subarachnoid space also has been implicated as a central cause for fever.

In 1999, we reviewed the incidence of fever in the neurologic ICUs of our hospital (17). During a 12-month period, 428 patients were admitted with stroke (34%), severe TBI (32%), subarachnoid hemorrhage (13%), and a smaller proportion of other acute neurologic diseases. Rectal temperatures were routinely obtained and recorded every 2–4 hrs. For the purposes of this study, a febrile episode was defined as a rectal temperature of >38.5°C. In all cases, the nursing staff was directed to aggressively treat fever with acetaminophen and cooling blankets. Despite this directive, febrile episodes occurred in 46.7% of the patients. There was no apparent correlation with their admission diagnosis, but there was a significant correlation with length of stay in the ICU: febrile episodes were observed in only 15.5% of those who spent <24 hrs in the ICU but occurred in 92.6% of those who were in the ICU for ≥2 wks. Other studies have found an even higher incidence of fever for patients in the ICU, confirming a strong association with duration of ICU stay and with endotracheal intubation (18).

Correlation of Brain Temperature with Rectal and Bladder Temperature

Another concern, and one that is certainly magnified by the animal studies showing a strong association between secondary brain injury and elevated brain temperatures, is the observation that brain temperatures are usually higher than rectal or bladder temperatures after TBI. We compared brain, rectal, and bladder temperatures for 5 days in eight patients with severe TBI (19). Deep brain temperatures were measured using a microthermister attached to a ventriculostomy catheter. Simultaneous brain, bladder, and rectal temperatures were obtained each minute during that time, for a total of 30,000 measurements. At virtually all time points, the brain temperatures were higher than the rectal or bladder temperatures. Brain temperatures averaged 1°C higher than rectal temperatures, and in nearly 10% of measurements, brain temperatures were 2°C higher. The differences between brain and bladder temperatures were slightly less, on average, 0.8°C. However, differences were greatest when the rectal or bladder temperatures were elevated. Thus, patients with rectal temperatures of 38–39°C were very likely to have brain temperatures of 40–41°C. Rumana et al. (20) completed a similar study of brain and systemic temperatures in patients with severe TBI and found that brain temperatures were frequently 1.1°C higher then rectal temperatures. Jugular venous temperatures were measured and were found to correlate with core body temperatures, but not with brain temperatures. The greatest differences between brain and core body temperatures were observed when the cerebral perfusion pressure decreased to <50 mm Hg and the smallest differences when patients were treated with high-dose barbiturates for control of elevated intracranial pressure.

Can the Incidence of Fever in the ICU be Reduced?

During the last decade, several groups have developed invasive devices designed to more rapidly reduce body temperature or to better maintain normal temperature. Laboratory investigations have shown that direct cooling of the venous blood with heat-exchange devices inserted into the vena cava can more rapidly cool the patient, or better maintain normal temperature, than surface cooling techniques. In 2000, a multiple-center clinical trial was initiated by the Alsius Corporation to determine if a heat-exchange catheter it developed could significantly limit the incidence of fever in patients with several acute neurologic diseases. Twelve hospitals participated in the study and enrolled 296 patients. Adult patients with spontaneous intracerebral hemorrhage, subarachnoid hemorrhage, severe TBI, and severe cerebral infarction were studied. Patients were randomly assigned to a group of patients who had their body temperature regulated via a heat-exchange catheter placed into the superior vena cava or a group of patients who had conventional fever management using antipyretic medication and cooling blankets. The former group had the heat-exchange catheter placed into the superior vena cava by percutaneous insertion through the subclavian or internal jugular vein, and cooled saline was infused through two heat-exchange balloons attached near the distal end of the catheter. The temperature of the saline solution infused through the balloons was adjusted automatically according to feed back to the external pump/refrigerant device from a microthermister attached to a Foley bladder catheter. The device was set to maintain a body temperature of 37°C. In the control group, temperatures of >38°C were aggressively treated with a acetaminophen, ibuprofen, and cooling blankets as needed. The primary end point of the study was the time the bladder temperature was of >38°C, expressed as the "fever · time product," during a 72-hr interval beginning soon after admission to the ICU. At the completion of patient enrollment, the majority of patients had either subarachnoid hemorrhage or severe TBI as their primary diagnosis, and patients in both the control and experimental groups had a similar distribution of diseases. Likewise, the age, sex, race, weight, body mass index, Glasgow Coma Scale score, and National Institutes of Health Stroke Scale score were not significantly different between the two groups. Final analyses of the temperature data revealed that there was a 64% reduction in the fever burden for patients with the heat-exchange catheter compared with the control patients.($p < .0001$). Differences between the two groups were comparable among study sites and among presenting diseases. There also was a 61% reduction in the use of cooling blankets, 66% reduction in the use of other physical means of cooling, and 28% reduction in the use of antipyretic agents in the heat-exchange catheter group. There was no significant difference in the use of antibiotics or sedatives between the two groups. There was no increase in the incidence of infection, sepsis, deep venous thrombosis, or other medical complications attributable to the heat-exchange catheter. *Post hoc* analysis also revealed that the fever burden was significantly higher in patients who died

Intravascular temperature modulation has been shown to be more effective for preventing fever than conventional methods, such as antipyretic medications or surface-cooling techniques.

(13.1°C hours) than in those who survived (7.7°C hours).

Summary

Preclinical studies of cerebral ischemia and trauma find increased brain tissue injury and worsened functional outcomes if the brain temperature exceeds 39°C. Several retrospective studies of patients with new-onset stroke, intracerebral hemorrhage, or subarachnoid hemorrhage support these observations. However, fever is very common among these patients early after the onset of their disease, particularly if they are in the ICU for a week or more, and brain temperatures are likely to be as much as 2°C higher than rectal temperatures. Finally, intravascular temperature modulation has been shown to be more effective for preventing fever than conventional methods, such as antipyretic medications or surface-cooling techniques. Further study is needed to establish if such better control of temperature will lead to improved outcomes.

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Suspended animation for resuscitation from exsanguinating hemorrhage

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Cardiopulmonary resuscitation with artificial respirations and external chest compressions have enabled initiation of life-saving interventions by lay persons and medical personnel, anywhere, anytime (1, 2). During normovolemic cardiac arrest, external chest compressions have a physiologic basis for efficacy. Open-chest cardiopulmonary resuscitation is physiologically superior (3, 4), although clinical studies have been inconclusive (5, 6). During exsanguination cardiac arrest, however, external chest compressions are not physiologically effective. Clinically, trauma victims who suffer cardiac arrest from exsanguination have almost no chance for intact survival, even after emergency department thoracotomy and open-chest cardiopulmonary resuscitation (7). Rapid attempts at fluid resuscitation and hemostasis lose the race against the tolerance limits for complete ischemia of 5 mins for the brain (8) and about 20 mins for the heart (8, 9).

The majority of soldiers killed in action in Vietnam without brain trauma had penetrating truncal injuries (10). They exsanguinated internally within a few minutes. Such casualties are still considered unresuscitable, although many have technically repairable injuries on autopsy. In 1984, Bellamy, a U.S. Army surgeon, and Safar met and pondered recent military casualty data and agreed that a novel approach was necessary (i.e., suspended animation). Suspended animation is defined as treatment to preserve the viability of the entire organism during ischemia, such as no flow (cardiac arrest) or low flow (shock). The goal is to induce suspended animation with hypothermia, drugs, and fluids. If instantaneous preservation of the viability of brain and organism could be achieved, one could buy time for transport and major hemostasis during clinical death, to be followed by restoration of blood volume and resuscitation, using cardiopulmonary bypass (CPB).

Suspended Animation Animal Outcome Studies

Since the late 1980s, researchers at the Safar Center for Resuscitation Research of the University of Pittsburgh have been engaged in systematic outcome studies in dogs for the development of suspended animation (11). In the initial series of experiments, Tisherman et al. (12–16) and Capone et al. (17) explored hypothermic preservation at tympanic membrane temperatures (Tty) of 15°C (deep hypothermia) or 5–7°C (profound hypothermia) after 30 mins of hemorrhagic shock at a mean arterial pressure 40 mm Hg. Suspended animation was induced by closed-chest CPB with hemodilution by crystalloids. After circulatory arrest of 60–120 mins, CPB was used for reperfusion and rewarming. Tty of 34°C was maintained for 12 hrs, controlled ventilation to 24 hrs, and intensive care to 72 hrs. End points included functional outcome in terms of overall performance categories (OPC 1 = normal, 2 = moderate disability, 3 = severe disability, 4 = coma, 5 = death) and neurologic deficit scores (0–10% = normal, 100% = brain death). Standardized necropsy included perfusion fixation of the brain and histopathologic damage scoring of 19 brain regions.

Profound cerebral hypothermia (Tty 5–7°C) induced at the beginning of exsanguination cardiac arrest improved neurologic outcome compared with that with deep hypothermia (15°C) (12, 13). The University of Wisconsin organ-preservation solution in the microcirculation during circulatory arrest did not add cerebral benefit over that achieved with standard plasma substitutes (14). These initial studies had been performed with standard CPB systems and systemic anticoagulation, which would be contraindicated after trauma. In a separate study, use of a heparin-bonded CPB circuit without systemic anticoagulation did not offset the beneficial effect of profound hypothermia (15). The optimal hematocrit during no flow under profound hypothermia is unclear (16).

The last study of this series was the most important (17). Sixty minutes of normothermic hemorrhagic shock was followed by rapid cooling using CPB and 60 mins of cardiac arrest at Tty of <10°C. Complete functional recovery was achieved, and, documented for the first time, the brains were histologically normal.

Clinically, CPB cannot be initiated within the critical 5 mins of recognizable cardiac arrest. A different approach is needed. Rapid placement of an aortic catheter could allow targeting of the brain and heart with a flush of cold fluid. A double-balloon catheter could allow differential flushing of the heart and brain while assisting with hemostasis.

Hypothermia Strategies. Subsequent studies have utilized a single-balloon catheter (Cardeon, Saratoga, CA) for flushing the aorta with isotonic saline, at a rate of 1–2 L/min, starting at 2 mins of no flow. Catheter design seemed to influence outcome; with the opening at the tip, the straight flush resulted in better outcome than that achieved using a catheter with the tip closed and the flush

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through multiple lateral openings. This flush at 0–4°C could lower Tty by 3°C per minute. The outcome model used included rapid, controlled hemorrhage from aorta and vena cava over 5 mins to cardiac arrest (which was ensured by inducing ventricular fibrillation), and aortic cold saline flush started at 2 mins of arrest, with drainage via the vena cava catheter (Fig. 1). The period of circulatory arrest was varied from 15 to 120 mins (18–21) under preservative Tty levels decreasing from 34°C to 6–10°C. Reperfusion and rewarming were accomplished with closed-chest CPB, primed with Ringer's and dextra 40 in saline.

With cardiac arrest of 15 mins of no flow, saline flush volume of 25 mL/kg (a clinically feasible, portable volume) at 24°C (room temperature) achieved Tty of 36°C and, at 72 hrs, functional normality with histologic damage, whereas the same protocol with saline at 0–4°C achieved Tty of 34°C, and two of six brains were histologically normal (18). With cardiac arrest of 20 mins (19), aortic arch flush rapidly lowered Tty to 34°C and achieved survival to 72 hrs with functional normality and minimal histologic brain damage.

For cardiac arrest of 15 or 20 mins, the catheter balloon was inflated in the descending thoracic aorta for aortic arch perfusion. With longer arrest times, ischemia of the spinal cord, gut, and liver became apparent. Hind leg weakness was observed. The authors found that the most reliable flush method might be the simplest: flush via a large-bore cannula in the femoral or iliac artery to include the entire organism. For circulatory arrest periods of >30 mins, very large volumes of cold flush solution would be required. For example, for a 70-kg adult human, this would translate to 7 L of iced saline, which is feasible for ambulances or emergency departments but not for field medics. For cardiac arrest of 30 mins (20), the flush volume of saline at 0–4°C was increased to 100 mL/kg via the femoral artery to achieve a Tty of 28°C; this achieved functionally normal brains (in some dogs, even histologically normal brains).

Cooling to a Tty of 20°C, 15°C, or 10°C preserved the brain and organism to achieve intact survival (OPC 1) after 60, 90, and in some dogs, even 120 mins of no flow (21) (Fig. 2). All six dogs with cardiac arrest of 90 mins and a Tty of 10°C were functionally normal, with no or minimal histopathologic damage. One dog, after cardiac arrest of 90 mins, one after cardiac arrest of 60 mins, and one normal dog without cardiac arrest had normal cognitive function based on a battery of tests 3 months later. Of concern clinically, however, was that delaying the start of flush to 8 mins of arrest in the 30-min cardiac arrest model negated the preservation achieved with flush starting at cardiac arrest of 2 or 5 mins (22).

To achieve a Tty of 10°C in an adult human with the flush strategy above would require enormous amounts of ice-cold fluid, which would be impractical in the hospital and impossible prehospital. Another approach would be to start with a single, small flush to achieve mild cerebral hypothermia and then to recirculate diluted venous drainage blood, with or without an oxygenator, through a cooler-heat exchanger, to reduce Tty to profound hypothermia (11). Nozari et al. (unpublished observations) found that the recirculation strategy enabled intact survival with full neurologic recovery after 90 mins of cardiac arrest at least as reliably as the initially used one-way flush but with one tenth the volume.

Pharmacologic Strategies. Pharmacologic approaches with novel drugs and solutions would be advantageous for induction of suspended animation by synergizing with hypothermia and, perhaps, decreasing the volume of flush that is needed (23–27). Even if the aorta could be accessed and cold flush initiated within the first 5 mins of normothermic no flow and a drainage catheter inserted into the vena cava, the 10- to 20-L cold solution (0–4°C) estimated to be required for a 70-kg adult human to lower Tty to 10°C (and core temperature to about 20°C) would not be feasible in the field. Although difficult in the ambulance or hospital emergency department, such large amounts of solutions could be stored in a refrigerator.

The same Pittsburgh team conducted

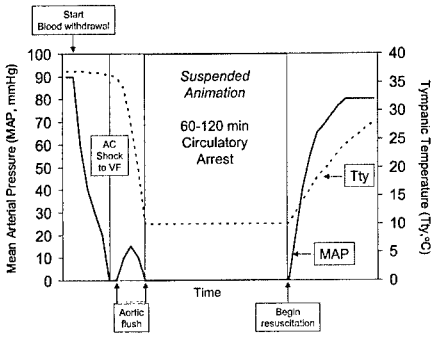

Figure 1. Model of exsanguination cardiac arrest, preservation via aortic flush, circulatory arrest for 15–120 mins, and resuscitation using cardiopulmonary bypass. *AC*, alternating current; *VF*, ventricular fibrillation.

	Overall Performance Category				
Arrest time	**1 Normal**	**2 Moderate Disability**	**3 Severe Disability**	**4 Coma**	**5 Dead**
15 min Tty 34°C	●●● ●●●	●			
20 min Tty 34°C	●●●●	●	●		
30 min Tty 28°C	●●●●	●●●●●*			
60 min Tty 10°C	●●●●				
90 min Tty 10°C	●●● ●●				
120 min Tty 10°C	●●	●	●	●	

Figure 2. Overall performance categories after exsanguination cardiac arrest of 15–120 mins with preservation via hypothermic aortic arch flush. *Tty*, tympanic membrane temperature. *Hind leg weakness.

the first systematic exploration of pharmacologic cerebral preservation potentials of 14 different drugs in 73 dogs (Fig. 3). The model used was 20 mins of exsanguination cardiac arrest with a potentially portable volume of flush solution (25 mL/kg) at ambient temperature, which achieved only mild cerebral hypothermia. In controls, saline flush started at 2 mins of cardiac arrest achieved survival with brain damage (19). In groups of three to six experiments per drug, various doses were flushed into the aortic arch via a balloon catheter, and in some experiments, additional intravenous medication was given during reperfusion with CPB. The drugs were selected and grouped according to six mechanistic strategies (26): 1) delaying energy failure, 2) protecting membrane integrity, 3) preventing structural degradation, 4) regulating protein synthesis, 5) preventing reoxygenation injury, and 6) preserving mitochondria. Selection of drugs and doses was influenced by published beneficial results (mostly in rodents) and guidance by expert consultants. Pharmacologic properties that would allow blood–brain barrier penetration were also considered. The goal was to identify a breakthrough effect (i.e., the majority of dogs in the miniseries to achieve OPC 1 at 72 hrs). None of the 14 drug treatments resulted in a breakthrough effect (23–25) (Fig. 3). Only an occasional dog achieved OPC 1 (but with some histologic damage) after thiopental plus phenytoin or glucose plus insulin. The antioxidant tempol, however, gave a suggestion of benefit (26). Tempol is available and inexpensive and penetrates the blood–brain barrier, but it is not approved by the U.S. Food and Drug Administration. All eight dogs that received 150–300 mg/kg tempol in the aortic arch flush at the start of cardiac arrest achieved OPC 1 or 2 (good outcome), whereas none of the eight control animals achieved good outcome ($p = .03$). Of concern, however, is that histologic damage was not significantly mitigated by tempol. Various explanations for this have been discussed (26). The only negative side effect of tempol, minimal transient methemoglobinemia, was clinically not significant.

One may criticize this exploratory approach because it is not possible to rule out some benefit possibly revealed by larger sample sizes and randomized concurrent controls. The cost and time involvement needed to conduct such studies in large animals would be prohibitive.

Solutions. In the studies described above, isotonic saline solution was used for flush and dextran 40/Ringer's solution for reperfusion via CPB. Solutions designed specifically for profound hypothermia have been explored (27–30). Using the 30-min cardiac arrest model with Tty of 28°C (20), polynitroxylated albumin plus tempol (Synzyme, Irvine, CA) slightly improved neurologic deficit scores and histopathologic damage scores compared with saline, whereas 5% or 25% albumin did not (27). Using the 120-min cardiac arrest model with Tty of 10°C (21), Normosol (a pH-normalized Ringer's solution) was used for cold flush and "Unisol" (two solutions: an "intracellular fluid" with composition designed for stasis and an "extracellular fluid" designed for reperfusion), designed by Taylor et al. (29, 30) (Organ Recovery Systems, Charleston, SC), was used. With these "optimized" solutions, OPC 1 and only minimal to moderate histologic damage was achieved in five of six dogs. Additional studies to optimize the solutions are needed.

Trauma. Exsanguinating hemorrhage in trauma patients does not occur without significant tissue trauma. Nozari et al. (31) explored the above suspended animation approach with trauma added in the form of thoracotomy, laparotomy, and splenic transection. Splenectomy was performed during arrest. The coagulopathy due to hemodilution, hypothermia, and ischemia was greatly worsened by trauma, even with use of fresh donor blood during resuscitation. Nevertheless, exsanguination cardiac arrest of 60 mins plus severe trauma could be reversed to intact survival, but multiple organ failure occurred in several animals. The encouraging finding was that brain histopathology was normal. This suggests that, with prolonged intensive care and rehabilita-

	Overall Performance Category				
Drug	1 Normal	2 Moderate Disability	3 Severe Disability	4 Coma	5 Dead
Control	•	•••	••••••	••••	
Adenosine			••		
Thiopental	••		••	•••••	
Thiopental Phenytoin	•		••	••••	
Fructose Biphosphate			••	•••	
MK801			••	•••	
YM872			•	••	
Nimodipine			•	•	
Diltiazem			•	•	
Lidocaine			••	•	
Insulin Glucose	•		••	•	
W7			•	•	
Cycloheximide			•••		
Tempol	•••••	•••	•	•	
Cyclosporine A			•	•	

Figure 3. Overall performance categories after exsanguination cardiac arrest of 20 mins with preservation via aortic arch flush and novel pharmacologic potentials.

tion (as could be utilized clinically), long-term intact survival would be expected.

Plasma exchange can decrease the microangiopathy seen in some patients with sepsis and multiple organ system dysfunction. Nozari et al. (unpublished observations), found that plasma exchange not only decreased the organ system dysfunction seen after trauma and suspended animation, but may also have improved neurologic outcomes.

Other Approaches. In addition to the Pittsburgh group, two other groups have explored the concept of suspended animation, although from somewhat different perspectives. Taylor et al. (29) and Bailes et al. (32) were interested in developing a method for protecting the brain during otherwise infeasible neurosurgical procedures. They showed that asanguinous low-flow perfusion of the organism with CPB of >3 hrs, under ultraprofound hypothermia (<5°C), could be survived with normal neurologic function. Specialized fluids were used during cooling, stasis, and resuscitation/rewarming. Long periods of total circulatory arrest were not explored, however. From a clinical perspective, in the exsanguinated trauma patient, intermittent low flow during suspended animation may be helpful for finding bleeding sites and, perhaps, improving preservation, although this remains to be explored.

Rhee et al. (33) have also explored suspended animation in a clinically relevant exsanguination model in pigs. Using readily available equipment, they induced profound hypothermia by aortic flush, both proximally and distally, via a thoracotomy and direct aortic cannulation. Repair of the aortotomy was accomplished during no flow. After total circulatory arrest of up to 40 mins, normal neurologic recovery could be achieved (33). The same group under Alam et al. (34) found normal cognitive function after exsanguinating hemorrhage from a vessel injury and prolonged asanguinous low flow (by CPB) at 10°C.

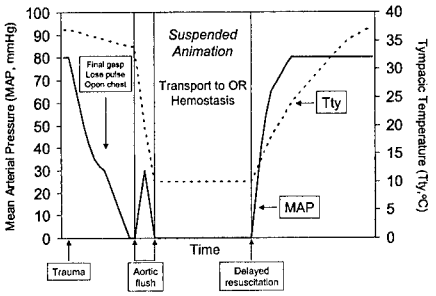

Figure 4. Possible clinical scenario for suspended animation in trauma victims with exsanguination cardiac arrest. As the patient becomes profoundly hypotensive, a last gasp and loss of pulse would be indications for rapid thoracotomy. If cardiac arrest is not rapidly reversed, the aorta can be cannulated and suspended animation can be induced via hypothermic flush to buy time for transportation to the operating room for control of major bleeding and delayed resuscitation using cardiopulmonary bypass. *OR*, operating room.

Cryobiology. Attempts at further extending the so far maximal duration of reversible cardiac arrest of 90–120 mins with hypothermia alone would take suspended animation research into cryobiology. Could one further extend the preservation time by going below 5°C? Profound hypothermia (5–15°C) has been shown in itself not to damage brain tissue (34, 35), but going below 5°C can cause denaturation of proteins and permanent cell damage, irrespective of the damage caused by ischemic anoxia (36). Ultraprofound cerebral hypothermia (<5°C) with special acellular synthetic solutions as blood substitutes, however, has been shown to preserve viability of rat hippocampus (36) and to achieve good outcome in dogs with low-flow CPB (32).

Future Directions

Potential Clinical Trials of Suspended Animation. For traumatic exsanguination cardiac arrest, clinical feasibility trials for the initiation of suspended animation are indicated, at least in emergency departments of major trauma centers (Fig. 4). Later, when appropriate devices become available for initiation of suspended animation outside the hospital, such feasibility trials could become part of emergency medical services research.

During severe hemorrhage without anesthesia, patients become unconscious when mean perfusion pressure decreases to <40 mm Hg, which is also about the point at which pulses are not palpable in large arteries. When apnea then ensues and pulsations are no longer palpable, one can assume cardiac arrest. Frequently, if the patient has had signs of life not long before this, emergency department thoracotomy is performed, particularly for victims of penetrating trauma. If a pulse cannot be rapidly restored, this could be a signal for accessing the aorta and administering the cold flush (i.e., inducing suspended animation). Drainage could be achieved rapidly by opening the right atrial appendage. The other potential approach for access would be cannulation of the femoral artery and vein via cutdown.

Given that the mortality rate for trauma patients who become pulseless from exsanguination and undergo emergency department thoracotomy is near 100% (7), clinical trials cannot be randomized. A reasonable approach would be to induce suspended animation after a brief period of unsuccessful resuscitation attempts, including thoracotomy and open-chest cardiopulmonary resuscitation. As clinical studies begin and experience grows, there are important questions that should be addressed. Who may benefit from expensive and labor-intensive suspended animation? What logistic problems need to be overcome to initiate suspended animation?

Device Development. To take suspended animation outside the hospital, devices for implementation will need to be developed. These devices should include a "smart catheter" to facilitate rapid percutaneous access to the aorta and vena cava, without thoracotomy and a miniaturized cooling-pumping device. Ideally, for portability in the field, the maximally miniaturized cooling source with pump could be developed for dual use: 1) for venovenous extracorporeal cooling for rapid induction of mild systemic or cerebral hypothermia in conditions with circulation (after normovolemic cardiac arrest, hemorrhagic shock, traumatic brain injury, stroke) and 2) for profound hypothermic aortic flush in conditions without circulation (i.e., suspended animation for cardiac arrest).

Other Applications. The main goal of suspended animation development has been to save some of the presently unresuscitable victims of traumatic cardiac arrest. It is worth keeping in mind that the suspended animation approach could also be useful when surgeons and anesthesiologists are unexpectedly losing ground with unmanageable hemorrhage during various surgical operations and for performing otherwise infeasible cardiovascular or neurosurgical procedures.

Summary

In dogs, isotonic saline at 0–4°C, flushed into the aorta at a rate of 1–2 L/min, with drainage of the vena cava, can achieve deep to profound hypothermia of vital organs at a cooling rate of up to 3°C per minute. This achieves preservation of viability of the organism during predictable durations of no flow: cardiac

arrest of 15–20 mins at Tty of 30–35°C, cardiac arrest of 30 mins at Tty of 25°C, cardiac arrest of 60 mins at Tty of 15°C, and cardiac arrest of 90 mins at Tty of 10°C. So far, pharmacologic approaches have not resulted in any breakthrough effect on outcome above that achieved with hypothermia, except perhaps the antioxidant tempol. Additional studies of novel drugs and, perhaps, combination therapies remain warranted. The optimal fluids to have in the circulation during circulatory arrest and reperfusions need to be determined. As laboratory studies to optimize suspended animation proceed, clinical trials should be initiated. In addition, devices should be developed to facilitate induction of suspended animation, eventually in the field.

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Smart aortic arch catheter: Moving suspended animation from the laboratory to the field

Lyn Yaffe, MD; David Abbott, BS; Bruce Schulte, BS

The objective of the ongoing smart aortic arch catheter research and development program is to engineer "smart" catheter systems for enabling rapid vascular access and catheter placement, primarily within the aorta, for emergency hypothermia and suspended animation induction (1–6). The catheter systems are being designed and engineered to emphasize easy and rapid vascular access and catheter placement, in a compact and portable system, for use by civilian paramedics, military medics, or other trained first responders. The rapid vessel access devices will ultimately provide the necessary means for inducing suspended animation or preservative-resuscitative hypothermia, initially for use in hospital emergency rooms, then mobile intensive care unit ambulances or helicopters, and eventually for paramedics at the point of injury and in the field for combat medics.

The catheters will have the capability of delivering a large volume of cold (~2°C) saline flush into the aorta within several minutes. Immediate and targeted emergency hypothermia interventions may be able to isolate vital organs such as the heart, brain, spinal cord, and associated vasculatures and to impose a state of clinical preservation until transport can be provided to a facility for acute surgical care and delayed resuscitation. The smart catheter program encompasses stepwise design and development of smart catheter components for vascular imaging, trocar guidance and insertion, catheter placement, cold-flush connections, and monitoring of hypothermia by first responders in the field. Prototype catheter designs, aortic arch ultrasound imaging, three-dimensional position tracking of trocar and catheter tips, and system integration thus far have demonstrated the clear feasibility of rapidly accomplishing smart catheter placement for suspended animation induction. Specific catheter designs and guidance systems provide easy, rapid insertion and placement of catheters within the aorta and thereby facilitate the use of lifesaving emergency hypothermia for otherwise unresuscitable conditions. Initially, catheters are being designed and developed for 1) direct aortic insertion by the trauma surgeon in an emergency room via a thoracotomy site, 2) transthoracic aortic placement by a paramedic in the field using semiautomated ultrasound guidance and magnetic position tracking, and 3) aortic placement via femoral access by a paramedic in the field, initially by ultrasound guidance.

The successful design and development of a smart catheter and its guidance and placement system must provide easy-to-use, safe, and efficacious self-sealing, multiple-lumen, aortic balloon catheters, for both civilian and military trauma scenarios, with sufficient portability for field use at or near the point of injury. The aortic arch balloon catheter system will enable: 1) easy, semiautomated, foolproof insertion, sealing against the aortic wall via thoracotomy or transthoracic access, and guidance and confirmation of ascending, descending, or aortic arch placement; 2) rapid delivery of cold-flush solutions into the aorta from an external reservoir; 3) hypothermic preservation of the brain, heart, and spinal cord; 4) access for continued suspended animation and transition to cardiopulmonary bypass; and 5) access for optimal rewarming and transition to normothermic cardiac function.

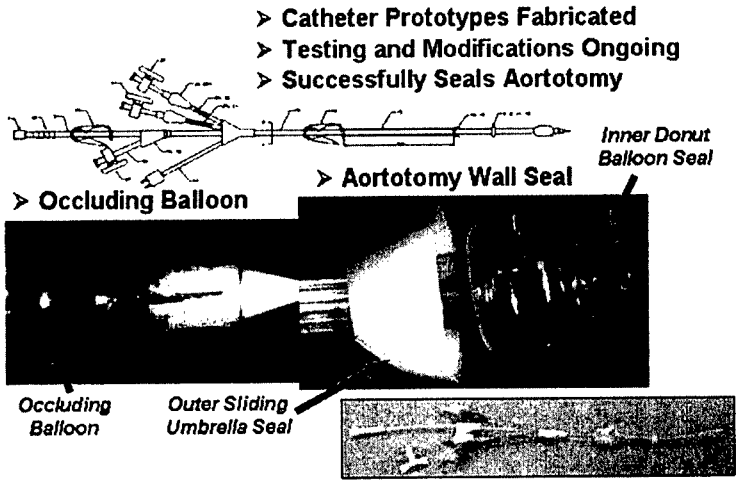

Figure 1. Thoracotomy catheter that has been designed and successfully tested in large animals. The catheter features include a mechanical seal for the aortotomy site consisting of an inner balloon seal and an outer sliding umbrella seal, which together compress the aortic wall to provide a tight seal. The aortic occluding balloon catheter provides aortic access for the delivery of cold-flush solutions.

From Alion Science and Technology, McLean, VA.

Key Words: suspended animation; hypothermia; delayed resuscitation; catheter; aorta; vessel access; portable ultrasound; magnetic position tracking

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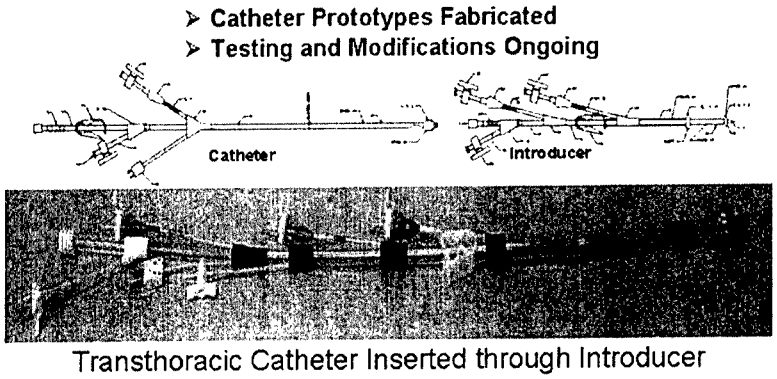

Figure 2. Similar to the thoracotomy catheter, the transthoracic catheter features include an introducer with a mechanical seal for the aortotomy site consisting of an inner balloon seal and an outer sliding umbrella balloon seal, which together compress the aortic wall to provide a tight seal. The transthoracic aortic occluding balloon catheter is then inserted through the introducer, as shown, to provide aortic access for cold-flush solutions.

Designs and Results

Catheters. Currently, the insertion of a catheter through the femoral artery into the aorta or directly into the aorta after left thoracotomy may be very quickly achieved. At trauma centers, surgeons are able to perform open chest heart massage in ≤1 min after confirming cardiac arrest and other options are exhausted. Similarly for closed chest scenarios, surgeons are able to cannulate the femoral vessels in humans within 3–4 mins during normovolemic cardiac arrest, while standard cardiopulmonary resuscitation is ongoing, well within the 4–5 mins before serious cerebral ischemic consequences. Ultimately, for exsanguinous no-flow, a direct femoral cutdown, left thoracotomy, or preferably, as proposed in this article, a smart catheter inserted transcutaneously is feasible and needed that quickly facilitates brain and heart cold flush. Rapid and easy vascular or aortic access is critical for the induction of emergency hypothermia and suspended animation at the point of injury to provide a brain and heart cold flush followed by continued fluid cooling. Even for experienced emergency room staff, identification and dissection of peripheral femoral vessels for insertion of arterial and venous catheters may take at least 15 mins in a pulseless patient, or even in a patient with low blood pressure. Typically, this emergency room intervention may be necessary to save the life of a victim using cardiopulmonary bypass for cardiopulmonary-cerebral resuscitation. The smart aortic arch catheter system is being designed for a fast, easy, and safe method to cannulate the aorta for targeted organ cooling. Catheter design and development has been ongoing and will continue by using approved materials for large-diameter balloon catheter and cannula designs. Both single and coaxial catheter designs have been explored. Simulation models have been constructed to produce breadboard configurations of the catheter and guidance systems working within closed-loop models of the aorta and phantoms for initial testing. Catheters and introducers have been fabricated with the assistance of Catheters and Disposables Technology (Minneapolis, MN).

For immediate interventional access, the smart catheter has been designed so that rapid access through the chest wall, from a parasternal approach, may be accomplished with subsequent direct insertion into the aortic arch. On insertion through the aortic wall, the catheter design includes the ability to provide a tight-sealing mechanism at the point of entry through the aortic wall to prevent fluid leaking from the aorta. Balloon-cuff concepts have been conceptualized and designed that may be adapted for this aortic catheter. An aortic arch catheter has been designed so that safe, easy, and rapid access to the aorta may be achieved through the chest wall from a transthoracic, percutaneous, or thoracotomy approach. Prototype, donut-shaped, balloon-cuff concepts have been designed and are used for this aortic catheter as one potential approach (Figs. 1 and 2). These designs maintain tight, leak-proof pressure on each side of the aortic wall. Ultimately, after delayed resuscitation, the point of aortic access would have to be closed surgically. Alternatively, access could be via the femoral artery, with a long catheter being extended to the appropriate position within the thoracic aorta or arch. The benefits of this approach include less potential damage to the aorta and the ability to have a lower placement of the catheter for increased cooling to the lower portions of the spinal cord and abdominal organs in the event of prolonged suspended animation, assuming the availability of adequate volumes of cold fluids.

Guidance and Placement System. For placement of the transthoracic introducer and catheter, portable ultrasound devices have demonstrated the ability to image the ascending aorta, the aortic arch, and the proximal descending aorta. Key images depend on suprasternal notch ultrasound probe placement. The ability to couple the image with access guidance and positioning of an introducer and catheter against the aortic wall was also demonstrated to be feasible using a bench-top prototype and ultrasound phantoms. Studies of the catheter placement challenge revealed the requirement for a location and placement capability based on ultrasound imaging integrated with three-dimensional position tracking. The initial details for integration of real-time ultrasound aortic arch images together with the trocar/catheter tip three-dimensional position have been developed. A software approach to provide this capability has been developed using ultrasound image and position data integration technology available through Cedara Software Corporation (Mississauga, Canada).

The smart catheter guidance, placement, and positioning system has been designed at this point to utilize three-dimensional ultrasound technology based on Cedara Software Corporation's Volume Explorer Framework technology. Position tracking has been successfully demonstrated using Ascension Technology's (Burlington, VT) miniBird magnetic tracking system. Although the smart catheter ultrasound system was initially configured to work with the Terason 2000 laptop-based portable ultrasound system (Terason, Burlington, MA), the current placement, positioning, and tracking system may be integrated with other portable or stationary ultrasound devices. The working prototype system is shown in Figure 3.

At this point in development, the demonstration prototype for the integrated

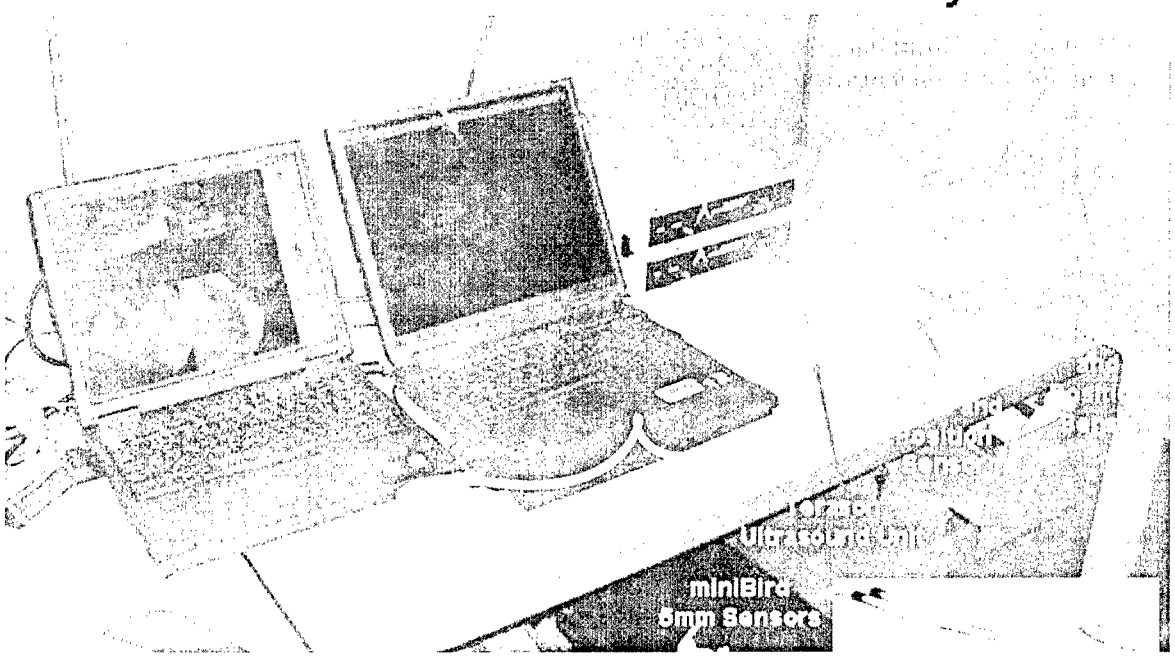

Figure 3. Current smart catheter guidance and placement demonstration prototype system, including the Terason 2000 portable ultrasound unit and ultrasound probe; the Ascension miniBird magnetic trackers, transmitter, and 5-mm position sensors; and ultrasound laptop and targeting laptop. Ultimately, all software and necessary interfaces will be integrated onto a single laptop or LCD for display.

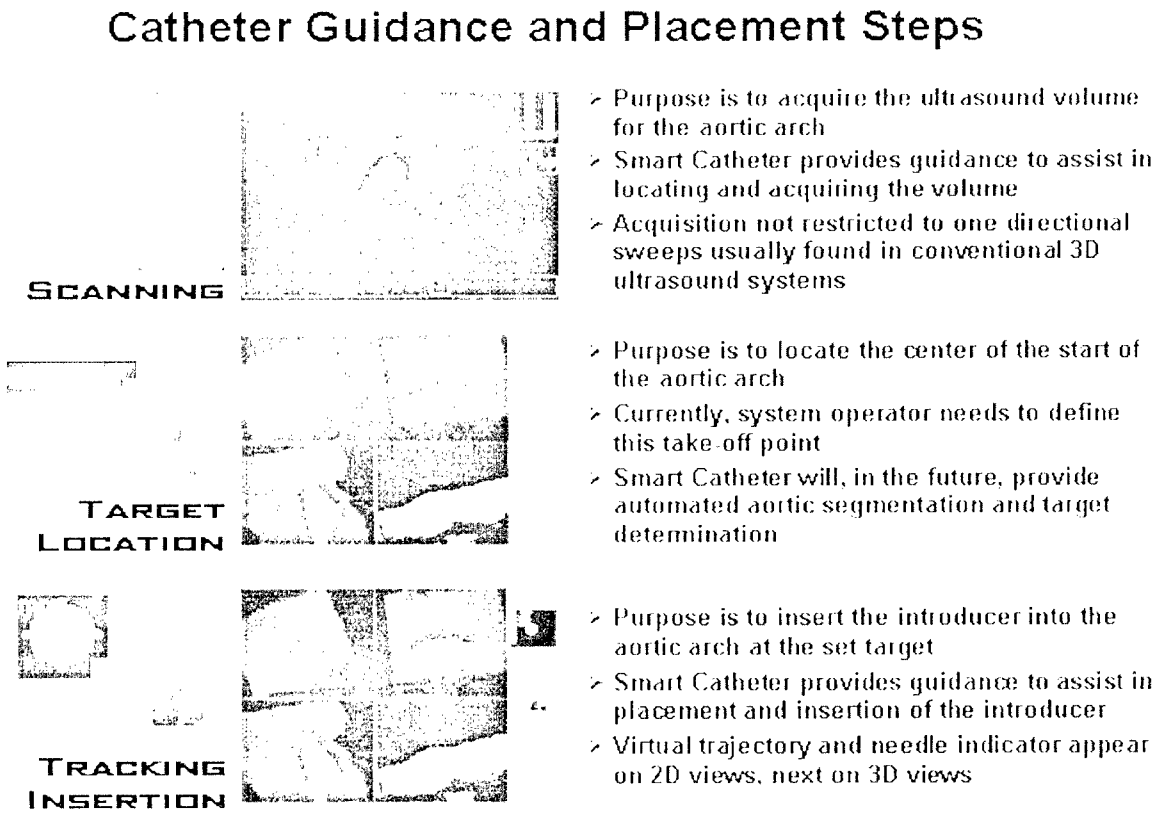

Figure 4. Three primary steps in the ultrasound-based guidance and placement system for the smart catheter into the aorta via a transthoracic approach include: scanning, target location, and tracking insertion. Ultimately, scanning will be continuous and in real time, target location will be fully automated based on aortic arch segmentation as is currently performed, and target insertion will be tracked in real time using a three-dimensional (*3D*) view and virtual trajectory for the introducer/catheter. *2D*, two dimensional.

Moving suspended animation from the laboratory to the field is now fully feasible and achievable in the near future.

guidance and positioning system includes: 1) the Terason laptop ultrasound system and ultrasound probe; 2) the Ascension miniBird magnetic tracker, transmitter, and 5-mm position sensors; 3) Cedara smart catheter–specific software; and 4) smart catheter introducer and catheter. The smart catheter software system divides the catheter placement and positioning procedures into three phases, including acquisition, targeting, and insertion. These functions are detailed in Figure 4, including computer interfaces displayed during the procedures. The design includes automatic target determination of the aortic arch point for catheter insertion. The system currently provides two user interfaces, one relatively complex interface displayed on the laptop and a second simplified interface displayed on a small LCD. Ultimately, when adequate resolution is available, a heads-up display will be employed to provide the user with catheter placement and positioning information.

The current system prototype seeks to incorporate a semiautomated to fully automated aortic/vascular target identification capability with image visualization enhancements. This is being accomplished through automated segmentation of the target of aortic ultrasound image followed by automated location of the catheter insertion target point on the wall of the ascending aorta. Ongoing work will also include the display of the introducer's trajectory in a three-dimensional view. Ultimately, for the transthoracic approach, a smart catheter "bib" concept, as shown in Figure 5, has been designed for stepwise development and will be prototyped. This smart catheter system bib will be placed on the chest and positioned to specific anatomic landmarks to aid in the positioning of the ultrasound probe, the placement of the magnetic positioning reference point, and the entry point for the catheter introducer.

Conclusions

The smart aortic arch catheter project goal is to meet the development challenge for field induction of suspended animation. Catheter seals have been successfully developed and tested, and the feasibility of an ultrasound based guidance, placement, and tracking system for the smart catheter has been demonstrated using the Terason laptop ultrasound system integrated with Ascension's miniBird magnetic position trackers and Cedara's three-dimensional ultrasound imaging and navigation software specifically adapted for the smart catheter system. Based on these initial design developments and prototype demonstrations, moving suspended animation from the laboratory to the field is now fully feasible and achievable in the near future.

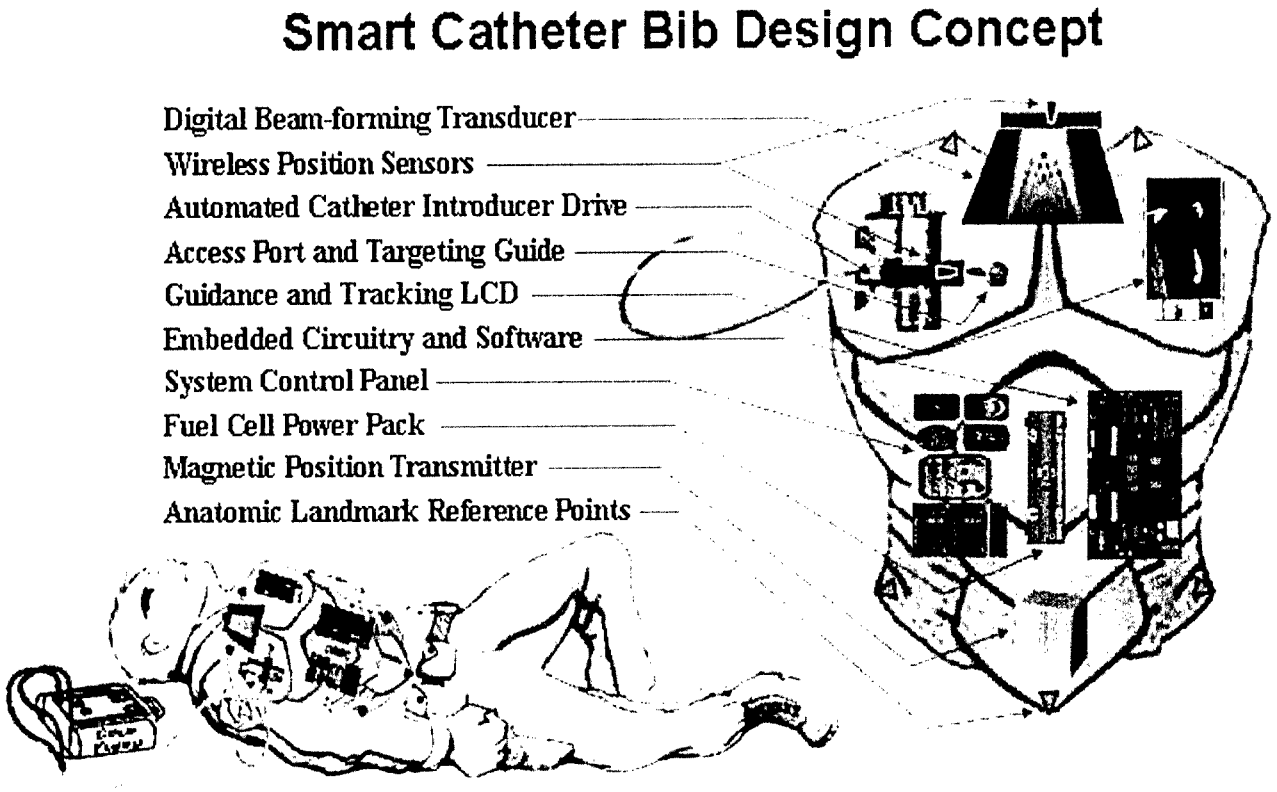

Figure 5. Smart catheter "bib" design concept that has been developed and will be prototyped in a stepwise fashion as key technologies become available. Initially, the bib will include only the ultrasound transducer, access port and targeting guide, guidance and tracking LCD, magnetic position transmitter, and anatomic landmark reference points.

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From Resusci-Anne to Sim-Man: The evolution of simulators in medicine

Ake Grenvik, MD, PhD, FCCM; John Schaefer, MD

Simulators were introduced in education as a tool to make advanced training standardized, less expensive, and without danger to those involved. In 1922 in the United States, Edward Link presented his homemade flight simulator, which became common place in both military and civilian aviation, known as the "Link Trainer." However, several decades passed before this form of training became accepted in medicine.

Already in the early 1960s, Peter Safar had become involved in medical simulation through opportunistic exposure and innovative research. Interested in potential reversal of death from accidents and medical problems causing cardiac arrest, he was disturbed by the poor results of the current resuscitation technique of nonbreathing victims. In discussions with Dr. James Elam, Peter Safar learned that artificial ventilation could be efficiently provided with normal arterial blood gases in anesthetized individuals simply by blowing into the endotracheal tube (1).

In the late 1950s, as chief anesthesiologist at Baltimore City Hospital, Dr. Safar undertook his daring experiments on sedated and curarized volunteers. He demonstrated unequivocally the lack of effect of arm lift/chest pressure ventilation efforts, whereas exhaled air provided through mouth-to-mouth ventilation was not only superior but also resulted in both adequate oxygenation and CO_2 elimination. This study was published in *JAMA* in 1958 (2), and Peter Safar reported on his results at an anesthesiology/cardiopulmonary resuscitation congress in Norway. In 1961, Bjorn Lind and other prominent Norwegian anesthesiologists, who participated in this congress, brought the idea of providing appropriate cardiopulmonary resuscitation training equipment to the attention of Asmund Laerdal, a successful entrepreneur in Stavanger, Norway, whose main business was the manufacturing of toys made of soft plastic materials. Laerdal promptly designed a full-size training mannequin for mouth-to-mouth ventilation. The airway could be obstructed, and it was necessary to use hyperextension of the neck and forward thrust of the chin to open the airway before initiating insufflation of air into the mannequin by mouth-to-mouth technique as described by Peter Safar.

At the recommendation of Dr. Lind, Asmund Laerdal visited Peter Safar in Baltimore for a demonstration of his mannequin. At that time, Kowenhoven, Knickerbocker, and Jude had just published their observation, showing that external chest compression could produce blood flow in cardiac arrest victims. Peter Safar advised Asmund Laerdal to include an internal spring attachment to the chest wall that would permit simulation of cardiac compression; thus, the possibility of training the ABC of cardiopulmonary resuscitation on the simulator was born, with A standing for airway, B for breathing, and C for circulation. This early simulator of a dying victim not breathing and without a heart beat became known as Resusci-Anne, and its utilization rapidly spread around the world.

In 1968, Ake Grenvik of Sweden joined Peter Safar's critical care medicine training program in Pittsburgh. He realized the many problems in training physicians to use proper technique when managing critically ill and injured patients, in whom relatively minor complications could create life-threatening problems leading to death. Through the close collaboration between Peter Safar's department of anesthesiology and critical care medicine on the American side and the Laerdal Corporation in Norway on the European side, Ake Grenvik, too, became very much involved in the exchange of ideas between Pittsburgh and Stavanger. After Asmund Laerdal's premature death of cancer in 1981, his son Tore Laerdal became the leader in their Norwegian family business. He continued the traditionally close relations and support of the Safar group. Having used a Link trainer as a former flight surgeon in the Swedish Air Force, Ake realized the need for advanced simulation training in critical care medicine and made repeated recommendations for the Laerdal Corporation to expand into modern computerized simulation technology. The Laerdal Corporation wisely awaited the right opportunity to start this expansion.

In 1995, only two, and very expensive, human simulators were available in the United States. At that time, Dr. Peter Winter served as chairman of the department of anesthesiology and critical care medicine after Peter Safar, who had withdrawn into his International Resuscitation Research Center for full-time investigations in the field of reanimatology.

Peter Winter had the foresight to acquire one of the available simulators, although at the very high cost of approximately $250,000. Drs. Rene Gonzales and John Schaefer of his Department were appointed director and associate director, respectively, of this simulation center at the University of Pittsburgh. These two ingenious young anesthesiologists designed a far less expensive, much more practical, realistic, and mobile simulation module, which was patented. The Medical Plastics Limited Corporation in Texas assumed responsibility for manufacturing of this new simulator. This company was

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Key Words: simulation-based training; Peter Safar; cardiopulmonary resuscitation; evidence-based education

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Simulation in medicine has been greatly influenced by Peter Safar and his collaborators in the University of Pittsburgh Department of Anesthesiology and Critical Care Medicine in the United States and in the Laerdal Corporation in Norway.

later acquired by the Laerdal Corporation, and the Laerdal Sim-Man was born. It is of interest that this simulator is provided at only one tenth of the cost of a human simulator in the mid-1990s.

Because of Dr. Winter's importance to the initiation of the use of human simulators in anesthesiology training, the Pittsburgh simulation center was renamed WISER, standing for the Peter M. Winter Institute for Simulation, Education, and Research. John Schaefer, who is the current director of WISER, has continued to improve the invaluable human simulators manufactured by the Laerdal Corporation. In addition to the full-size Sim-Man, there are also a large number of task trainers available. Gradually, some of these tasks are being incorporated into Sim-Man. Currently, an infant simulator is also in the final stages of completion, named Baby-Sim.

Medical simulators are not only realistic models of real patients, they also involve the most advanced information technology, providing a major simulation center such as WISER with the ability to offer standardized, repetitious training in various invasive procedures and in the decision-making process in crisis management. There are opportunities to acquire performance data online, providing analysis and immediate feedback to the trainees. Scoring is also available, and all performances are video-recorded for immediate or later demonstration to the trainee so that the trainee can see at which points the technique was considered correct or a failure. Statistical analysis of group performance is available, and research in education is therefore a simple task for publication purposes of the efficiency of this new and fascinating training technique.

In conclusion, the evolution of simulation in medicine has been greatly influenced by Peter Safar and his collaborators in the University of Pittsburgh Department of Anesthesiology and Critical Care Medicine in the United States and at the Laerdal Corporation in Norway. This collaboration has already led to cardiopulmonary resuscitation technique and learning on a worldwide basis. What started in cardiopulmonary resuscitation is now continuing, with physicians, nurses, and other healthcare personnel having the opportunity to learn complicated invasive procedures without endangering any patients. Modern, computerized simulators also offer unlimited possibilities for research on education in medicine, and evidence-based training may result in discontinuation of less effective education. Evidence-based education and training in medicine is likely to grow rapidly into a very important domain in our medical schools throughout the entire world.

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National Medical Simulation training program in Denmark

Doris Østergaard, MD

The general purpose of this article is to highlight selected aspects of the integration of simulation-based training in postgraduate medical education in Denmark. In the past decade, a broad range of simulators has been developed and introduced in the education of physicians and nurses. These tools were first used sporadically, but they are now formally integrated in the education of healthcare personnel as part of the former theoretical national compulsory courses for anesthesiologists. Simulation-based training seems to be useful for both novices and experts because the complexity can be controlled and the learners can reflect on their own practice and receive feedback. Postgraduate education is now facing a paradigm shift in Denmark, with assessment on a broader spectrum of competences (1) (discussed later) and training moving away from large-group teaching to interactive learning. From a theoretical point of view, simulation seems to be useful both for practical skills training and for the training of other aspects of competence, such as decision making, communication, leadership, and cooperation. Status for the implementation and perspectives for further use of simulation-based training are outlined.

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Key Words: simulation-based training; medical education; Denmark; anesthesiology; clinical practice

The Danish Institute of Medical Simulation is a subdivision of the Department of Anesthesia and is primarily funded by Copenhagen County. To this date, the simulation-based national courses have taken place in this center in collaboration with trained facilitators coming from several hospitals and simulation units in Denmark; the National Board of Health funded this activity.

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Start of Anesthesia Simulation in Denmark

The development of a Danish full-scale anesthesia simulator, Sophus, started in 1991 at the Department of Anesthesiology at Herlev University Hospital in collaboration with Roskilde University, Risoe National Laboratory, and an industrial partner. The idea of using simulation-based training and the concept of crisis resource management came from aviation and was introduced in anesthesia as anesthesia crisis resource management by Gaba et al. (2). The course focuses on skills such as decision making, communication, leadership and cooperation, and stress and resource management. In Europe, these are known as nontechnical skills (3). A Danish version, rational anesthesia, was introduced, and during the next decade, the anesthesia simulator was brought to local hospitals all over Denmark (4). Hence, training took place in an environment familiar to the trainees, and their own anesthesia equipment was used. A number of scenarios with critical incidents were included in the courses, and local procedures and guidelines were tested. Each scenario was followed by a debriefing session guided by a trained instructor, who facilitated the discussion and showed short video recordings of the participant's performance. The purpose of this debriefing session was to allow the anesthesia team of physicians and nurses to reflect on their own performance (medical expertise and nontechnical skills). Simulation was rapidly introduced in all areas of Denmark, and the enthusiasm from the instructors transferred to the teams of doctors and nurses, who evaluated the tool as useful and effective. They preferred this interactive learning to lectures and appreciated these courses, in which nurses and physicians were able to train and learn as a team. Looking back, these courses at local hospitals might be one of the reasons for the successful implementation of simulation-based training in Denmark. The nonthreatening, widespread use of this new tool was important. During the next 10 yrs, simulation was introduced as an educational tool in the formal training programs for physician and nurse anesthetists. In the beginning, the participants were limited to the anesthesia team, and anesthetists played the role of the surgeon; however, new courses for the cardiac arrest team, the neonatal resuscitation team, and the trauma team, including the actual team players, are now frequently run in our hospital (4). The learning concept has changed over the years, and simulation is now also used for building competence, providing the participants with the case in advance so that they may prepare themselves for the scenario.

Why Use Simulation?

Simulation is a technique for interactive activities and includes computer-based learning, practical skill training, full-scale simulation (human patient simulators), role playing, and simulated patients and relatives.

Today, patients often do not accept being used for the purpose of training; rather, they expect the health professionals to be competent. The major advantage of simulation-based training is that patients are neither harmed nor at risk. Simulation allows the trainee to focus, errors are allowed, and repetition is possible. This is not possible in clinical practice, in which the focus is on the patient rather than education. In a simulation scenario, all trainees can obtain the necessary level of competence before the task is performed on an actual patient. Furthermore, a wide range of scenarios, including uncommon but critical events, can be presented to the trainee. Systematic learning and practice of critical job skills and procedures, behavioral skills, attitudes, and values are possible. Last, complexity can be controlled, which allows training of both novices and experts.

From a theoretical point of view, simulation-based training seems to be very useful, as it fulfils the principles for effective learning. It is possible to start at a level consistent with the student's expertise, build on his or her knowledge base, encourage active participation, reflect, and evaluate progress on an individual basis.

Furthermore, it is possible to train individuals to become competent in the difficult setting of critical clinical situations, such as cardiac arrest. Based on the literature, this is needed. Several studies have shown that guidelines for advanced life support are not followed (5, 6), and focus group interviews with junior physicians have made it clear that they feel incompetent as team leaders (Lippert et al., abstract at the ASA Annual Meeting, San Francisco, CA, 2000). The qualifications needed for the anesthesiologists in this situation are theoretical knowledge and the consistent use of algorithms (medical expertise), manual skills and team performance skills (such as communication, leadership, cooperation, and the distribution of workload). These complex skills and attitudes cannot be taught in clinical practice or in lectures but are best taught in small groups and in situations in which the trainees are encouraged to reflect on their own practice.

Educational System in Denmark

In 2001, the Danish National Board of Health introduced new guidelines for postgraduate medical education, addressing a broad spectrum of competencies derived from the seven roles and competences defined by the CanMEDS 2000 Project (1). The seven roles are medical expert, scholar, communicator, health advocate, manager, collaborator, and professional. These roles are in agreement with the six competences described by the Accreditation Council for Graduate Medical Education in the United States. Focus has now changed from being solely on the medical expert role to skills such as communication and leadership. Hence, the question of how to teach the trainees a specific set of knowledge, skills, and attitudes becomes important. The outcome-based educational approach—exemplified by the three-circle model presented by Harden et al. (7)—has been an inspiration to the new anesthesia curriculum in Denmark. The layers in the circle illustrate the layers of competence. The inner circle represents what the trainees should be able to do, the middle circle illustrates the approach of the trainees to the task, and outer circle illustrates professionalism. A total of twelve learning outcomes serve as a framework. Issenberg et al. (8) have illustrated this in the cardiovascular program.

The clinical training program is being redesigned, as is the existing national theoretical program. The National Board of Health is financially responsible for the national compulsory courses that are given during the main part of the educational process. Until 1998, these courses were primarily theoretical courses based on lectures. The Danish Society of Anesthesia and Intensive Care Medicine Educational Committee appoints an individual as being primarily responsible for the learning objectives and hence the content of the courses.

National Compulsory Courses

Due to the growing interest in human factors, anesthesia crisis resource management, and new educational methods, the National Board of Health accepted a supplementary 3-day-long compulsory course in 1998. Thirty-eight residents participated in the first national simulation-based course in clinical decision making immediately before they received their specialist certificate. The program included four full-scale scenarios covering anesthesia and intensive care medicine, lectures, and cases in human factors and in group discussions. The participants were divided into groups of four, and the participants were matched with individuals attending from various hospitals and areas of Denmark. They rotated between the different simulator stations. In the scenarios, the participants had a high degree of exposure to the simulator as they worked in teams of two, while the others either participated as assistant surgeons or as active observers, who were directed to take notes. Debriefing was structured by the facilitator in order to match the learning objectives; however, the trainees could choose the topic they found necessary to focus on. The facilitator selected the parts of the video recording to be seen that were necessary to support learning. At this course, emphasis was on learning and not assessment, and although the simulation setting was new to the physicians, they saw it as a safe learning environment. The evaluations were overwhelmingly positive, and the trainees stated that this was the best of the courses that were offered. Comments included "preferred this type of training to lectures" and "more courses like this and at an earlier stage." After a 2-yr trial period, the course was included as one of the national, compulsory courses. In recent years, advanced technology has made it possible to use not only full-scale simulation, but a variety of different tools, and these are now implemented in the curriculum after a proper needs assessment and description of the learning objectives. Hence, we now use a mixture of case-based learning, computer-based learning, practical skill trainers, full-scale simulation, role playing, and simulated relatives.

The aim for years 2003 through 2006 is gradually to change all the national courses and to integrate new educational tools and methods in the curriculum for doctors during their second, third, and fourth year of training. The responsibility for the courses for first-year residents is regional, and in eastern and southern Denmark, simulation-based training is already integrated in the curriculum for nurses and doctors. This has been possible because of a close collaboration with the doctors responsible for education at all the teaching hospitals in these regions of Denmark.

Does It Work?

In Denmark, evaluation of educational activities is usually carried out solely by measuring the reaction of the trainee, the lowest level of evaluation according to the model of Kirkpatrick modified by Barr et al. (9). The evaluation of simulation-based activities is very positive; the tool is regarded as realistic and helps the trainee to reflect. In the medical domain, however, there is limited evidence of the effect of simulation-based training at higher levels, such as acquisition of knowledge and change in attitudes, changes in organizational practice, or changes in patient outcome (9). The gold standard would be to evaluate whether any learning activity had an effect on patient outcome, but because so many factors influence this variable, this would be difficult to carry out. Because of a lack of familiarity with the assessment of competence in Denmark, we have decided to start assessment of competence in the clinical setting, and a total of 21 specific tests are used (1) for first-year residents. A program for the main part of the education is now being introduced in Den-

We now use a mixture of case-based learning, computer-based learning, practical skill trainers, full-scale simulation, role playing, and simulated relatives.

mark. Assessment of competence in the simulator setting is possible in the future, but the setup needs to validated and the evaluators trained.

Status and Perspectives

In Denmark, the challenge has been to describe a competence-based curriculum focused on a broad spectrum of competences and to integrate new methods of learning and new educational tools, such as simulation-based training, in the curriculum and in the educational plans. The next major challenge is to evaluate the overall effect of this change.

From a theoretical point of view and according to the reaction of the trainees, simulation-based training seems to be useful. The experience the trainee has in the simulator is followed by a debriefing session, in which they can reflect and receive feedback. This is in accordance with the experiential learning cycle described by Kolb (10). Evidence of the positive effect of these learning methods or tools in the medical domain is, however, needed. The quality of educational research is dependent on a certain number of trainees, and this supports the building of simulation centers instead of a local setup. Collaboration between hospitals and simulation centers seems essential for studies of simulation-based training, as previously done by Schwid et al. (11) in the United States. Locally, less advanced techniques, such as simple skill trainers and computer-based learning programs might be available as these are relatively inexpensive and can be used with less instruction than the full-scale simulators. In contrast, expensive simulators and training in complex skills might be centralized for optimal use and most cost-effective training. It is mandatory that educators describe the need for new tools and collaborate with developers on future advances in simulators and educational programs.

Educational activities should be planned after a proper needs analysis and description of goals and objectives. This should be followed by the selections of the proper tools with respect to the context of the educational program and with plans for evaluation. Patient simulation provides a unique opportunity to train clinical skills, decision making, and team building. Hence, some of the simulation-based activities can be arranged as monodisciplinary activities, whereas others, such as team training, should be planned as multidisciplinary training (i.e., trauma team training and advanced life support) (4).

The use of simulation-based training is steadily increasing in our center; 1,200 physicians and nurses participated in full-day simulation-based training courses in 2002. Several hospitals now have access to anesthesia simulators and have started training locally. To this date, the national courses have taken place at our institution with the help of facilitators from other simulator units and hospitals. However, as soon as the local units have acquired competence as facilitators for larger courses, the national courses will be conducted at a regional level.

Collaboration is important to meet the objectives and improve quality. Establishing a simulation center is a complex project, especially with respect to staff education. The role of the facilitator is somewhat different form the role of a lecturer because the most important role is to ensure that learning takes place. It is a challenge to ensure consistency and quality of the activities and to establish quality improvement programs to prove that certain standards are met.

As described previously, we have chosen to assess competence in clinical practice, but in the coming years, assessment in simulation laboratories might be possible after the development of valid and reliable tools and appropriate training of the assessors. First, however, it is essential that we provide scientific evidence for the effect of the training methods used, close the loop between education and clinical reality, elucidate whether training makes a difference in the real world (transfer), and demonstrate that patient safety is improved. Hence, collaboration in high-quality research studies is needed.

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Improving medical crisis team performance

Michael A. DeVita, MD; John Schaefer; John Lutz; Thomas Dongilli; Henry Wang

Human patient simulation is an effective tool in medical education for individuals (1–6) and trauma teams (7). However, there are no reports of training teams to respond to other medical crisis situations. Although not widely reported in the medical literature, many professionals recognize that in-hospital team response to a medical crisis may be chaotic. To try to improve crisis response at the University of Pittsburgh, we created the Crisis TEAM Training course that utilizes Web-based computerized human simulator technology (TEAM is capitalized for emphasis). Our preliminary experience in improving design of a crisis response and training multidisciplinary teams to respond to in-hospital crisis events is described in this article.

Setting

The University of Pittsburgh Medical Center Winter Institute for Simulator Education and Research is a medical education center staffed with four personnel and possessing ten full-body Laerdal SimMan simulators and 12 partial-task trainers. The Institute occupies 7000 square feet of space on two floors in one of the University of Pittsburgh Medical Center hospitals.

Simulator

The Laerdal SimMan simulator is a computer-based mannequin with human physiology emulation capability. For example, the airway is dynamic and can simulate a variety of pathologic conditions. Air flows through the airways. A number of different breath sounds are possible, including wheezes, rales, rhonchi, and normal breath sounds. Heart sounds can be simulated, as can a variety of arrhythmias. The chest rises with respiration, whether "spontaneous" on the part of the mannequin or after manual or mechanical ventilation. A speaker enables the "patient" to speak. Pulses are palpable, blood pressure may be obtained, and fluids are infused into "veins." Pulse oximetry is also possible.

Video Recording Capability

We utilized two video cameras in the simulation patient room using a digital video recorder from EZCam (VT400, Trenton, MI). The SimMan patient monitor video was also captured by the VT400. The EZCam software resident on the digital video recorder allows playback of the cameras and patient monitor onto any computer via a Web browser.

Trainees

We have now trained >200 individuals. All trainees for the Crisis TEAM Training course were advanced cardiac life support (ACLS) certified within 2 yrs of their simulation training. We rationalized that because we wanted to focus on team skills like organization, communication, and interdependency, we needed learners who already had the knowledge of what treatment is required and what skills to provide in emergency situations. The trainees include critical care nurses, respiratory therapists, and physicians. Every session has at least one person from each discipline. Physicians are predominantly trainees, including fellows in critical care medicine and pulmonary/critical care medicine and junior and senior residents in internal medicine, anesthesiology, and emergency medicine. Hospitalists and critical care medicine attendings have participated as well.

Curriculum. The Crisis TEAM Training course consists of four components: 1) a Web-based power point presentation that trainees view before coming to the simulator, 2) a brief didactic session by one of our faculty members, 3) video-recorded simulations, and 4) a facilitator-moderated debriefing, aided by a customized Excel spreadsheet for performance evaluation.

Two of our crisis-response experts developed the PowerPoint presentation that was placed on our Web site. This presentation describes the need for crisis teams as opposed to cardiac arrest teams (the latter respond after cardiopulmonary arrest in an attempt to restore life, whereas crisis teams respond before arrest in an attempt to prevent death). A full description of the process and rationale for it has been reported by several authors and is outside the scope of this discussion (8–12). The presentation reviews some barriers to error-free responses. Importantly, we describe our design for team response: team member roles, the goals for each team member, and the tasks delegated to that role (Fig. 1). We have used automobile racing pit crews as an example of effective teamwork: delegation of task responsibility to specific team members, choreographing of movements so that team members do not interfere with each others' activities, and prioritization of tasks. We also model after Advance Trauma Life Support, which teaches positioning of team members based on skill set and task responsibility. All Crisis TEAM Training participants are required to view the presentation and complete a pretest.

Simulation Scenarios

We created five simulator scenarios for the training sessions (Table 1) and use three different simulated crisis scenarios during each course. No scenario was repeated for any group, and three were used to prevent trainees from discovering before the course all the situ-

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Key Words: human simulation; medical emergency teams; medical crisis; medical education; advanced cardiac life support; resuscitation; cardiac arrest; team training; error prevention; patient safety; medical errors

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ations they would encounter. Each scenario begins by reading a scenario introduction to a trainee, who would then alert the crisis team. The team then responded and treated the simulated patient. We stopped the response when the definitive treatment was delivered and a triage decision was made, or at 5 mins, which ever occurred first.

Measuring Crisis Response Performance

The primary goal of the crisis team is to achieve mannequin survival. Survival required effective airway management ventilation and maintenance of circulation. In addition, selected scenarios contained a definitive therapy (like defibrillation with 300 joules within 3 mins for ventricular fibrillation) that was considered a key element of successful crisis response.

Sometimes, treatment that saved the life was delivered but other important goals that may have improved outcome (like delivering an appropriate dose of naloxone for opioid overdose) were not completed and a critical incident designation was assigned. Such critical incidents were still considered simulator survival.

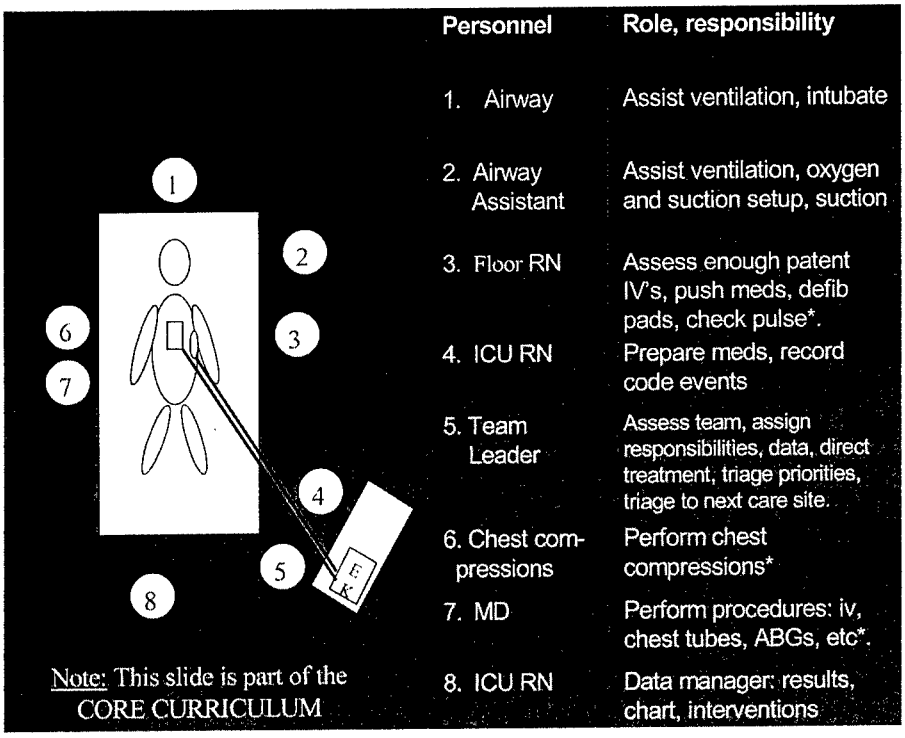

Figure 1. Roles, goals, and positioning for crisis team response. Detailed planning is needed for most effective and efficient team response. *IV*, intravenous; *meds*, medications; *defib*, defibrillator; *ICU*, intensive care unit; *ABG*, arterial blood gases; *RN*, registered nurse; *MD*, physician.

Another outcome we measure is the completion of key organizational and treatment tasks. We assess the task completion rate by consensus of the trainees and facilitator after reviewing the recording of their response. A set of 29 tasks was defined, although not every task was required for every scenario. The task completion rate is assigned for the number completed divided by the number applicable for each scenario. The tasks fall into three domains: 1) patient assessment and treatment (e.g., assessing cardiac rhythm, delivering defibrillation), 2) organizing the response (e.g., delivering essential equipment, positioning personnel in appropriate locations, allocating work), and 3) communication (e.g., utilizing closed loop communication, data transfer). We are able to determine source of failure because we assess the task completion rate for each role, each individual, and for the whole team.

Debriefing Sessions. Session scoring is recorded at the time of debriefing on a preformatted Excel spreadsheet. Tasks are determined to be completed or not and are assigned a score of 1 or 0, respectively. We play the video for the first 60 secs, and then the trainees assign scores for each task. The next 2 mins are then reviewed, followed by scoring of the 3-min goals. Finally, the remainder is shown and discussed. The facilitator's role is to ask questions regarding barriers to care, elicit suggestions for improvement, and attempt to focus on the organizing team's response. Team performance rather than individual performance was promoted. For example, the team gained credit even if the individual who completed a task was not responsible for that task. We emphasized the multiple-step processes needed to accomplish "simple" tasks like chest compressions: the team

Table 1. Scenarios and definitive treatments

Scenario	Scenario Description	Definitive Treatments	Time Frame, Mins
1	Ventricular tachycardia induced dyspnea	Cardioversion	3
2	Acute myocardial infarction and arrhythmia	Cardioversion	3
		Request for "chest pain team"[a]	3
3	Morphine overdose during patient-controlled analgesia	Mask ventilation	1
		Naloxone[a]	3
4	Acute stroke with mental status change	Mask ventilation	1
		Request for "stroke team"[a]	3
5	Ventricular fibrillation	Chest compressions	1
		Mask ventilation	1
		Defibrillation	3

[a]Denotes goals, which if not completed, permit survival but are a "critical incident."

must 1) place the backboard immediately, 2) allocate two individuals to check for the presence of a pulse, 3) initiate chest compressions, and 4) assess effectiveness of compression.

Hypothesis: Crisis TEAM Training Improves Simulated Survival and Team Organization

Increased task completion rate seems to be associated with improved simulator survival. Among the first ten groups trained, in the first three scenarios of a single training course, survival was 0%. In contrast, the teams successfully treated the mannequin in the third scenario 90% of the time (Fig. 2). This difference was statistically significant (Cochran's Q, 12.6; $p = .002$). The team task completion rate significantly improved from 31% to 89% (Kendall's W, 0.91; $p < .001$) (Fig. 2). Every team showed improvement in their task completion rate, and all but one successfully delivered indicated treatment to cause simulator survival.

It is interesting but disturbing that initially all teams performed poorly even though each team member had previous ACLS certification. We believe our simulator data corroborate the findings of others that ACLS training may not predict future successful performance of ACLS (13, 14).

We suggest that ACLS training is effective in improving knowledge of certain diagnoses and indicated treatment (e.g., recognition of arrhythmias like ventricular fibrillation and the need for defibrillation) but less effective in training skills. In contrast, our simulator exercises focus on individual and team skills directed at organization and task completion (i.e., how to get it done). We have observed that it can be difficult to complete simple tasks when a large number of professionals from many disciplines respond. It is easy for any number of tasks to "fall between the cracks." A crisis situation requires a number of simultaneous, sequential, and coordinated interventions, usually performed by a variable number of responders who are arriving in an uncoordinated order. Our training program attempts to organize these interventions, from selection and placement of equipment to roles and goals of each individual that responds to the crisis.

Our preliminary experience suggests that this model for teamwork is not only feasible but potentially results in superior resuscitation process and outcome. Because we do not train medical procedural skills (like endotracheal intubation) but rather communication and teamwork skills, we believe that our data suggest that these latter skills may be highly important for an effective clinical management of life-threatening emergencies.

Standardization

To organize a crisis team response, the response must be planned in detail and then taught. First, organizers must identify who will respond, what equipment will be available (and how it will get there), what tasks need to be done, in what order, and who will perform them. Equipment should be identical for every response. If each response team uses different equipment, or equipment and medications on the crash cart varies, responders will need to "learn" at every event what equipment is present, where it is located, and how to operate it. This is obviously inefficient and potentially dangerous. Figure 3 shows how confusing various types of defibrillators can be. Second, it is important to consider each step needed to accomplish a task and allocate responsibility for each step. Groups of individuals are more likely to accomplish multiple-step tasks efficiently (once trained) than a single individual because they can delegate the work and perform the needed tasks in parallel. For example, defibrillation is not a task but a goal that requires 14 steps (or tasks) be completed (Table 2).

Third, practice is needed because it helps improve both task delegation and performance. When the team response is choreographed and rehearsed, it may become obvious that certain team members are overburdened or underutilized. Practicing in the simulator setting enables redesign of the response to achieve the best efficiency and effectiveness. One can also use the simulator practice sessions to identify common errors. For example, we found that team members often are incorrect about the presence or absence of a pulse. Because this presence of a

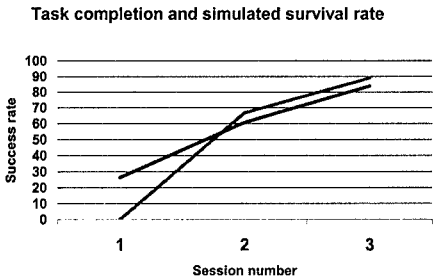

Figure 2. Overall team task completion (*dark line*) and simulated survival rate (*light line*) during first, second, and third scenario encountered by trainees during a 3-hr Crisis TEAM Training program.

Figure 3. A variety of defibrillators with varying capabilities and requirements for accessory equipment. Some defibrillators have pacing capability, others have hands-free technology using defibrillator pads, and others use paddles and require gel pads to augment conductivity. All utilize different operating procedures. With a variety of equipment, it is easy to understand why user errors are common.

pulse is a critical clinical finding, getting it right is essential to make the team deliver the appropriate treatments. We changed our response so that at all times two team members are palpating the pulse, making it less likely that an error will occur. Because two individuals are searching for an event, they are able to cross check findings. Designing in certain redundancies such as this may prevent important errors. Another common error is failure to communicate key data to a decision maker. For example, one person may be observing a pulse waveform on a pulse oximeter at the same time as another person may lose the pulse and report asystole to the team leader. The team leader may incorrectly request chest compressions even though there is evidence that effective circulation already exists. For this reason, we also emphasize proper communication techniques (i.e., identify who needs to know a fact, address that person directly, and the receiver should repeat it back to be sure the message is correct). This speak–repeat back technique has been used in the military and civil aviation for decades to prevent error. The Joint Commission for Accreditation of Healthcare Organizations favors repeat-back methodology for verbal orders for the same reason.

Our training program emphasizes team cooperation more than just leadership. When we began team training, we thought that the chaos during a crisis response was lack of effective leadership. Therefore, in our first efforts, we attempted to train team leaders to both direct tasks to individuals for completion and to direct therapy. We found that this overloaded the team leader, and key tasks failed repeatedly. We then changed our focus to team training. We reasoned that if each team member knew what the team needed, his or her role in the team, and the tasks associated with that role, the team leader instead could focus on assimilating and analyzing data and then directing treatment interventions. This strategy, although tougher to train, resulted in improved performance (Tables 3 and 4). It also more clearly resembles the strategy used by our model, automobile racing pit crews. We have found that team training using a human simulator may increase the success rate for specified tasks, and there is possibly an association between the processes we measured and the simulated outcome. We believe we saw that knowledge of what treatment is needed in a particular circumstance is not enough to ensure overall successful performance, and it certainly does not preclude error. Our experience suggests that practice of a designed response using human simulation, facilitated video recording review and debriefing, and rehearsal of the team response seem to improve performance. Repetition of a specific role by an individual does not explain the improvement, as we ask each team member to assume a different role for each simulated scenario in a training course.

Table 2. Fourteen steps to defibrillation using hands-free electrode pads

1. Take pulse
2. Determine pulselessness
3. Bring defibrillator to bedside
4. Place defibrillator pads on patient
5. Connect defibrillator pads to defibrillator
6. Turn on defibrillator
7. Tune defibrillator to correct electrocardiographic lead (paddles)
8. Look at electrocardiographic tracing
9. Recognize ventricular fibrillation
10. Make medical judgment to defibrillate
11. Select energy
12. Charge defibrillator
13. Clear staff from patient
14. Push defibrillate button or buttons

Future Needs for Crisis TEAM Training Using Human Simulation

We hope this project will trigger much needed investigation. We acknowledge our experience is not a controlled research trial but a quality improvement project that we believe has been effective. We cannot prove whether the response design, the simulator practice, or the debriefing was responsible for the improvement. However, the dramatic improvement in task completion within strict time intervals and simulated survival indicate that further research is warranted. We acknowledge that completion of our Crisis TEAM Training course, like ACLS training, does not necessarily correlate with improved clinical performance and, more importantly, clinical outcome. However, the clinical effect of crisis team training has not been tested yet needs to be assessed. Our scoring system can be utilized in a clinical arena if the crisis response is recorded. Another area of needed research is to assess our scoring system for interrater reliability. It is important to assess precisely performance and track improvement. We hope that because the skills we teach focus on or-

Table 3. First simulation scenario during a course commonly has many deficiencies in completing tasks by all the team members

Sixty Seconds (Session 1)			
Station	Team Member	Items	Complete Task
Airway	XX	Identify self	No
		Check airway	No
		Open airway in <60 secs	No
		Check breathing	No
		Assist ventilation in <60 secs	No
Airway assistant	XX	Identify self	No
		Set up oxygen	No
		Set up oxygen bag	No
		Set up mask	No
Floor nurse	XX	Identify self	No
		Check pulse in <30 secs	No
		Place defibrillator pads in <60 secs	No
		Check intravenous access in <60 secs	No
ICU nurse	XX	Identify self	No
Team leader	XX	Identify self	No
		Assign roles	No
Recorder ICU nurse	XX	Identify self	No
		Hand identification stickers to responders	No
Procedure doctor	XX	Identify self	No
		Check pulse	No
		Assist in cardiopulmonary resuscitation	No
Chest compressions	XX	Identify self	No
		Initiate chest compressions	NA
		Assess adequacy of compressions	NA
		Assess pulse as requested	No

ICU, intensive care unit; NA, not applicable.

Table 4. After team training, task completion rate for each position improves, and the team leader can focus on acquiring and analyzing data instead of organizing the response team

Sixty Seconds (Session 3)			
Station	Team Member	Items	Complete Task
Airway	YY	Identify self	Yes
		Check airway	Yes
		Open airway in <60 secs	Yes
		Check breathing	Yes
		Assist ventilation in <60 secs	Yes
Airway assistant	YY	Identify self	Yes
		Set up oxygen	Yes
		Set up oxygen bag	Yes
		Set up mask	Yes
Floor nurse	YY	Identify self	Yes
		Check pulse in <30 secs	Yes
		Place defibrillator pads in <60 secs	Yes
		Check intravenous access in <60 secs	Yes
ICU nurse	YY	Identify self	Yes
Team leader	YY	Identify self	Yes
		Assign roles	Yes
Recorder ICU nurse	YY	Identify self	Yes
		Hand identification stickers to responders	Yes
Procedure doctor	YY	Identify self	Yes
		Check pulse	Yes
		Assist in cardiopulmonary resuscitation	Yes
Chest compressions	YY	Identify self	Yes
		Initiate chest compressions	Yes
		Assess adequacy of compressions	Yes
		Assess pulse as requested	Yes

ICU, intensive care unit.

ganization and communication rather than procedures like chest compressions, the skills might be better retained. Retention of skills needs to be assessed. The clinical effect of crisis team training has not been tested, but it is worthy of investigation. The final goal of crisis intervention is to save lives, and no assessment of benefit is complete until a clinical improvement is demonstrated. To be sure, our determination of simulated survival is for teaching purposes only and may not correlate with the clinical survival of real patients.

Our crisis response was designed for our institution, and it may not be appropriate at other centers. Nevertheless, we believe our methodology may be universally useful. We believe that team simulation training will improve team performance. The components of crisis-response design, education, and rehearsal using a human simulator may be effective at any site if properly carried out. Tailoring specifics to the resources available is probably appropriate. We are in the process of designing a four-person response team for smaller hospitals, outpatient facilities, and subacute care institutions.

Conclusions

We believe that it is feasible and appropriate to use a computerized human simulator as part of a comprehensive program to teach crisis intervention team skills. Standardization of the equipment, medications, personnel responding, and detailed planned response are necessary prerequisites to teaching a coordinated crisis response. Multidisciplinary teams of healthcare professionals are the norm in clinical care, yet teaching and rehearsing team skills is rare in healthcare education. We suggest that such training improves efficiency and effectiveness of completing key tasks in a crisis situation, and we predict that it will improve clinical outcome.

ACKNOWLEDGMENT

It is said that we stand on the shoulders of our teachers when we make changes to improve. There is no doubt that we who seek to improve resuscitation medicine, and especially those of us at the University of Pittsburgh, are standing on the shoulders of a giant. Standing on his shoulders, we have been challenged to look far into the future and see the road to get there. Peter Safar was the consummate physician, teacher, researcher, and leader. Using his intellect, drive, and wit, he led generations of physicians. He prodded us all to do more, better. This work builds on his work and his vision. We are indebted to him for his support and input. His contribution to making this work possible is rightfully acknowledged.

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Experience with medical student simulation education

William R. McIvor, MD

The anesthesiology department at the University of Pittsburgh School of Medicine has offered human mannequin simulator courses to medical students since 1994 (1). The first simulation course was part of the required anesthesiology clerkship and used a patient simulator with a mathematical model of physiology. Classes focused on inducing general endotracheal anesthesia, managing a patient with a right main-stem intubation, anaphylaxis, and postoperative myocardial ischemia. Scenarios were executed from scripts run by a simulation technician who manipulated the simulator's vital signs. The course was taught with groups of four students and a single simulator; therefore, instructors used the simulator as a demonstration device as they guided participants through the exercises.

Face-mask ventilation was difficult with this simulator because it was not possible to establish an adequate seal. However, because its physiology model required ventilation, many simulation sessions frequently degenerated into unintended ventricular fibrillation codes. Because the scenarios were not programmed, the classes relied on the faculty to be familiar with and facile at executing the scenario scripts. These factors contributed to inconsistent application of the simulator as a teaching tool and probably discouraged new faculty involvement.

Prophetically, the new millennium brought a new simulator, SimMan (Laerdal Corporation, Stavanger, Norway). SimMan has supple, lifelike facial features that facilitate face-mask seals. The Laerdal simulator does not use a mathematical model of physiology; vital signs change either in response to interventions or can be directly entered into the simulator's computer controls.

The simulator's stable physiology and simple controls made it possible to expand the content of simulation courses. In July of 2001, the "Introduction to Anesthesiology" simulation course for first-year anesthesiology residents began. The course curriculum is similar to the third-year medical student course, stressing intravenous induction of general endotracheal anesthesia and task-specific objectives like room setup and anesthesia machine check. In July of 2002, a simulation course was added to the clinical anesthesiology elective for senior medical students. The course helped expand the clinical scope of the elective by emulating scenarios involving neuroanesthesiology, obstetrical anesthesiology, placing and managing double-lumen endotracheal tubes, and preoperative management of patients in congestive heart failure.

Table 1 shows the medical student and first-year anesthesiology resident simulation classes taught in the academic year beginning July 2002. Clearly, the volume of courses and the number of participants and facilitators was expanding. To meet this challenge while improving quality and consistency, the simulation course curricula would have to become more self-contained and easily managed. Our Winter Institute for Simulation Education and Research (WISER) made that transformation possible.

The WISER Center offers a sophisticated infrastructure of physical facilities, simulators for full or partial-task training, the ability to easily measure participant performance objectives, and Web support to enable simulation education. Intuitively, simulation education will benefit from participants beginning the simulation with a thorough understanding of the cognitive goals of the course. Participants are best to be prepared to induce general anesthesia on a simulated patient after they understand the objectives of general anesthesia, drugs used to produce the objectives, and the algorithm for inducing it. The WISER Web site (www.wiser.pitt.edu) displays the course curriculum, including video discussions and demonstrations of cognitive and psychomotor skills. Course surveys are also collected. Responses are stored and analyzed through a secure database, providing instantaneous course feedback. Logistic information such as faculty and participant course assignments and locations are posted. The school of medicine and the University of Pittsburgh Medical Center can also access the Web site to facilitate and simplify course documentation and reporting.

WISER Center personnel also assist in programming SimMan. Running simulations from programs is central to medical student simulation education. Participants work, explore, and experiment during the simulation exercise. By internalizing those experiences, simulation participants presumably develop a deeper, more personalized understanding of the course goals and objectives. A simulation program must respond consistently so that participants' actions demonstrate the course objectives. For example, if a student chooses propofol to induce unconsciousness in a hypovolemic patient, our course objective dictates that the simulator respond with hypotension and tachycardia. The simulator teaches students about the pharmacodynamics of the drug without relying on the facilitator to remember to change the vital signs.

Although consistent response to participant actions makes simulation education possible, the physiology displayed during the simulation makes that education applicable in the real, clinical world. If we ask participants to rehearse clinical skills in a simulated environment, then the onus falls on those who create simu-

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Table 1. Simulation courses offered to medical students and first-year anesthesiology residents during academic year 2002–2003

Participants	Curriculum	Faculty Contact Hours	Simulator: Student Ratio
150 Second-year medical students	Bag-valve face mask ventilation	75 during 3 days	1:1–1:2
150 Third-year medical students	Anesthesiology clerkship	334 during 96 sessions	1:4
35 Fourth-year medical students	Neurologic, obstetric, thoracic preoperative evaluation	177 during 40 sessions	1:4–1:1
22 First-year anesthesia residents	Introduction to anesthesiology	24 during 3 days	1:4–1:1

Faculty contact hours are number of faculty teaching the course multiplied by hours teaching.

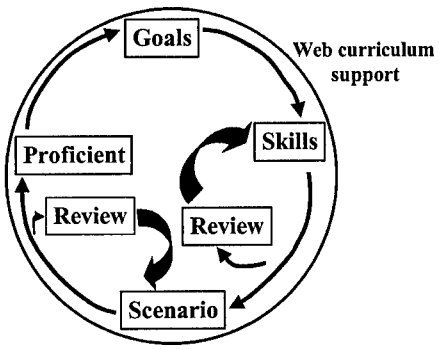

Figure 1. Model of independent study and skill acquisition possible using human simulation courses.

lations to build programs that accurately reflect reality. Human data have been applied to the programming at WISER in both the medical student and difficult airway courses.

WISER courses benefit from objective performance assessment, data compilation, and immediate participant feedback after the simulation. In our nomenclature, the actions that SimMan responds to and registers in a simulation log are called events. The simulator can sense some events like lung ventilation, chest compressions, or palpating pulses or an observer may document this by clicking on that event and filing it in a drop-down menu. Events can trigger a change in the simulation scenario, as when the simulator senses ventilation and starts an increasing oxygen saturation trend, or can simply note in the log that an action was taken (e.g., checking for patient consciousness). Time points for event completion are recorded into the participant's simulation log, to be used during debriefing. Video recording of the participant's performance can be indexed to specific events. Immediate feedback may better help participants recognize the results of their actions.

Collecting performance data provides feedback not only to the participants, but also for the course. Participants not achieving the simulation course's goal may indicate that the goal was unrealistic or that the curriculum was ineffective or flawed. Conversely, if the goals are being achieved too easily, the course might not offer enough challenge, threatening participants' interest and motivation.

Many complex tasks, like inducing general anesthesia, can be divided into component subroutines (e.g., bag-mask ventilation or direct laryngoscopy and endotracheal intubation). Some of these skills can be isolated and acquired using partial-task training before attempting the more complex full task on a simulator. WISER has various airway labs in which students learn and practice bag-mask ventilation, direct laryngoscopy, and endotracheal intubation before attempting an anesthesia induction during a full-scale simulation.

Kollef et al. (2) showed that physicians could hinder patient progress by actively managing care during weaning from mechanical ventilation (2). Likewise, facilitators may hinder simulation participants' progress by aggressively managing the learning experience. To most effectively use simulation education, Socratic, didactic teaching must not be the mainstay of the experience. Students should work through the emulation on their own to internalize and synthesize the experience on the most personal and, presumably, useful level. Figure 1 demonstrates a model of this proposed simulation experience. WISER makes this possible by providing high-quality, continuously accessible descriptions and demonstrations of the cognitive and psychomotor domain of the simulation; reproducible and realistic partial-task training and full-scale simulations; and the prompt, accurate feedback required for such independent study.

WISER courses can also facilitate faculty involvement and increase educational efficiency. Our first simulation courses required faculty to gain familiarity with the simulations, usually through serving an apprenticeship to an experienced faculty member and learning how to run the simulation. In WISER courses, the learning objectives are built into the scenario; thus, the scenario teaches the lessons. Facilitators ensure the objectives are performed correctly and provide appropriate, sensitive debriefing. This obviates the need for a simulation technician because the facilitators can run the simulation themselves. Finally, the "package" nature of WISER courses means that they can be shared between institutions. This could greatly enhance simulation education acceptance and research and test the utility of the application globally.

Second-year University of Pittsburgh medical students participate in a clinical procedures course before beginning clinical rotations. As the name implies, the course teaches students how to perform common clinical procedures (e.g., intravenous and Foley catheter insertion and simple casting of fractures). In April 2003, the first clinical procedures course class to use human mannequin patient simulation, "Introduction to Bag-valve Mask Ventilation" began. This was also the first medical student simulation course designed from the outset to take advantage of the WISER format.

The goal of the bag-valve mask course is that students will ventilate a simulated patient using a bag-valve device. Placing the patient into the sniffing position, obtaining a face-mask seal, recognizing effective or ineffective ventilation, and placing an oral airway are the objectives stressed. Basic mask ventilation skills were chosen for these neophyte clinicians to start their airway management training, help them develop confidence with bag-mask ventilation skills for clinical care, and introduce them to human simulation.

All 150 medical students from the class of 2005 took the 48-min course in groups of 8–12 students. Before coming to the simulation center, they were provided with written descriptions of the relevant airway skills. Participants began the class by watching a 5-min video pre-

sentation demonstrating the skills and their proper performance. The video concluded with a demonstration of how to apply the bag-valve mask skills to the actual simulation scenario the students were about to perform. Students then paired up to practice the bag-valve mask skills on SimMan simulators, supervised by an anesthesiology faculty member. After 15 mins of practice, the students performed the simulation scenario designed to assess the performance objectives.

Figure 2 shows an overview of the simulation scenario. Because the bag-valve mask course focuses solely on face-mask ventilation skills, the scenario uses an apneic, monitored "patient" with an Spo_2 of 85% but otherwise normal vital signs (blood pressure, 120/80 mm Hg; heart rate, 80 beats/min). This scenario was chosen to direct student attention toward the patient's airway and need for ventilation and to not overwhelm them with premorbid physiology. It was easy to establish this physiologic scenario with SimMan, and the conditions were maintained effortlessly while the students performed ventilation. Two simulators operated by course facilitators were used for the scenario. Another faculty member proctored participants during the scenario.

The scenario program required that the events "sniffing position" and "oral airway placed" be noted to relieve an imposed upper airway obstruction before students could ventilate the simulator. Those events could be performed in either order (sniffing position first, then oral airway, or vice-versa). Once properly positioned and with an oral airway in place, the students could face-mask ventilate the simulator. When the simulator sensed the first breath, a trend started bringing the oxygen saturation to 100% in 1 min; 100% Spo_2 marked the completion of the simulation.

To protect students from undue distress, 20-sec breaks were written into the simulation program. If a student did not attempt an intervention within 20 secs of starting the scenario or after completing a previous objective, the software triggered a recorded voice stating, "Twenty seconds have elapsed." This cued the proctor to prompt the student about solutions to the simulated problem, such as, "After placing the patient in the sniffing position, what was the next thing done in the video?" It was intended that all 150 students successfully apply bag-valve mask skills during the simulation; therefore, the faculty prompts were employed to keep students progressing through the scenario with appropriate expedition.

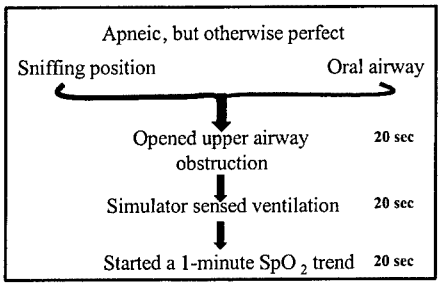

Figure 2. Schematic representing the simulation program used for the introduction to bag-valve mask ventilation course.

Because the events were entered into the simulation log, time when participants placed the simulator into the sniffing position, attempted bag-mask ventilation, and placed an oral airway were documented. The simulator's ventilation sensor also produced an entry, noting when the first breath was delivered. The logs were saved on a secure WISER database, making the data available for retrospective review. This is an example of the simulator noting a participant's successful completion of simulation course performance objectives.

Because of time constraints and the relative simplicity of the scenario, the students did not review their performance logs after the scenario. Rather, the course director and another faculty member who observed performances debriefed all students after completing the simulation. Students were offered the chance to perform the scenario again, queried about the scenario's difficulty, their anxiety, and their stress while performing it, and given a chance to ask questions or address concerns about their performance.

Exit surveys indicated that the students thought the exercise was relevant to the clinical procedures course and that the scenario was realistic, not too difficult or stressful, and yet not trivial. Students indicated that they had enough instruction and opportunity to practice before the scenario and that they were properly debriefed at the completion. Students were enthusiastic about their performance during the simulation and were looking forward to more simulation courses in the future.

Performance data collected from these simulations could be used toward a myriad of aims. Students' progress can be documented, both for their edification and for their educational institutions'. Standards of performance can also be established, for both individuals and groups. These standards may indicate students who require remediation or extra training, and they can provide rational expectations for future simulation experiences. Given the time it took second-year medical students to ventilate in this isolated airway scenario, reasonable expectations for initiating face-mask ventilation can be applied to future emulations that have this scenario imbedded. In this way, student performance can be analyzed to determine whether problems exist in recognizing the need for an intervention, such as bag-valve mask, or in implementing that intervention.

Our simulation center (WISER) at the University of Pittsburgh School of Medicine is an evolution, an extension of Dr. Safar's commitment to advancing medicine and its service to our society.

The bag-mask ventilation course represents a gateway into medical student airway training using human simulation. The Institute of Medicine report, *To Err is Human: Building a Safer Health System* (3), describes the tremendous cost, in dollars and lives lost, from preventable medical errors in the United States. The American Society of Anesthesiology closed-claims study showed that 34% of adverse outcomes from anesthesia were related to respiratory events (4). Inadequate ventilation, esophageal intubation, and difficult tracheal intubation accounted for three fourths of the adverse respiratory events. Assuming anesthesiologists are at least as adept with airway management as other clinicians, the Institute of Medicine report suggests significant improvement in patient safety and mortality could be realized by training all future physicians in airway management. Incidentally, the Institute of Medicine re-

port complimented the decreasing mortality in anesthesiology, which it ascribed in part to developing and adopting practice guidelines and training with human patient simulation.

The ability to practice the proper response to a given clinical situation is a logical application for human patient simulation. Demographics, epidemiology, and statistics can provide insight into which clinical scenarios medical students will commonly face as physicians. Simulation courses can be designed that illustrate rationale, best practices responses to those scenarios. All physicians at some time have been medical students; therefore, a global improvement in patient safety and outcome could be realized by using human patient simulators in training students to respond to anticipated common clinical scenarios, especially those that involve airway management.

Dr. Safar, while chairman of the combined anesthesiology and critical care medicine department, personally attended every Pittsburgh medical student during an endotracheal intubation before his or her graduation. Indeed, our simulation center (WISER) at the University of Pittsburgh School of Medicine is an evolution, an extension of Dr. Safar's commitment to advancing medicine and its service to our society.

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Simulation in medical students' critical thinking

Paul L. Rogers, MD

Developing an educational curriculum that teaches medical students to assess and manage life-threatening illness must be a focus for medical educators because 44,000 to 98,000 patients die each year because of medical error according to the Institutes of Medicine (1). Traditional medical education occurs in the classroom; it is teacher centered, is provided in lecture format, is authoritarian, and is noninteractive. Although this may be an efficient way to cover a large body of knowledge, there are several limitations to this method of instruction. First, the goal of the course is to teach students how to manage unstable patients. These cognitive and psychomotor skills are very difficult to teach in a lecture. Second, classroom instruction is not interactive. When a curriculum is not interactive, it is less likely to engage students, foster interactive discussions, and force students to problem-solve (2). Finally, although a teacher can require students to attend lectures, they cannot always ensure the students will value and incorporate the material into their daily patient care (3).

Teaching using the simulator effectively addresses each of these issues. Students must demonstrate that they can evaluate signs and symptoms, intervene, and evaluate if their treatment has been effective. They must know what to do and demonstrate that they have mastered the cognitive, motor, and communication skills to implement their plan of care. Second, the instruction is interactive, student-centered, and involves active learning, thus increasing students' enthusiasm for learning. Finally, it is easy to get students to value and incorporate safety practices into their management. Because they have had the opportunity to see and experience the adverse events that can occur in the simulated environment, they want to incorporate and avoid these experiences in their patient care. If medical students are given the opportunity to manage crisis scenarios in an environment in which mistakes do not result in untoward outcomes, in which feedback is immediate, and in which they can repeat their performance until they acquire these skills, then perhaps mistakes could be reduced.

Simulators have been used since the 1960s to teach crisis management skills to personnel in military, aviation, space flight, and nuclear power plant operations (4). Recently, the human simulator has given educators a unique opportunity to extend this educational tool to physicians. What initially began as computerized software with separate torso apparatus has evolved into complex, whole-body, computerized mannequins with a functional mouth and airway, allowing bag-mask ventilation and intubation (5). The chest wall expands and relaxes; there are heart and breath sounds and real-time display of physiologic variables including electrocardiogram, noninvasive blood pressure, temperature, and pulse oximetry. The human simulator has individual operator controls for upper airway obstruction, tongue edema, trismus, and reduced cervical range of motion. These computerized human simulators require trainees to integrate cognitive and psychomotor learning along with multisensory contextual cues to aid in recall and application in clinical settings. This type of simulation has been successfully incorporated into curriculum to teach management of obstetrical emergencies (6), management of difficult airway in the operating room (7), crisis management in the operating room (8), and management of unstable patients for critical care medicine trainees (9).

Simulator as an Educational Instrument

Since 1994, the Department of Critical Care Medicine at the University of Pittsburgh School of Medicine has utilized the human simulator to teach medical students crisis management skills. Third- and fourth-year medical students spend a significant portion of their critical care medicine clerkship in the Simulation Center practicing the cognitive and motor skills to manage unstable patients. Examples of some educational objectives for third-year medical clerkship and fourth-year medical student electives are shown in Tables 1 and 2.

Simulator as an Evaluative Instrument

Unfortunately, there are no data to show that instruction using the simulator reduces practitioner error compared with didactic instruction. There is, however, data to show the simulator is a superior evaluation tool, and unlike written examinations, the whole-body computerized simulator gives the teacher an opportunity to evaluate a student's cognitive and motor skills in real time. Because students receive immediate physiologic feedback from bedside monitors and communication from the simulator operator, the students' analytic and evaluative skills are critiqued. Data from our fourth-year medical school elective supports the conclusion that performance-based examinations using the simulator are superior to written examinations because written examinations overestimate the students' ability to reach their stated educational objectives (9).

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Key Words: medical education; medical simulation; crisis management; medical errors; curriculum

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Table 1. Learning objectives for third-year critical care medicine course

Respiratory distress
Evaluate a simulated patient in respiratory distress (tachypneic and hypoxemic)
Initiate appropriate oxygen therapy
Evaluate effectiveness of therapeutic intervention
Demonstrate effective bag and mask ventilation
Insert intravenous catheter for resuscitation
Evaluate patient for potentially difficult airway
Cardiovascular
Evaluate a patient with hypotension
Initiate therapy for a patient with hypotension (initiate intravenous fluid)
Order appropriate diagnostic tests for evaluation of a patient with hypotension
Evaluate effectiveness of therapeutic intervention
Evaluate a patient with sinus tachycardia, develop a differential diagnosis, and order appropriate diagnostic tests
Arrhythmias
Evaluate a patient with sinus tachycardia, develop a differential diagnosis, and order appropriate diagnostic tests
Demonstrate defibrillation of ventricular fibrillation and pulseless ventricular tachycardia
Demonstrate airway management and cardiovascular resuscitation for simulated patients with ventricular fibrillation, ventricular tachycardia, pulseless electrical activity and asystole

Table 2. Learning objectives: Simulation scenarios

Scenario	Educational Objective
Patient with chronic obstructive pulmonary disease, respiratory distress, and hypercarbia who develops pulseless electrical activity after intubation	Recognize hemodynamic consequences of rapid ventilation after intubation Discontinue bag-mask ventilation Check for a pulse Decrease ventilation rate
Patient unresponsive and pulseless	Initiate effective bag-mask ventilation and chest compression Assign specific tasks to specific team members Ask to be told when task is complete Apply advanced cardiac life support algorithm Instruct team members to be prepared for next step
Patient with inadvertent loss of newly placed tracheostomy tube	Assess patient stability Call ear, nose, and throat specialist if the patient is unstable Intubate if unstable
Patient with new-onset substernal chest pain	Assess vital signs Begin resuscitation Qualify characteristics of chest pain Obtain electrocardiogram within 5 mins Begin nitrates, aspirin, oxygen, and morphine (if appropriate) Consult cardiology for thrombolytic or percutaneous transluminal coronary angioplasty

Simulation technology is an effective teaching and evaluation tool for medical education and has the potential to reduce errors in real-life situations.

Conclusions

In conclusion, the human simulator gives students the opportunity to make a clinical assessment, develop a hypothesis, initiate a therapy, anticipate consequences of intervention, communicate treatment goals to staff, and evaluate effectiveness of therapy in a safe environment with the goal of reducing errors in judgment in the future.

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Pediatric simulation: A valuable tool for pediatric medical education

Melinda L. Fiedor, MD

Children are not little adults, and this is especially true when it comes to cardiopulmonary resuscitation. The pediatric patient differs in multiple ways, making resuscitation issues very difficult. First, children have different anatomy and physiology. In terms of resuscitation, the differences in airway anatomy are very important. Overall, the pediatric airway is smaller in diameter and shorter in length than the adult airway. This is significant because a relatively small amount of edema or obstruction causes a large reduction in the diameter of the pediatric airway. Next, the tongue in a pediatric patient is larger relative to the size of the pediatric oropharynx, and posterior displacement of the tongue is a common cause of upper airway obstruction. The relatively large tongue is often a hindrance to a full view of the vocal cords during intubation. Finally, the larynx in infants and toddlers is relatively cephalad in position, and the vocal cords have a lower and more anterior attachment (1). These airway differences are even more important when one considers the cause of pediatric cardiopulmonary arrest; nearly 80% of pediatric cardiopulmonary arrests are respiratory in origin, making pediatric airway management a vital resuscitation skill. Second, medication dosage is another difficulty inherent to pediatric cardiopulmonary resuscitation. All doses of medication in pediatrics are weight based, and this includes the voltage used in defibrillation or cardioversion. Pediatric resuscitation algorithms have another level of difficulty then because doses need to be calculated and cannot simply be memorized. Finally, pediatric cardiopulmonary arrest is a relatively rare event, occurring one tenth as often per year as adult cardiopulmonary arrest. Thus, the ability to practice pediatric lifesaving skills in real time is limited.

Need for Additional Expertise

These differences in pediatric patients make their resuscitation more challenging than adults. A large body of evidence exists supporting the need for better expertise in pediatric resuscitation. These data come from the two main arenas where pediatric cardiopulmonary arrests occur, the hospital setting and the prehospital environment. A study from Nadel et al. (2) evaluated senior pediatric resident knowledge, technical skills, and perception of confidence related to pediatric resuscitation. The study took place in a large tertiary pediatric hospital, designated a level-1 trauma center, and a regional and international referral center for pediatric subspecialty care. The third-year residents had completed a pediatric advanced life support course in July of their first year and again in October of their third year of training. The study took place in March of the third year. The residents completed the standard pediatric advanced life support examination and 12 short-answer questions. Technical skills were assessed as the resident performed four advanced resuscitation procedures, including airway maneuvers, endotracheal intubation, intraosseous needle placement, and femoral vein access using the Seldinger technique. The residents performed well on the cognitive portion, with a mean score on the pediatric advanced life support examination of 93.2% ± 5.5%. They showed deficits, however, in the performance of technical skills. Only 18% of the residents correctly performed ancillary airway maneuvers, including airway management and bag-valve mask ventilation. Seventy-eight percent of the residents demonstrated errors in endotracheal tube placement. Only one third of the residents successfully demonstrated intraosseous needle placement and Seldinger technique. An earlier study from the University of Washington in Seattle gave similar results (3). A total of 45 pediatric residents previously trained in pediatric advanced life support were observed and scored on four key resuscitation skills (bag-valve mask ventilation, endotracheal intubation, intraosseous catheter placement, defibrillation) and tested with four written scenarios. Regardless of experience or year of training, the residents performed well on the written exam, with a score of 5 (range, 1–5). More than 80% of the trainees achieved the primary end point of a resuscitative skill but performed poorly on the subcomponents of each skill. For example, 39 residents (87%) were able to place the endotracheal tube into the mannequin trachea, but only 27% checked for functioning suction equipment before intubation and only 15% ensured bag-valve mask equipment was available. When a scenario required defibrillation, most residents could discharge the defibrillator (89%), but only 12 (25%) chose the asynchronous mode for a patient in ventricular fibrillation.

Prehospital personnel have similar difficulties with pediatric resuscitation skills. Aijian et al. (4) evaluated prehospital personnel's intubation skills during pediatric cardiopulmonary resuscitation. Of 63 pediatric arrests during a 38-month period, 42 had a paramedic trained in intubation at the scene. In patients >1 yr of age, 66% had endotracheal intubation attempted, with a success rate of only 39%. In patients aged <1 yr, intubation

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was attempted 38% of the time, with only half of them successful. A similar study in Milwaukee looked at pediatric patient calls requiring intubation during a 1-yr period. Overall, 78% of the patients were successfully intubated, but of those who were not in full cardiopulmonary arrest, only 48% were successfully intubated (5). A controlled clinical trial from Gausche et al. (6) compared the survival and outcomes of pediatric patients requiring airway management by Emergency Medical Services personnel. Patients were either treated with bag-valve mask ventilation or bag-valve mask ventilation followed by endotracheal intubation randomized according to the day of study (odd days received bag-valve mask ventilation and even days received endotracheal intubation). The authors found no difference in neurologic outcome and survival between the two methods of airway management. Of note, however, the results showed only a 57% rate of successful intubation, and of those who were successfully intubated, 58% had complications. The complications included, among others, esophageal intubation, right mainstem intubation, unrecognized tube dislodgement, or choosing improper endotracheal tube size. The consequence of unrecognized tube dislodgement and esophageal intubation was severe as all but one of these patients died. It is clear that expertise in pediatric airway management is lacking and that this is more dramatic when one understands that endotracheal intubation is the only resuscitative skill associated with survival in pediatric cardiopulmonary arrest. Indeed, Losek et al. (7) showed that in 114 pediatric cardiopulmonary arrests, only endotracheal intubation was associated with survival ($p < .04$). Sirbaugh et al. (8) found that return of spontaneous circulation at the scene of pediatric cardiopulmonary arrest was strongly associated with survival (odds ratio, 0.0; 95% confidence interval, 0–0.08), and in this group of patients, the only variable associated with on-scene return of spontaneous circulation was endotracheal intubation ($p = .032$).

A final point before leaving the literature revisits the lack of experience among those providing resuscitative skills to pediatric patients. A total of 50 Emergency Medical Services advanced life support providers in an urban setting averaged pediatric intravenous cannulation 3.7 times per year, endotracheal intubation 0.3 times per year, and intraosseous access 0.06 times per year (9). Mastery of these skills is difficult, and the scarce opportunity to practice them exacerbates the difficulty.

Opportunity for Simulation

Expertise in pediatric resuscitative skills is lacking, and proficiency in providing these skills can be vital to survival of the pediatric patient. Current resources for pediatric resuscitation education include pediatric advanced life support courses and other courses focusing on advanced skills for the pediatric patient. These courses are offered several times per year and include core lectures, case scenarios, and focused skill stations. The format and curriculum are very good; difficulties include cost, availability, and proximity of these courses to pediatric caregivers. For caregivers in a hospital setting, the opportunity for pediatric resuscitation education is available during intensive care unit or emergency department rotations. Unfortunately, these opportunities are becoming less available because pediatric residency programs have increased emphasis on training in ambulatory/outpatient settings vs. in-hospital management. White et al. provided evidence for this in reporting that in a tertiary care children's hospital, 44% of senior residents reported never having had the opportunity to lead a resuscitation by the end of their training (3).

As mentioned above, the pediatric patient differs significantly from the adult patient, and specific knowledge and skills are required in pediatric cardiopulmonary resuscitation. Studies show pediatric caregivers have suboptimal resuscitation skills, and current educational resources are not sufficient. The solution to this problem lies in an educational tool that is realistic, predictable, and more available. This tool is a pediatric simulator. Simulation has been widely used for many years in the aviation industry and for military training; recently, its use has become widespread in medicine. Simulation has found a place in adult medicine programs, including anesthesiology, trauma, critical care, and emergency medicine. Simulation is ideal for any type of medical trainee because it is available, predictable, and has repeatability. It also offers the opportunity for standardized experience for trainees in an environment in which mistakes can be made and immediately learned from. Specific scenarios can be created that allow the trainee to work through a diagnostic problem while practicing examination skills and performing technical skills. For the pediatric trainee, these characteristics of simulation are quite useful, but even more can be gained from pediatric simulation. An anatomy-specific pediatric simulator will allow for detailed education on pediatric airway management, providing the pediatric caregiver with the resuscitation skills that can be lifesaving in a pediatric cardiopulmonary arrest. Complications such as esophageal intubation or dislodged endotracheal tubes can be duplicated and managed in real time. Specific pediatric physiology can also be reproduced because simulators can be programmed for changes in vital signs and physical exam findings according to the particular scenario in use. For example, a critically ill child in shock presents with tachycardia and weak pulses long before hypotension occurs. Thus, shock in children is often unrecognized because this physiology differs from adults. Simulation provides the ability to duplicate this physiology and give caregivers the opportunity not only to learn but also respond in an appropriate manner.

The ability to recognize and evaluate threatening situations, choose appropriate interventions, and then perform required technical skills in real time makes pediatric simulation invaluable.

Simulation is not only useful for individual trainees, it is also excellent for team training. Pediatric cardiopulmonary arrests are emotionally very charged situations, whether they occur in the prehospital or hospital setting. Team communication and performance can be explored and rehearsed for any type of critical situation with the use of simulation.

In this article, I have focused on pediatric simulation utility in the critically ill child, specifically in situations involving pediatric cardiopulmonary arrest. Many

additional aspects of pediatric medicine can be explored using simulation, including physician/family communication, nursing assessment skills, and transport of the pediatric patient. The effect of pediatric simulation will likely be widespread because it is well suited for prehospital personnel, community physicians, emergency departments, and tertiary care facilities. More importantly, simulation will allow for the availability of pediatric-specific individual or team training in which there is little or no other opportunity.

In conclusion, pediatric simulators are educational tools offering distinct advantages in the training of all types of pediatric caregivers. It is an obvious asset in the practice and mastery of procedural skills, but the largest benefit of simulation is the simultaneous integration of technical and cognitive skills. The ability to recognize and evaluate threatening situations, choose appropriate interventions, and then perform required technical skills in real time makes pediatric simulation invaluable.

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Peter's Laws*
For the Navigation of Life

The Creed of the Sociopathic Obsessive Compulsive

1. **If anything can go wrong, Fix It!**
2. **When given a choice - Take Both!**
3. **Multiple projects lead to multiple successes.**
4. **Start at the top then work your way up.**
5. **Do it by the book but be the author.**
6. **When forced to compromise, ask for more.**
7. **If you can't beat them, join them, then beat them.**
8. **If it's worth doing, it's worth doing right now.**
9. **If you can't win, change the rules.**
10. **If you can't change the rules, then ignore them.**
11. **Perfection is not optional.**
12. **When faced without a challenge, make one.**
13. **"No" simply means begin again at one level higher.**
14. **Don't walk when you can run.**
15. **Bureaucracy is a challenge to be conquered with a righteous attitude, a tolerance for stupidity, and a bulldozer when necessary.**
16. **When in doubt, think!**
17. **Patience is a virtue, but persistence to the point of success is a blessing.**
18. **The squeaky wheel gets replaced.**
19. **The faster you move, the slower time passes, the longer you live.**
20. **Death is not the enemy, but occasionally needs help with timing.**
21. **When on thin ice, dance.**
22. **It is up to us to save the world.**

*Safar PJ; Fink BR, McGoldrick KE, eds: From Vienna to Pittsburgh for Anesthesiology and Acute Medicine. Careers in Anesthesiology, Volume V. Park Ridge, IL: Wood Library-Museum of Anesthesiology; 2000: 343.

SAFAR CENTER FOR RESUSCITATION RESEARCH

2002-03 ANNUAL REPORT

DEPARTMENT OF CRITICAL CARE MEDICINE

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE

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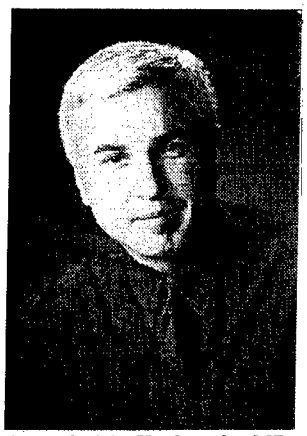
Featured on the cover: *From Left to Right, Drs. Paul Shore, Kate Felmet, Yi-Chen Lai, Hülya Bayır, and Trung Nguyen at the 2003 Congress of the Society of Critical Care Medicine. The number of awards that these fellows received at the SCCM congress from a single program highlights the high quality of our trainees and the strong commitment to training by our faculty. Drs. Shore, Lai, Bayır, and Nguyen were fellows in the programs of both the Safar Center and the Children's Hospital of Pittsburgh division of pediatric critical care medicine. Dr. Felmet worked with Dr. Carcillo in the pediatric critical care medicine program.*

MISSION STATEMENT

The global mission of the Safar Center for Resuscitation Research is to improve understanding of the mechanism of secondary injury after trauma and cardiopulmonary arrest, from whatever cause, and to contribute to the development and implementation of novel therapies. The treatment and prevention of secondary injury after these life-threatening catastrophic events is a major goal in each venue of investigation.

A letter from the Safar Center's Director



Patrick M. Kochanek, MD
Director, Safar Center for Resuscitation Research

As I write this letter summarizing the many accomplishments of investigators and trainees at the Safar Center in the 2002/2003 academic year, it is overshadowed by the recent loss of our good friend, colleague, CPR and acute medicine pioneer and the founder of our Center, Dr. Peter Safar. After a courageous 15-month battle against cancer, Dr. Safar passed away on August 3rd, 2003. Dr. Safar was a genius that inspired everyone that worked with him to search for clinical breakthroughs in resuscitation, never rest until they are implemented, and carry out this mission with elegance and humanism. His loss has been difficult for all of us at the Center, and we extend our deepest sympathy to Eva Safar and the entire Safar family. We are honored to be able to carry his work forward.

Academically, the 2002/2003-year was another strong one for faculty and trainees at the Safar Center. Our multidisciplinary Center continues to produce a unique and exciting environment and the productivity and successes of the investigators and trainees never cease to amaze me. Our multidisciplinary Center continues to grow.

As introduced in last year's report, we have expanded our efforts into five major areas of research and research training—including research in traumatic brain injury (TBI), training in pediatric neurointensive care and resuscitation research, hemorrhagic shock and suspended animation, CNS rehabilitation research, and most recently we have begun, through the efforts of Drs. Robert Clark and Robert Hickey, the programmatic study of cardiopulmonary arrest in children. We are also fostering an increasing collaboration with Dr. Clifton Callaway of the University of Pittsburgh Center for Emergency Medicine whose research focuses on cardiopulmonary arrest and resuscitation in adults.

Our TBI program is funded by a program project from the National Institute of Neurological Disorders and Stroke (NINDS), five RO-1 awards, two R-21, one KO-8, and K23 awards, and a variety of other grants. Our work in TBI spans a number of areas of study—including evaluation of novel resuscitative therapies targeting neuronal death, unraveling the mechanisms of secondary injury in both experimental models and in brain injured patients, the development of novel tools to facilitate detection of occult cases of child abuse, and the testing of new strategies in brain injury rehabilitation. Accomplishments in 2002/2003 in this program included the successful competitive renewal of the University of Pittsburgh Center for Injury Control and Research (CIRCL) grant by Dr. Hank Weiss in the Department of Neurological Surgery. Dr. Weiss has been a strong leader of this CDC-funded injury prevention grant. Safar Center investigators direct two of the projects in CIRCL. Dr. Amy Wagner, in the Department of Physical Medicine and Rehabilitation (PM&R), has a project entitled "Relationship of female sex hormones to CSF pathophysiology and outcome after TBI." Amy has a portfolio of projects both at the bench and bedside that address the important issue of the influence of

gender on outcome in TBI. Similarly, Drs. Rachel Berger and Kochanek have a project in CIRCL entitled "Improving the diagnosis and prognosis of inflicted head trauma in infants"—that is testing the use of a battery of blood tests to aid in diagnosing "silent brain" injury—specifically targeting missed cases of child abuse (i.e., the shaken baby syndrome). It is exciting to see that Drs. Wagner and Berger, both young clinician-scientists supported by K-awards from NIH, are developing into independent investigators. Dr. Wagner also is the assistant director of the Clinical Trials Cooperative Network in TBI—recently funded by the National Center for Medical Rehabilitation Research (NCMRR)/NIH. Dr. Ross Zafonte, Chairman of the Department of PM&R at the University of Pittsburgh, is the local PI for that project. I am also pleased that funding for Dr. Chien Ho's superb Pittsburgh NMR Center for Biomedical Research was renewed. We have had a longstanding and fruitful collaboration with Dr. Ho's group. They have provided contemporary magnetic resonance imaging methods to our TBI work and we look forward to continued interaction. Dr. C. Edward Dixon received an R21 award from NIH to apply gene array to study the delayed period of recovery in experimental TBI—work that capitalizes on the unique interaction between acute and rehabilitation medicine in our Center. Dr. Kochanek renewed his RO-1 from the NINDS entitled "Adenosine in TBI." I would like to thank Dr. Edwin Jackson for the incredible support of his laboratory toward this work. I also wish to thank Drs. Jiang-Fan Chen at Boston University and Dr. Jürgen Schnermann of the NIH for providing the A2a-receptor and A1-receptor knockout mice, respectively, that are instrumental to this project. We are pleased to report on the anticipated funding of the competitive renewal of the RO-1 award of Dr. Larry Jenkins in developmental TBI. Also in the area of pediatric TBI, Dr. David Adelson has been leading a clinical trial of moderate hypothermia in children that is centered at Children's Hospital of Pittsburgh. Several of our fellows have linked the biochemical and molecular expertise of the Safar Center to this project, resulting in a series of studies that are providing what we believe to be the most comprehensive assessment of the biochemical/molecular effects of hypothermia in any clinical trial. These bench-to-bedside studies (see later) typify the mission of our Center. Another major development in pediatric TBI was the publication of the first "*Guidelines for the Management of Severe Traumatic Brain Injury in Infant, Children, and Adolescents.*" The document, which was published as a supplement in three journals (*Pediatric Critical Care Medicine, Critical Care Medicine*, and *Journal of Trauma*), included substantial contributions from both Drs. Adelson and Kochanek. I know that I speak for the entire guidelines committee in thanking Drs. Mary Ellen Michel at NINDS/NIH and Michael Weinrich at NCMRR/NIH for their efforts toward providing the funding for this document. The guidelines committee owes a debt of gratitude to Drs. Randall Chesnut and Nancy Carney who led the charge on the production of this seminal document.

Research training remains the key priority in our Center –including the development of both postdoctoral fellows (MD and/or PhD) and junior faculty. This also represents the most important and enjoyable part of my own efforts. Postdoctoral clinician-scientist development in the field of pediatric critical care has been greatly facilitated by our T-32 grant from the National Institute of Child Health and Human Development (NICHD) entitled "Training in Pediatric Neurointensive Care and Resuscitation Research."

Related to Dr. Safar's death, Dr. Clark has assumed the role of co-principal investigator of this training grant. I wish to thank Drs. Ralph Nitkin, Michael Weinrich, Carol Nicholson, and Beth Ansel at NICHD for their valuable insight and support of this exciting program.

We are also grateful to the Department of Anesthesiology for their support of Dr. Hülya Bayır as the 2002 Charles Schertz Fellow. Dr. Bayır is a rising star in the field of Pediatric Critical Care Medicine who recently joined our faculty. A few additional postdoctoral fellowship positions are supported by individual faculty grants. Research productivity by the trainees continues to be spectacular, including a total of 10 fellow first-author peer-reviewed publications and 21 abstract presentations this academic year. The highlight of the year was the fact that Safar Center fellows received six awards at the 2003 Congress of the Society of Critical Care Medicine (see cover photo). In addition, Dr. Paul Shore received the Neuroscience Award for a paper entitled "Therapeutic hypothermia does not affect markers of injury, cellular energetics, inflammation, and regeneration in cerebrospinal fluid after severe TBI in infants and children" that he presented at the Congress of the World Federation of Pediatric Intensive and Critical Care Societies, in Boston, in June of 2003. Paul's work is a perfect example of the powerful link between the Safar Center and Dr. Adelson's pediatric hypothermia clinical trial at Children's Hospital. Finally, we are sad to report that this year, Dr. Nancy Caroline, one of Dr. Safar's early trainees who went on to become the mother of CPR in Israel, and later, the head of the Israeli Red Cross, died on December 12, 2002. In her honor, we have created the Nancy Caroline Fellow Award at the Safar Center. This award is given annually to the fellow working with a Safar Center Scientist who has made the greatest contribution to the field of resuscitation medicine. Dr. Safar presented the first award to Dr. Ala Nozari (see photo) for his work in neuroprotection and preservation that was described above. Congratulations to Dr. Nozari.

Dr. Ala Nozari (left) received the first Nancy Caroline Fellow Award at the Safar Center for Resuscitation Research during 2002/2003. His exciting work on the application of mild hypothermia during CPR is in press in the journal Critical Care Medicine. Also pictured from left to right, Drs. Kochanek, Safar and Tisherman.

Junior faculty development is supported by a number of grants, including KO8 awards to Drs. Robert Hickey in the Division of Pediatric Emergency Medicine (mentored by Dr. Steven Graham) and Amy Wagner in the Department of PM&R (mentored by Dr. Dixon), and most recently, a K-23 award to Dr. Rachel Berger in the Department of Pediatrics (mentored by Dr. Kochanek). Finally, Dr. Kochanek has begun to collaborate with Dr. Sam Poloyac in the School of Pharmacy on the study of the cytochrome-P450 metabolite 20-HETE in brain injury. Dr. Poloyac is a promising young investigator who is developing an RO-1 submission. I am especially proud of our successes in fellow, resident, student, and faculty development, which I feel is the most important facet of our work.

The hemorrhagic shock and suspended animation program thrived in 2002/2003 guided by the late Dr. Peter Safar and by Dr. Samuel Tisherman. This program, which is focused on novel approaches to resuscitation of traumatic hemorrhagic shock and exsanguination cardiac arrest, is supported through congressional plus-up funding via the United States Army. The program is focused on new approaches to the use of hypothermia and other pharmacologic strategies for protection and preservation of the entire organism during circulatory arrest. Studies in 2002/2003 tackled the difficult problem of the combination of multiple trauma and prolonged cardiac arrest using profound hypothermia and with the novel addition of plasma exchange therapy. In 2002/2003, we wish to thank Drs. Joseph Carcillo at Children's Hospital of Pittsburgh, Dr. Ann Hale of the Midwest Animal Blood Service, Stockbridge, MI, and Dr. Frank Bontempo at the University of Pittsburgh School of Medicine, for their expertise in plasma exchange, blood banking, and coagulation, respectively. Remarkably, we have been able to achieve intact survival after exsanguination cardiac arrests of 2 hours. This work continues to break new frontiers in the area of cerebral and whole-organism preservation and resuscitation. We also thank the investigators of our industrial partner, Ardiem Medical, for their work in the development of cooling devices for this project. We also thank Drs. Ala Nozari and Xianren Wu, two talented fellows working with us on this project. This area of study, with the loss of Dr. Safar, now represents a special challenge for Drs. Tisherman and Kochanek to continue to push into the future. Consultative and administrative support from Dr. Lyn Yaffe, former director of the United States Naval Medical Research Institute is instrumental to the program. Dr. Yaffe is a resource and a special friend to our Center. We cannot thank him enough for this support. We are also very thankful to Col. Dean Calcagni and Robert Read of the United States Army for their continued encouragement and support at the Telemedicine and Advanced Technology Research Center (TATRC) of the United States Army Medical Research and Materiel Command.

Investigators in the Center published 33 peer-reviewed papers, 21 chapters and editorials, and 60 abstracts in 2002/2003. Included among these reports were publications in the *Journal of Biological Chemistry*, *FASEB Journal*, the *Journal of Cerebral Blood Flow and Metabolism, Pediatrics*, *Critical Care Medicine*, *Pediatric Critical Care Medicine*, *Brain Research*, and the *Journal of Neurotrauma*. There were several noteworthy publications in 2002/2003. Lina Du, working with Dr. Clark, published an important report in the *Journal of Biological Chemistry* on the role of intra-mitochondrial PARP in the cascade of neuronal death after brain injury. Their work introduced a novel concept into the PARP cell suicide theory and garnered the cover of the journal. Dr. Rachel Berger authored a manuscript entitled "Neuron-specific enolase and S100B in cerebrospinal fluid after severe TBI in infants and children" that was published in *Pediatrics*. She described a more delayed pattern of release of the neuronal death marker neuron-specific enolase into the cerebrospinal fluid of infants and children after severe head injury from child abuse than from accidental injuries, supporting a unique mechanism of damage in those victims. Rachel's paper was voted at the Annual San Diego Conference on Child and Family Maltreatment to be the most important paper of the year in the field of research in child abuse. Dr. Xiaopeng Zhang, working in the

group of Dr. Clark, published a bench-to-bedside study of the caspase-8 neuronal death pathway in the *FASEB Journal.* Dr. Zhang is a talented clinician-scientist who has helped everyone in our Center with his molecular skills. These high-impact publications reflect the outstanding science of the Clark research group. I am pleased to report that Dr. Zhang was just accepted into the Neurosurgery residency program of the Massachusetts General Hospital. Although he will be a big loss to our group, this is a fabulous career opportunity for Xiaopeng, and we wish him well. Dr. Bayır reported, in the *Journal of Cerebral Blood Flow and Metabolism*, on the formation of nitrosothiols in cerebrospinal fluid of infants and children with severe TBI. This was the first report of nitrosylation in ischemic or TBI in humans, and was accomplished through the collaboration between the Safar Center and the outstanding laboratory of Dr. Valerian Kagan and his free radical biology group in the Department of Environmental and Occupational Health. We look forward to continued productive collaboration with Dr. Kagan. Manu Varma and Sumeeta Varma, summer students who worked in our Center, published manuscripts as first authors in *Brain Research* and the *Journal of Neurotrauma*, respectively. This is exemplary productivity for undergraduates, and attests to their hard work and dedication. Fellow, Dr. Wilhelm Behringer published an important paper in the journal *Critical Care Medicine* on the use of profound hypothermia to achieve neuroprotection for up to two hours in our suspended animation project. Also, Dr. Nozari, a talented visiting clinician-scientist in our Center from Uppsala University, is now at the Massachusetts General Hospital as a resident in Anesthesiology. One of our prior reports from 1997 entitled "Expression of Endothelial Adhesion Molecules and Recruitment of Neutrophils Following Traumatic Brain Injury in Rats" that was authored by Dr. Timothy Carlos, was recognized during the 2002/2003 academic year by the *Journal of Leukocyte Biology* as one of the five most highly cited articles in that journal over the last 5 years. Finally, I was honored to author an editorial on hypothermia in brain injury for the *Journal of the American Medical Association* with the late Dr. Safar. Although many subsequent papers will appear over the next few years on which Dr. Safar had an important role as co-author, this editorial in *JAMA* was the final publication that Dr. Safar worked on before his death.

Drs. Peter Safar (left) and Max Weil at the first Safar Symposium at the University of Pittsburgh School of Medicine. Drs. Safar and Weil were two of the pioneers of the field of Critical Care Medicine in the United States.

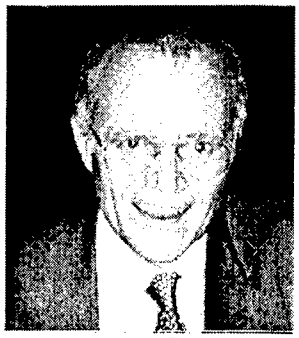
On November 20, 2002, we hosted the first Safar Symposium at the University of Pittsburgh School of Medicine. The symposium featured a morning session on *Breakthroughs in Resuscitation Research* and an afternoon session on the *Role of Human Simulation in Medical Education and Research.*

Two hundred clinicians, scientists, and allied faculty, fellows, paramedics, and students attended the symposium. The program was opened by Chancellor Mark Nordenberg of the University of Pittsburgh and was held at the new Peterson Events Center. The keynote address was given by Dr. Max Harry Weil, of the Institute of Critical Care Medicine, one of the three founding fathers of the field of Critical Care Medicine, a resuscitation pioneer, and a long-time friend of Dr. Safar. Invited speakers also included Drs. Mark Angelos and Larry Katz from the Departments of Emergency Medicine at the Ohio State University, and the University of North Carolina Chapel Hill, respectively.

Dr. Lyn Yaffe gave the 2002 Peter and Eva Safar Lecture for Sciences and Humanities at the University of Pittsburgh School of Medicine. His presentation was entitled "Future Medicine – Biomedical Technology Systems for Victims of Combat and Terrorism."

On November 21, 2002, Dr. Lyn Yaffe, of the Illinois Institute of Technology, and former director of the United States Naval Medical Research Institute was the 23rd Peter and Eva Safar Lecturer in Medical Sciences and the Humanities at the University of Pittsburgh School of Medicine. Dr. Yaffe's lecture was entitled "Future Medicine: Biomedical Technology Systems for Victims of Combat and Terrorism" and outlined a futuristic view of combat casualty care needs and novel potential innovations in the field for military and civilian trauma care, ranging from smart catheters to robotics. During 2002/2003, Dr. Yaffe spearheaded a group of investigators and companies in the development of novel devices for field resuscitation and continues to be an outstanding collaborator with our Center and its efforts in hypothermic protection.

A special visiting professor in 2002/2003 to the Safar Center was Dr. Heinz Redl of the Ludwig Boltzman Institute in Vienna, Austria. Dr. Redl is the scientific director of that renowned institute which shares many overlapping missions with our own work. He is one of the true gentlemen in academics and his comments to our trainees were greatly appreciated.



Dr. Heinz Redl, Scientific Director of the Ludwig Boltzman Institute, was a visiting professor at the Safar Center during the 2002/2003 academic year.

Once again, I would like to thank everyone working at the Safar Center for a terrific job this year. I am personally indebted to Linda Amick, Marci Provins, and Fran Mistrick for their administrative and secretarial excellence. Linda and Marci are extremely dedicated to the Safar Center and its success. Linda continues to take on an increasingly greater administrative role on the business end of the Center while Marci serves as our key secretarial resource for the academic programs in our Center –along with her dedicated work as my local editorial assistant for the journal *Pediatric Critical Care Medicine*. Fran Mistrick was the devoted personal secretary of Dr. Safar for 23 years. I owe her a tremendous gratitude for her help this year. Fran, along with Drs. Ake Grenvik, John Schaefer, did a remarkable job on the Festschrift to Dr. Safar that was published in the journal *Critical Care Medicine*, as we were preparing this report. I will say more about that in next year's annual report. I cannot tell you how pleased I am that Fran is staying on at the Safar Center. I would also like to thank Julian Smith and Val Sabo for their continued dedication and hard work I would also like to personally thank Henry Alexander, John Melick, Keri Janesko, Vincent Vagni, Xiecheng Ma, Lina Du, Paula Nathaniel, Ray Griffith, Jackie Pantazes, Grant Peters, and S. William Stezoski, who were senior administrative and technical staff members during the 2002/2003 academic year for their spectacular contributions to the individual missions of the Center. A special word of thanks is in order to Bill Stezoski. Bill has been the lab coordinator for Dr. Safar for over 30 years, and has been an important reason for the success of the work of Dr. Safar. Bill, I know that Dr. Safar would have wanted me to personally thank you and each of the technicians in the team that you directed for him for an outstanding job. I am similarly pleased that you are staying on to continue with the hemorrhagic shock and suspended animation program; your work is indispensable. I continue to be amazed by the work ethic of all of the technical and secretarial staff at our Center.

I would like to thank Dr. Mitchell Fink for his support as the Chairman of the Department of Critical Care Medicine and Susan Stokes, departmental administrator. I am grateful to them for their support with the renovation of our Center. I would like to thank Drs. Clark, Dixon, Jenkins, Zafonte, Callaway, Adelson, Zhang, Hong Qu Yan, and of course the late Peter Safar for their camaraderie and guidance with the continued development of the Safar Center and its programs. They have been instrumental in its success. I would also like to thank Dr. John Williams, Chairman of the Department of Anesthesiology, for supporting the Safar Symposium and the Peter and Eva Safar Lecture.

Special thanks are also due to Dr. Chien Ho and Kristy Hendrich at the Pittsburgh NMR Center for Biomedical Research, Dr. Edwin Jackson in the Center for Clinical Pharmacology, Dr. Valerian Kagan in the Department of Environmental and Occupational Health, Dr. Stephen Wisniewski in the Department of Epidemiology, Dr. Timothy Carlos in the Department of Medicine, Dr. Simon Watkins in the Department of Cell Biology and Physiology, Dr. Timothy Billiar in the Department of Surgery, Dr. Paul Paris in the Department of Emergency Medicine, Dr. David Perlmutter in the Department of Pediatrics, and Dr. Melvyn Heyes at the Curagen Corporation for outstanding collaborative expertise that raises the level of the research at the Safar Center.

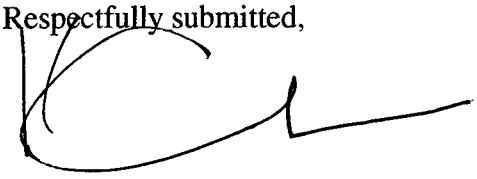
I also owe a debt of gratitude to Mr. Tore Laerdal of Laerdal Medical and to Mr. Hans Dahl of the Laerdal Foundation. Their generous support for the publication of the Festschrift to Dr. Safar was deeply appreciated. We also thank them for their continued support of grants to our Center through the Laerdal Foundation. We also congratulate Dr. John Schaefer, Mr. Tore Laerdal, Dr. Ake Grenvik, and of course, Dr. Peter Winter, for the recent completion of the new Winter Institute for Simulation, Education and Research in McKee Place, on the campus of the University of Pittsburgh. This spectacular new state-of-the-art simulation center will be a unique resource for education and research far into the future.

As this academic year comes to a close, we are about to embark on a new expansion of the Safar Center, to include nearly 8,000 additional square feet of space, increasing the size of the center to about 20,000 square feet. This new space is badly needed and will provide important upgrades for the laboratories of several very productive faculty in our Center, in particular a new cell culture and wet lab facility for Dr. Clark, and a new functional outcome suite for Dr. Dixon, along with several additional upgrades. We also plan on building a historical exhibit outlining the many accomplishments of Dr. Safar during his illustrious career. We thank Dean Arthur Levine for facilitating this expansion. We also thank Frank Adams, Doug Schlach, and Julie Polleta, architects involved in this project, for their dedication to our new facility.

Finally, with the help of Chancellor Nordenberg, we have begun a fundraising campaign to ensure the Safar Center for Resuscitation Research will continue in perpetuity. Based on Dr. Safar's wishes before his death, we have established a fundraising committee and three funds, including a "Safar Legacy Fund," to provide a core budget for the center, along with funds to support the "Nancy Caroline Fellowship Award" and, of course, the "Safar Symposium." We have enclosed a pledge card describing those funds in this year's report and thank you in advance for your support. I also thank each of the members of the fundraising committee for their ideas and hard work. I would also like to personally thank each of you who have already donated to these efforts. Our total goal for these three programs is an endowment of two million dollars toward Dr. Safar's goal of the resuscitation of "brains and hearts too good to die."

I once again look forward to success in 2003-2004 in our investigative efforts to develop new therapies in the field of resuscitation medicine, and thank you for your continued support our work.

Respectfully submitted,



Patrick M. Kochanek, MD

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Director, Traumatic Brain Injury

Clifton Callaway, MD, PhD
Associate Director, Cardiopulmonary Arrest

Robert S.B. Clark, MD
Associate Director, Molecular Biology

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Associate Director, Functional Outcome

Larry W. Jenkins, PhD
Associate Director, Molecular Biology

Anthony E. Kline, PhD
Associate Director, Rehabilitation Research

***Peter J. Safar, MD, Distinguished Professor**
Director, Shock and Suspended Animation

Samuel A. Tisherman, MD
Associate Director, Shock and Suspended Animation

Amy K. Wagner, MD
Associate Director, Rehabilitation Research

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Hülya Bayır, MD
Rachel Berger, MD
Nicholas Bircher, MD
Miroslav Klain, MD, PhD
Ernesto A. Pretto, MD
S. William Stezoski
Xiaopeng Zhang, MD

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Howard Ferimer, MD
Robert Garman, DVM
Steven Graham, MD, PhD
Kristy Hendrich, BS
Robert Hickey, MD
Sam Poloyac, PhD
James V. Snyder, MD
Stephen R. Wisniewski, PhD
Hong Qu Yan, MD

Visiting Scientists
Ann Radovsky, DVM, PhD
Lyn Yaffe, MD

Fellows
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Mandeep Chadha, MD
Xiangbai Chen, MD, PhD
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Josh Sokoloski
Chris Stangey
Matthew Tormenti
Mike Wenger
Lauren Willard

*Founding Director

Funding

During the 2002/2003 academic year, Safar Center investigators had a total of 41 active grants. 35 of these grants were extramural. The direct and indirect costs for the full award period of these grants totaled **$15,985,736** and this is plotted for the current and preceding eight academic years on the following page. The specific sources of this grant support are shown on the subsequent page. Remarkably, the Safar Center is continuing to grow and maintain a high level of extramural support. This has required a huge effort by our faculty since our support is almost completely derived from extramural grants. Congratulations to the faculty for their remarkable funding successes.

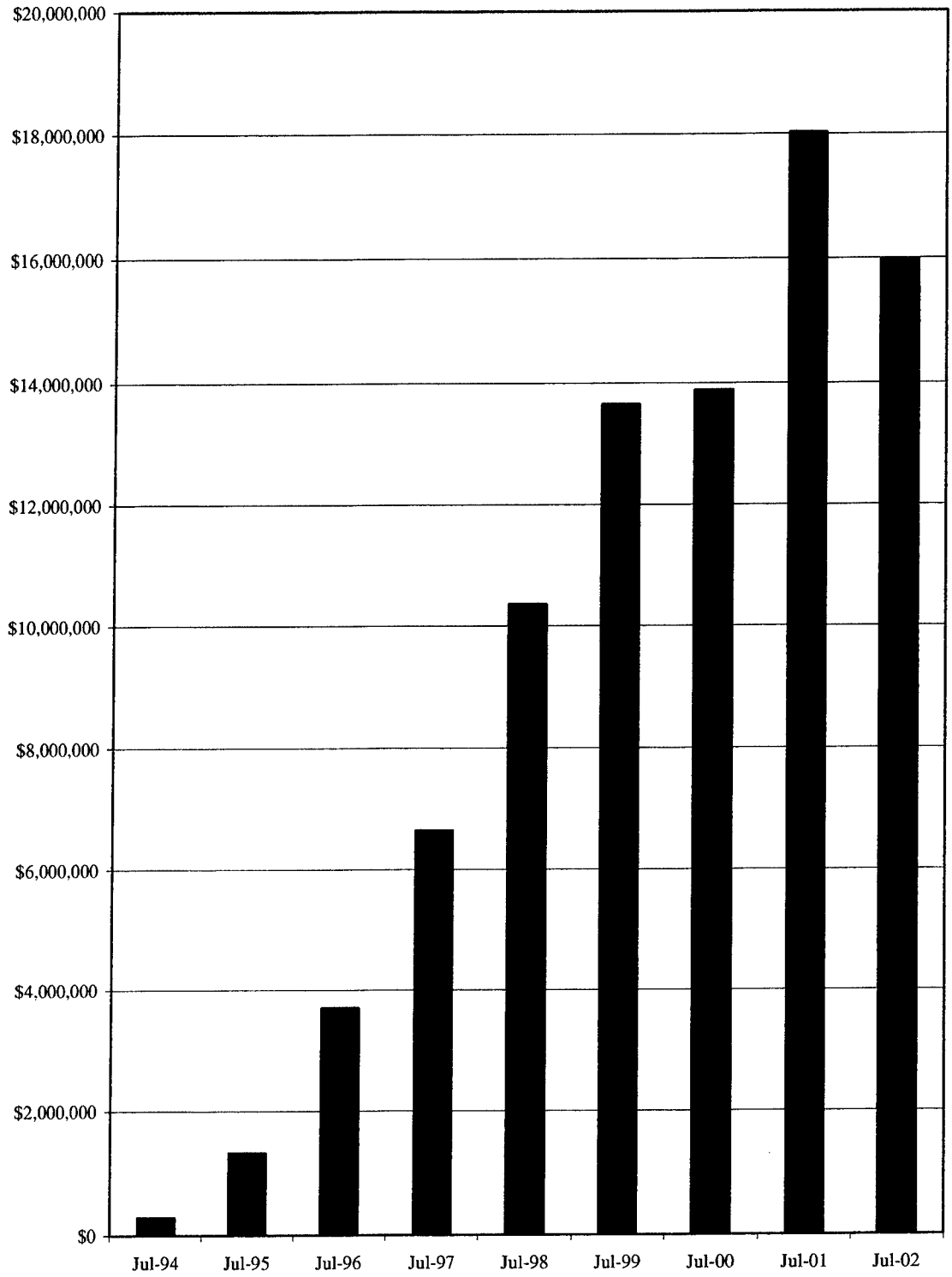
The portion of the budget for use in each academic year (July 1 through June 30) is also plotted for the current and preceding four academic years on the pages following. This represents direct and indirect costs and is shown for total, extramural, and intramural grant support.

Extramural funding sources included the National Institutes of Health, the United States Army, the United States Navy, the Centers for Disease Control and Prevention, the Laerdal Foundation, and a variety of other sources, including contributions made to the Safar Center in memory of Eric Bundy.

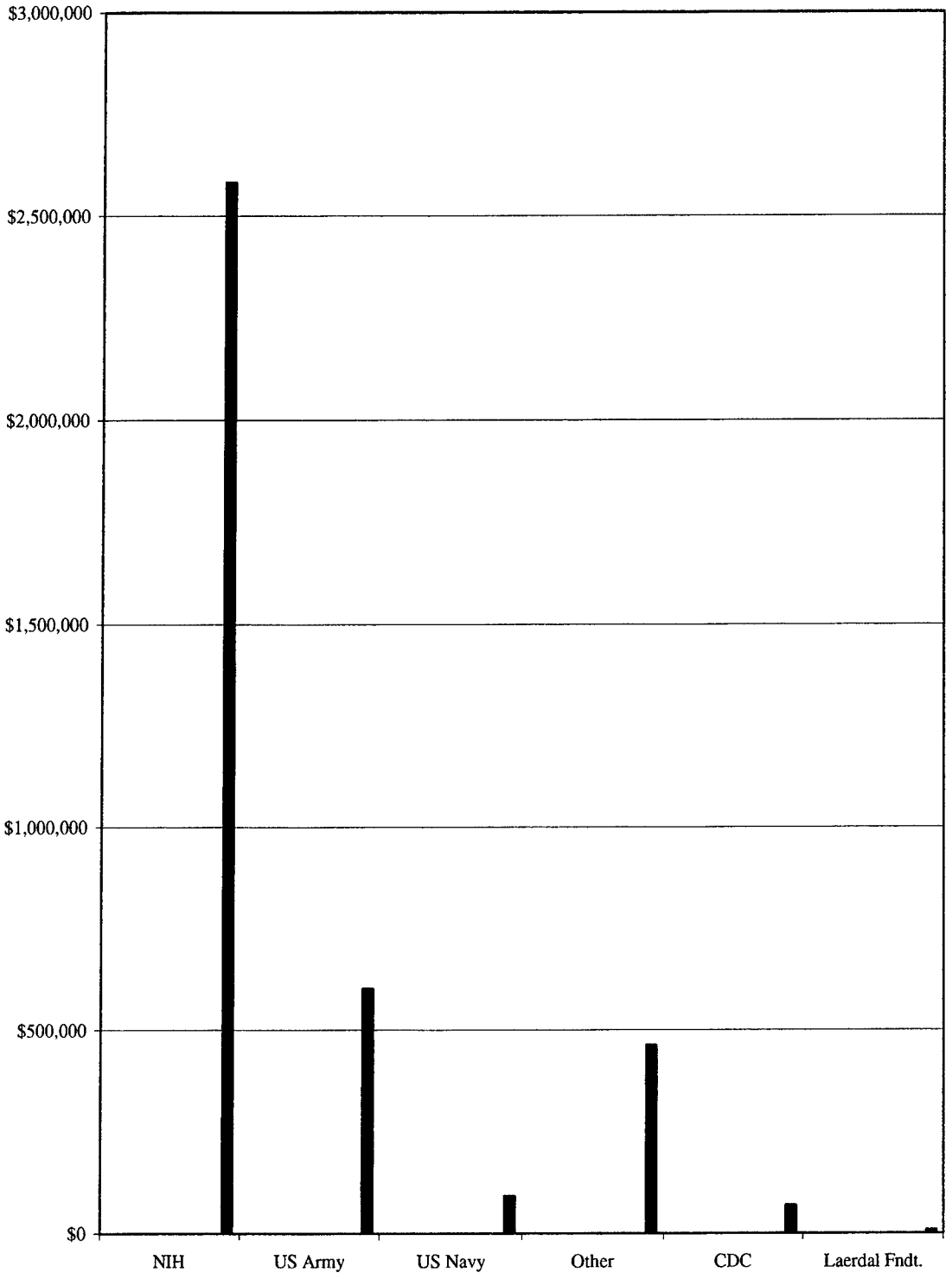
Intramural funding was provided by the Departments of Critical Care Medicine, Anesthesiology, the Children's Hospital of Pittsburgh, and the Pittsburgh Mercy Foundation, Mercy Hospital of Pittsburgh.

We are deeply grateful for the prior and current support from all of these granting agencies and donors.

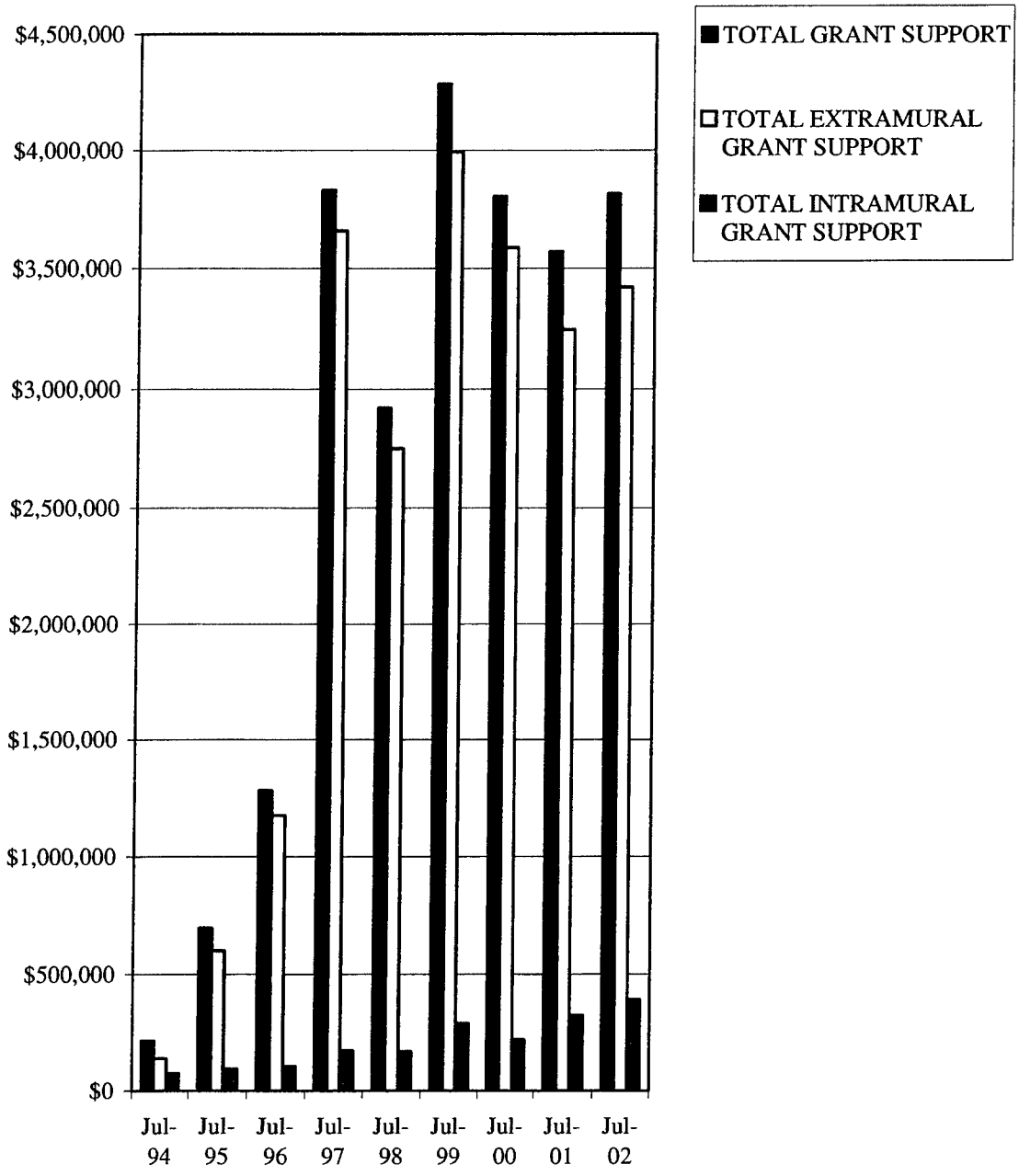
Direct and Indirect Costs for the Full Award Period of SCRR Grants



Specific Sources of Grant Support



Safar Center Grant Support through 2002/2003
use in each academic year



TRAUMATIC BRAIN INJURY (TBI) PROGRAM

Traumatic brain injury (TBI) affects 1.5 to 2 million people in the United States each year, making it one of the more prevalent and debilitating of all neurological disorders. Approximately 300,000 of the cases are severe enough to warrant hospitalization. Of the 250,000 survivors of severe TBI, 100,000 endure long-term disabilities that require rigorous, lengthy, and costly medical and rehabilitative care. In addition to the medical expenses associated with TBI, societal costs are also significant in terms of lost wages due to the inability to resume employment. While the true cost of TBI is incalculable, it is estimated at $100,000 annually per patient or about $48.3 billion per year. TBI is a serious and survivable medical problem with no acknowledged treatment. Therefore, investigation of therapeutic strategies that may facilitate the recovery process after TBI at the Safar Center are essential. Equally important are studies identifying mechanisms involved in the evolution of secondary damage after TBI and determining if pharmacological agents are detrimental to the recovery process.

TBI Investigation by Safar Center Director and Associate Directors

1. Studies directed by Patrick M. Kochanek, MD

Patrick M Kochanek, MD, Director, Safar Center for Resuscitation Research, Professor and Vice Chairman, Department of Critical Care Medicine, University of Pittsburgh School of Medicine. Professor of Anesthesiology and Pediatrics.

Dr. Kochanek's research at the Safar Center is accomplished through a collaborative effort between a number of investigators, fellows, students and staff located principally in the Department of Critical Care Medicine (CCM), including the Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA), Neurosurgery, PM&R, and Neurology at the University of Pittsburgh School of Medicine. A large number of collaborations are also ongoing with investigators in other University of Pittsburgh departments including the Center for Clinical Pharmacology, Environmental and Occupational Health Medicine, Pediatrics, Epidemiology, Anesthesiology, and Surgery. In addition, a long-standing collaboration is in place with the Pittsburgh NMR Center for Biomedical Research at Carnegie Mellon University. We have also had a number of important extramural collaborators, Dr. M Heyes at the Curagen Corporation, Dr. N Minamino at the National Cardiovascular Center Research Institute in Osaka, Japan, Dr. JF Chen at Boston University, and Dr. J Schnermann at the NIH. Taken together, these collaborations have allowed us to investigate a broad spectrum of mechanisms that may be important to the evolution of secondary damage after TBI. Our most important work continues to be in the area of defining the mechanisms important to secondary brain injury both after experimental TBI and in the human condition. Our studies of mechanism of secondary damage and repair in human materials (cerebrospinal fluid [CSF], brain tissue samples from resected contusions, and microdialysis samples) have generated new insight into the biochemistry and molecular biology of human head injury. Based on this mechanistic work, we are currently testing novel therapies in our

experimental models. Our goal is to develop new therapies that can be successfully translated to clinical application. Our clinical research of taking the bench to the bedside—particularly as it relates to child abuse—has been featured many times in the lay press.

A. Biochemical Assessment of Secondary Mechanisms of Injury and/or Repair after Severe TBI in Infants and Children: The Role of Child Abuse.

This continues to be an important area of research for our group and, as indicated above, continues to generate considerable publicity. We are using samples of CSF and blood collected from infants and children suffering severe TBI to study a variety of biochemical mediators of secondary damage and/or repair. These samples are collected by Dr. Rachel Berger in the Department of Pediatrics and member of our critical care team including Drs. Clark, Bayır, Shore, Ruppel, Lai, Chadha, and Fink in the division of Critical Care Medicine, Dr. Berger, in the Department of Pediatrics, and Dr. Adelson in the division of Neurosurgery at Children's Hospital of Pittsburgh. To generate a CSF bank for this purpose, Dr. Kochanek is funded by the CDC (University of Pittsburgh Center for Injury Control and Research [CIRCL]). We have now over 1000 samples from nearly 100 infants and children who have suffered a severe TBI—including over 20 victims of inflicted TBI (shaken baby syndrome). In addition, we continue to collaborate with Dr. Neal Thomas at the Hershey Medical Center, Hershey, PA, who is also collecting samples.

Studies using the pediatric CSF bank at the Safar Center

The pediatric CSF bank and related clinical projects have produced some of the most interesting findings in the area of TBI at the Safar Center in the 2001-2002 academic year. Work has progressed in seven major areas including 1) oxidative stress, 2) detection of "silent" inflicted childhood neurotrauma, 3) adenosine and related metabolites in TBI, 4) markers of neuronal death study, 5) growth factors and markers of regeneration and repair, 6) studies of the effect of hypothermia on markers of secondary damage after TBI, and 7) assessment of the effect of the mode of CSF drainage in pediatric TBI.

The potential use of CSF in understanding the pathophysiology of child abuse and potentially serving as a diagnostic adjunct originated from a small grant awarded to Dr. Kochanek within the University of Pittsburgh CIRCL focused on the use of inflammatory markers in CSF as a biological clock to provide insight into the timing of injury in infants who were victims of the shaken baby syndrome. The first report by our group in that area was by Dr. Michael Bell (see prior annual reports). This area of investigation has been broadened by Safar Center Scientist, child abuse specialist, and general pediatrician Dr. Rachel Berger to include the use of serum to assess for the possibility of "silent" brain injury in infants who are victims of inflicted childhood neurotrauma (abuse). Her exciting program of work in this area is described later in her section within the TBI program.

Oxidative stress in TBI

This is an exciting area of research spearheaded by Dr. Hülya Bayır, a senior PICU fellow and the 2002 Charles Schertz Fellow in the Department of Anesthesiology. Dr. Bayır's work entitled "Assessment of antioxidant reserve and oxidative stress in CSF after severe TBI in infants and children" was published as a full paper in *Pediatric Research.* That work, done in collaboration with Dr. Kagan, provided substantial evidence for oxidative stress in brain after severe TBI in infants and children. Dr. Bayır followed up on that study an equally important report entitled "Effect of hypothermia on oxidative stress after TBI in humans: a preliminary report" that she presented at the 2001 meeting of the National Neurotrauma Society and will present at the 2002 meeting of the SCCM. She has begun to use the battery of markers of oxidative stress and damage that she has developed with Dr. Kagan, to evaluate the effect of therapies—including moderate hypothermia in adults. Current studies by Dr. Bayır of the effect of hypothermia on oxidative stress in pediatric TBI are also underway—done in conjunction with the RCT being carried out by Dr. Adelson at Children's Hospital of Pittsburgh. Dr. Bayır has also worked under the direction of Dr. Kagan to study a novel marker of nitrosative stress in pediatric TBI, namely, S-nitrosylation. Their work in this novel area was presented at the 2001 meeting of the Society for Neuroscience and a full manuscript is *in press* in the *Journal of Cerebral Blood Flow and Metabolism.* Dr. Bayır will join our faculty next year in Pittsburgh and will be a welcome addition to the growing list of Scientists at the Safar Center.

Adenosine in TBI

Dr. Kochanek is beginning year-4 on an RO-1 from NINDS focused on adenosine in TBI. Translational work is an important part of this effort and the CSF bank represents a key resource. Dr. Courtney Robertson's article on CSF adenosine in pediatric TBI (see last year's report) was published this year in the journal *Critical Care Medicine.* Investigation of the effect of hypothermia on adenosine and purine related markers of energy failure are ongoing in collaboration with Dr. Edwin Jackson. Similarly, Ava Puccio is evaluating the relationship between CSF adenosine and tissue oxygen levels in adults with severe TBI, in work done with Dr. Marion at Presbyterian Hospital.

CSF markers of neuronal death in TBI

As part of the impressive work of Dr. Robert Clark's group on mechanism of neuronal death, including studies on caspases, apoptosis inducing factor (AIF), and poly ADP ribose polymerase (PARP), translational studies are similarly taking advantage of our CSF bank and brain tissue samples. Drs. Margaret Satchell and Xiaopeng Zhang have published a series of abstracts on PARP activation and protein kinase B signaling after TBI in humans. Some of Dr. Satchell's work was discussed in last year's annual report. This translational approach is providing important human data on contemporary and intensively investigated mechanisms of neuronal death in experimental TBI—and has the potential to help guide the development of novel therapies.

Growth factors and markers of regeneration and repair

Building on the prior work of both Dr. Steven DeKosky on nerve growth factor, and Edwin Jackson on the relationship between adenosine A2β receptor activation and elaboration of vascular endothelial growth factor (VEGF), Dr. Paul Shore presented a paper at the 31st Congress of the SCCM reporting marked increases in VEGF after severe TBI in infants and children. At the same meeting, Dr. Erica Fink, a senior pediatric resident working with Dr. Clark reported increases in hepatocyte growth factor in CSF after injury. We have been struck by the robust and rapid regenerative response that occurs after TBI and by the fact that this is readily detected using CSF.

Effect of modes of CSF drainage

Dr. Paul Shore is carrying out a comparative study (in collaboration with Dr. Neal Thomas at Hershey Medical Center) assessing the effect of continuous versus intermittent CSF draining on mediator levels and pathophysiology after severe TBI in infants and children. We are pleased to collaborate with Dr. Thomas, a former fellow in our program, in this study that addresses a basic treatment approach (CSF drainage) that has been subjected to remarkably little investigation.

Our pediatric CSF bank continues to represent a key research tool of our trainees to help bring the bench to bedside in the study of secondary injury mechanism in clinical TBI research.

Support: Quinolinic Acid in CSF Early after Severe Head Injury in Victims of Child Abuse R49/CCR310285-03, (9/1/01-8/31/02), $45,110, P Kochanek, PI, M Heyes, PhD, [Curagen Corporation], R Berger, S Wisniewski, PhD, D Marion, MD, and P David Adelson, MD, Co-investigators); collaborators. CDC, CIRCL (D Marion, MD, PI); Adenosine and TBI, NS38037, (8/2/01-7/31/02) $263,910, P Kochanek, PI; iNOS and TBI, NS30318 (P Kochanek, PI), Project 3 within the University of Pittsburgh Brain Trauma Research Center (BTRC), D Marion, PI. Protocol #3480500 (5/1/00-4/30/01), $11,215, R Berger, PI, CHP GCRC. Oxidative Stress after Severe Head Injury in Infants and Children: Effect of Therapeutic Hypothermia, Laerdal Foundation, H Bayır, PI.

B. Adenosine and TBI

Adenosine is produced during the breakdown of adenosine triphosphate (ATP) after TBI. Its powerful vasodilator, anti-excitotoxic, and anti-inflammatory effects may represent an important endogenous defense mechanism in the injured brain. The role of adenosine as an endogenous neuroprotectant molecule, particularly early after TBI, and its potential participation in delayed cerebral swelling are being pursued both in the rat TBI model and in patients after TBI. We are beginning the 4th year of this RO-1-funded project. This project continues to be the most active area of research in Dr. Kochanek's laboratory this year and has produced a number of reports of studies in both patients and experimental models of brain injury. This work is being carried out in collaboration with Dr. Edwin Jackson in the Center for Clinical Pharmacology. In laboratory aspects of the research on this project, we have continued to evaluate the effect of local injection of adenosine receptor agonist and antagonists on cerebral blood flow. That work is carried

out in collaboration with Dr. Chien Ho and Kristy Hendrich at the Pittsburgh NMR Center. A recent study was presented at the 2001 meeting of the National Neurotrauma Society—and demonstrated that adenosine receptor agonist mediated cerebrovasodilatory effects are mediated by the A2a receptor and can increase cerebral blood flow in both the normal and traumatically injured rat brain. A number of outcome studies of adenosine agonists are ongoing in collaboration with Dr. C. Edward Dixon in our center using the controlled cortical impact (CCI) model. Manu Varma, an undergraduate from the University of Michigan who worked on that project in our laboratory again this summer, was just informed that his manuscript on this work is accepted for publication in the journal *Brain Research.* Using our CCI model, we are currently studying the A2a-receptor knockout mouse, obtained from Dr. Jiang-Fan Chen at the Massachusetts General Hospital and the A1-receptor knockout mouse obtained from Dr. Jurgen Schnermann at the NIH to begin to unravel the role of specific adenosine receptors in the mechanisms of secondary damage and repair after experimental TBI. Key collaborators on the RO-1 are Drs. E Jackson, CE Dixon, C Ho, S Graham, D Marion, and Ms. K Hendrich.

Support: NIH RO-1, Adenosine and TBI, ($1,593,730, 08/02/99-07/31/03, P Kochanek, MD, PI).

C. Role of Inducible Nitric Oxide Synthase (iNOS) in the Inflammatory Response after TBI

iNOS is induced by cytokines and NF-κB is suggested to play an important role in the pathophysiology of sepsis outside of the central nervous system. Both beneficial and detrimental actions of iNOS have been reported. Using both inhibitors of iNOS and knockout mice, Dr. Elizabeth Sinz (1996-97 Charles Schertz Fellow) reported a powerful endogenous neuroprotectant effect of iNOS in experimental TBI. This area of study is carried out as part of our funded project within the University of Pittsburgh Brain Trauma Research Center (BTRC) Program Project. In collaboration with Drs. Kagan and Timothy Billiar, Hülya Bayır has been studying protein nitration and nitrosylation after experimental TBI using iNOS knockout mice. Nitrosothiols may represent a nitric oxide reservoir and could play important roles in signal transduction, immunomodulation, vascular regulation, and neurotransmission.

Support: NIH 2P50 NS30318, iNOS and TBI, ($582,986), P Kochanek, MD, PI, Key Collaborators: RSB Clark, MD, CE Dixon, PhD, T Billiar, MD, V Kagan, PhD, L Jenkins, PhD, X Zhang, PhD, H Yan, MD, and T Carlos, MD.

D. Emergency Interventions after TBI: Effect on Secondary Damage

Studies in this area of investigation were funded, this year, by both the Laerdal Foundation and the Curagen Corporation. Dr. Kimberly Statler (one of our T-32 fellows) has been the leading investigator on this work. Dr. Statler presented a surprising paper showing that moderate hypothermia, applied after experimental TBI, expands lesion

volume at 72 h after injury in rats anesthetized with the narcotic fentanyl. That work was presented at the National Neurotrauma Society meeting and is *in press* as a full manuscript in the journal *Critical Care Medicine*. In that study, Dr. Statler discovered that hypothermia after TBI produces an enhanced stress response—reflected by higher serum catecholamine levels—compared to the normothermic condition. These studies are in contrast to the remarkable neuroprotection that others and we have consistently observed with hypothermia in rats anesthetized with isoflurane. The importance of this work lies in the fact that patients are sedated with narcotics after TBI. It may be that to maximize the potential benefit of therapeutic hypothermia after TBI, sedation must be optimized. To further understand the mechanism underlying the effect of hypothermia on experimental TBI, we are carrying out studies evaluating the effect of hypothermia on gene expression using our mouse model of controlled cortical impact. This work is being carried out in collaboration with Dr. Melvin Heyes at the Curagen Corporation, a leader in gene culling technology. In an initial report, two summer students, Becky Sullivan and Gilna Alce published an abstract of work in *Critical Care Medicine* showing a robust beneficial effect of the resuscitative application of transient, moderate hypothermia in this model. This, to our knowledge, is the first report of the beneficial effects of hypothermia in a mouse model—and sets the stage for studying the combined effects of hypothermia in genetically modified mice. Finally, Dr. Statler published an invited review on this area of work in the *Journal of Neurotrauma* that was based on a plenary talk by Dr. Kochanek, entitled "The Simple Model Versus the Super Model: Translating Experimental TBI Research to the Bedside." We hope to also soon apply proteomics approaches to the study of hypothermia in TBI in collaboration with Dr. Larry Jenkins in our Center.

Support: Laerdal Foundation, MRI Assessment of cerebral blood flow and calcium accumulation after TBI in rats: Effect of isoflurane versus Fentanyl, ($7,500, 1/1/00 – 6/30/01, K Statler, PI). Training in Pediatric Neurointensive Care and Resuscitation Research, T32-HD40686, National Center for Medical Rehabilitation Research (NCMRR), National Institute of Child Health and Development (NICHD), P Kochanek, PI 9/25/00-4/30/01.

E. Magnetic Resonance Imaging (MRI) Assessment of Experimental TBI

Contemporary and novel MRI methods are being used to characterize our injury model and facilitate the testing of novel therapies in experimental TBI in rats. The goal of this work is to use non-invasive NMR methods to access acute physiologic derangements early after injury and to couple these to assessment of functional outcome at more delayed times after TBI. MRI methods were used to augment investigation in our study of both adenosine and anesthetics in experimental TBI. We have begun to expand the use of MRI to our mouse model of experimental TBI with the help of Kevin Hitchens and Lesley Foley. Dr. Ho's outstanding multidisciplinary NMR center for biomedical research continues to be a key collaboration for our work in experimental TBI.

Support: NIH-NINDS 2P50 NS3031809 A1, Rat/Surgery/Imaging Core C, ($470,095 over 5 years, P Kochanek, MD, PI, C Ho, PhD, Co-PI, K Hendrich, D Williams, PhD, and S DeKosky, MD, Co-investigators). NIH Grants RR-03631 and RR-10962, (C Ho, PI) support the Multidisciplinary Pittsburgh NMR Center at Carnegie Mellon University. NIH PAR00-031, In-Vivo MR Microscopy Instrumentation at 11.7 Tesla ($500,000, C Ho, PhD).

2. Studies directed by C. Edward Dixon, PhD

C. Edward Dixon, PhD, Professor of Neurological Surgery, Anesthesiology, Neurobiology, and PM&R, University of Pittsburgh School of Medicine. Director, University of Pittsburgh Brain Trauma Research Center

Research Interests

Research in Dr. Dixon's laboratory is directed towards understanding the molecular mechanisms of cognitive deficits following TBI. Current studies are evaluating the effects of brain injury on dopaminergic and cholinergic systems and the relationship between these changes and the induction and recovery cognitive deficits. Experimental neurotherapeutic studies are ongoing to evaluate the effects of neurotrophic growth factors and neurotransmitter receptor activation on recovery of function. Clinical studies include measuring CSF and extracellular levels of catecholamines and markers of oxidative injury in humans acutely after brain trauma.

A. Dopaminergic/Cholinergic Mechanisms of TBI

Recovery of cognitive function after TBI is a dynamic process in which alterations in neurotransmitter systems do not likely occur in isolation. During the prior funding period we noted that substantial cholinergic neurotransmission deficits occur without a chronic (4-wk post injury) loss of cholinergic cell bodies. We also have extensive data that TBI causes chronic changes in key dopaminergic proteins that occur concomitantly with these cholinergic changes. Numerous studies have shown that the dopaminergic innervation of medial septum and diagonal band of broca (medial septal area [MSA]) regions that are dense with cholinergic neurons, can affect hippocampal acetylcholine (ACh) release, especially via D1 receptor agonists. Furthermore, we have compelling preliminary data that dopaminergic innervation of cholinergic nuclei is reduced after TBI. In this project, we propose to extend our previous findings to hypothesize that cognitive deficits after TBI may be, at least partially, attributable to decreased dopamine (DA) modulation of septohippocampal cholinergic function. A systematic series of studies are proposed to test this hypothesis. We will focus on DA modulation of the selectively vulnerable septohippocampal cholinergic system. To better grade an effect of TBI on these systems, we will compare in the MSA the effects of TBI to an established model of DA deafferentation effects; 6-hydroxydopamine (6-OHDA)-induced DA denervation. We will examine the effects of TBI and 6-OHDA lesions on DA modulated ACh release in

the hippocampus and DA release in the medial septum. We will also determine whether changes in hippocampal ACh release are associated with altered D1 receptors in the MSA. Dr Dixon's group will determine the effect of exogeneous administration of neurotrophic factors on DA biochemical markers, cognitive deficits, as well as hippocampal ACh release and MSA DA release after TBI. Lastly, we will determine the effects of clinically relevant DA agonist therapies on cognitive deficits, as well as hippocampal ACh release and MSA DA release after TBI. Our long-term goal is to develop new therapies to accelerate cognitive recovery following TBI.

During this year, we have found that TBI can produce chronic changes in proteins necessary for DA neurotransmission. We have also found that TBI can produce a reduction in DA release in the MSA at 2-wks postinjury and that the number of TH-positive fibers with the medial septum and diagonal band are decreased after TBI. Immunohistochemical and Western blot studies have revealed a distributed up-regulation of TH and downregulation of DAT protein levels. Western blot studies have found decreases in D2 receptor protein levels in the striatum at 4-wks postinjury. We have also demonstrated that DA agonists can enhance recovery of cognitive function after TBI. Overall, there is new evidence that ACh and DA systems are altered chronically after TBI. We also have preliminary data that markers of DA innervation of the septal region are chronically diminished after TBI.

Support: NIH-NINDS, Chronic Changes in Neurotransmission Following TBI, R01 NS-33150-06 ($1,000,000/$484,819 over 5 years, 4/1/00-3/31/05, CE Dixon, PhD, PI).

B. Functional Outcome Core

During this year, the Functional Outcome Core has evaluated post-injury function in several hundred rats and mice for seven different Principal Investigators associated with the Safar Center.

The Functional Outcome Laboratory Core Facility provides a centralized site and highly standardized procedural control for all animal experiments employing functional outcome as an endpoint following TBI to rats. The Functional Outcome Laboratory Core gives the investigators of the University of Pittsburgh BTRC the capability to assess the effects of physiological manipulations and therapeutic interventions of recovery of function after experimental brain injury.

Support: NIH, BTRC Supplement—Functional Core to P50 NS-30318-041A ($274,583 over 4 years, 4/1/96-3/31/00, CE Dixon, PhD, PI).

C. Examination of the Cellular Mechanisms of Mesocortical Dopaminergic Deficits after TBI in a Rodent Model Using Biochemical Indices of DA Autoxidation and Biochemical, Molecular Biological and Immunohistochemical Indices of DA Metabolism and Neurotransmission.

The goal of this project is to examine the cellular mechanisms of mesocortical dopaminergic deficits after TBI in a rodent model using biochemical indices of DA autoxidation and biochemical, molecular biological and immunohistochemical indices of DA metabolism and neurotransmission. Neurochemical and immunohistochemical markers of DA neurotransmission in the dopaminergic ventral tegmental/forebrain systems, as well as functional deficits, will be assessed after injury. The effects of therapies that either reduce oxidative damage of DA terminals and/or chronically stimulate DA activity on neurochemical and immunohistologic markers, and on functional performance will be assessed following TBI. Lastly, the relationship between early biochemical markers of DA activity to neuropsychological outcome measures specific to frontal lobe function will be evaluated in severe TBI patients. This project represents the first systematic examination of the mechanisms of induction and recovery of catecholaminergic cognitive deficits after TBI. Our long-term goal is to develop new therapies to attenuate the induction and enhance the recovery of DA-mediated neurobehavioral deficits after TBI.

Support: NIH-NINDS, Mechanisms of Prefrontal Dysfunction Following Brain Trauma, R01 NS-40125-01 ($800,000/$376,775 over 4 years, 3/1/00-3/31/04, CE Dixon, PhD, PI).

D. Transcriptomic Analysis of Therapeutics in Brain Trauma

Recovery of cognitive function after TBI is a dynamic process that likely involves multiple neural systems. Several studies by our laboratory and others indicate that cognitive recovery can be enhanced by post injury activation of dopaminergic systems or exposure to an enriched environment. The effectors of such therapeutic activation are likely to involve simultaneous gene expression changes in numerous neural systems. The recent development of DNA microarrays has allowed scientists for the first time the ability to observe thousands of gene expression changes in parallel. While there are limitations, DNA microarrays provide a new systemic view to study brain injury and the treatments that stimulate and enhance recovery of function. We have evaluated a number of DA agonists that are clinically used "off label" for their ability to enhance recovery of cognitive function in our experimental model of TBI and found three to be beneficial: amantadine hydrochloride, bromocriptine, and methylphenidate. While all are putative DA agonists, they have varying degrees of specificity. We have also observed that bromocriptine treatment, when initiated 24 h after TBI, can attenuate hippocampal cell death and lipid peroxidation. This suggests that DA agonists may have mechanisms of action beyond just being DA replacement therapies (e.g. cell survival effects). Supporting this concept, we have new pilot microarry data indicating that relative to a vehicle treatment, the DA agonist methylphenidate can enhance the gene expression of DA receptors and alter injury-induced inflammatory responses. DNA microarrays are well suited to investigate the effects of DA agonists on multiple pathways. The overall goal of the project is to determine common genes that are changed by these therapies and whether these gene expression changes can be further enhanced by the addition of enriched environment therapy. This project will obtain the preliminary information

needed for a larger-scale R0l study to increase the number of cases, refine and increase the number of genes analyzed, and to more comprehensively study those genes whose expression are related to recovery of function after TBI.

Support: NIH-NINDS, R21 NS47919, Transcriptomic Analysis of Therapeutics in Brain Trauma. CE Dixon as PI, 10% effort. 07/01/03–06/30/06. $95,000-annual direct costs.

Grant Support

NIH, R21 NS47919, Transcriptomic Analysis of Therapeutics in Brain Trauma. CE Dixon as PI, 10% effort. 07/01/03 – 06/30/06. $95,000-annual direct costs; $138,000 total indirect costs; $285,000 total direct costs; NIH, R01 NS40125, Mechanisms of Prefrontal Dysfunction Following Brain Trauma. CE Dixon PI, 22.5% effort. 03/01/00-03/31/04. $200,000-annual direct costs; $472,499 total indirect costs; $1,000,000 total direct costs; NIH, R01 NS33150, Chronic Changes in Neurotransmission Following TBI. CE Dixon PI, 26% effort. 04/01/00-03/31/05. $200,000-annual direct costs; $804,064 total indirect costs; $1,645,223 total direct costs; CDC, R49 CCR312296, CIRCL: Acute Care Core Project 1–Effects of Amantadine Hydrochloride on Functional Outcome After TBI: a Randomized, Multi-Center, Placebo-Controlled Clinical Trial; and Acute Care Core Project 2-Relationship Between Amantadine Hydrochloride Efficacy and Brain Function Using PET Imaging, CE Dixon PI, 15% effort. 09/01/98-08/31/02. $106,000-annual direct costs; $1,261,222 total indirect costs; $2,709,778 total direct costs; USAMRMC, 00-451-4360, Novel Resuscitation from Lethal Hemorrhage. P Safar PI, CE Dixon Co-I, 5% effort. 09/15/02-09/14/03. $347,418 annual indirect costs; $712,336 annual direct costs; NIH, R21 NS40049, Protein Synthesis, Memory and Pediatric Brain Injury. LW Jenkins PI, CE Dixon Co-PI, 15% effort. 04/01/00-03/31/03. $125,000-annual direct costs; $187,031 total indirect costs; $375,000 total direct costs; NIH, R01 NS38087, Adenosine and TBI. P Kochanek PI; CE Dixon Co-PI, 7% effort. 08/02/99-07/31/03. $747,440 total direct costs; NIH, R03 HD41399, Gender Differences in DA Function after TBI. AK Wagner PI, CE Dixon Co-PI, 5% effort. 02/06/02 – 01/31/04. $50,000 annual direct costs; $45,535 total indirect costs; $100,000 total direct costs; NIH, K08 HD40833, DA Function in TBI and Effects of Therapeutic Intervention. AK Wagner PI, CE Dixon Primary Sponsor. 09/01/01-09/30/06. $114,365 annual direct costs; $576,165 total direct costs; NIH, R03 HD043851, Interaction of Serotonin and Cholinergic Systems after TBI. AE Kline PI, CE Dixon Co-I, 5% effort. 04/01/03–03/31/05. $50,000 annual direct costs; $44,233 total indirect costs; $100,000 total direct costs.

3. Studies by Robert S. B. Clark, MD

Robert SB Clark, Associate Professor of Critical Care Medicine and Pediatrics, University of Pittsburgh School of Medicine, Fellowship Director, Pediatric Critical Care Medicine Program, Children's Hospital of Pittsburgh.

A. Endogenous Neuroprotectant Gene Expression after TBI

This research focuses on the genetic regulation and execution of delayed neuronal death in selectively vulnerable neurons after TBI. We have now characterized the expression of several potential cell death-suppressor genes and their translated proteins including bcl-2 gene family members and heat shock protein 72 (endogenous neuroprotectants), as well as potential cell death-effector genes including the pro-apoptotic bcl-2 gene family member bax. These genes appear to be up-regulated and/or activated after TBI in both our experimental model (CCI injury with secondary hypoxemic insult followed by resuscitation in rats) and in humans. Studies documenting that bcl-2 family genes may be important in both adult and pediatric patients after TBI were reported previously in the *FASEB Journal* and the *Journal of Pediatrics*, respectively. A role for heat shock proteins after human head injury is also being investigated. Regulation of some of these proteins is via post-translational modification, including the bcl-2 family members and bag-1. Bag-1 regulates the chaperone function of heat shock proteins, pointing to a direct interaction between these two classes of endogenous neuroprotectants. As pictured on the cover of this report, PCCM fellow Yi-Chen Lai received a research award form the SCCM for his work on two papers in this area of research including "Mitochondrial over-expression of HSP-70 protects neurons from oxidative stress" and "Age-related increases in protein kinase B after pediatric TBI." In both of these studies, Dr. Clark mentored Lai.

B. Caspase-Mediated Neuronal Death after Head Injury

Increasing evidence suggests that activation of caspases regulate and execute programmed cell death after TBI in experimental models and in humans. Accordingly, the objective of this research is to develop pharmacological and molecular treatment strategies that reduce caspase-mediated programmed-cell death after TBI. We previously described potential roles for caspase-1 and –3 after severe TBI in humans in a paper published in the *FASEB Journal.* Studies examining other more potent caspase inhibitors, and combination treatment strategies targeting multiple points in the programmed cell death cascade are ongoing.

C. Divergent Pathways of Cell Death after Brain Injury

It is clear that both apoptotic and necrotic cell death contribute to neuronal cell loss after acute brain injury; however, recent data suggest that this is in fact over simplistic, and that multiple, interrelated pathways exist. A key regulator in this regard is the mitochondrial protein AIF. Work by Dr. Xiaopeng Zhang under the direction of Dr. Clark has clearly demonstrated that AIF-mediated cell death occurs after experimental TBI. That work was published last year in the Journal of Neurochemistry. This year Drs. Zhang and Clark demonstrated an important role for an additional pathway of delayed neuronal death after experimental and clinical TBI—namely—the Fas/Fas ligand pathway. Specifically, they reported, in the *FASEB Journal*, caspase-8 expression and proteolysis in human brain after severe TBI. This work suggests the need for additional experimental and clinical investigation of this pathway in TBI, and the possibility of

novel avenues for therapy. Ongoing studies are determining the contribution of these divergent pathways of cell death to secondary damage in TBI using multiple strategies in collaboration with Drs. Jun Chen, Steven Graham, Patrick Kochanek, Csaba Szabo (Inotek Corp., Beverly, MA), Simon Watkins, Hector Wong (Cincinnati Children's Medical Center), and Ian Reynolds.

D. PARP Activation after TBI

The study of PARP in experimental TBI is an expanding area of investigation at our center. PARP is an abundant nuclear enzyme with a role in DNA repair pathways. However, in the setting of energy failure, it is suggested that excessive ADP-ribosylation of proteins resulting from activation of PARP leads to marked nicotine adenine dinucleotide (NAD) depletion and exacerbation of energy failure. Drs. Whalen, Clark, and Kochanek collaborated with Dr. Csaba Szabo (an expert in the area of PARP and sepsis at the Inotek corporation) to study the PARP knockout mouse in our model of experimental TBI. We previously reported highly significant level of protection against functional deficits after TBI in PARP knockout vs wild-type mice, and a role for PARP inhibitors in improving outcome in experimental TBI in mice. However, we also noted deleterious effects of PARP inhibitors on memory acquisition in normal mice—supporting a role for PARP in memory acquisition. This year, we also published a report showing that intra-mitochondrial PARP activation contributes to NAD depletion and cell death both in neuronal culture and in experimental TBI. That work was published by Lina Du in the *Journal of Biological Chemistry* and was featured on the cover of the journal. This work provides novel and valuable insight into the cascade of cell death in the setting of PARP activation—a mechanism that is believed to contribute importantly to a number of important diseases in critical care medicine including CNS injury, stroke, cardiac arrest, sepsis, shock and MOF. In addition, this work further establishes the presence of PARP in mitochondria.

Support: RO1-NS38620-03, Caspase-Mediated Neuronal Death After Head Injury ($584,022 total direct costs over 4 years beginning 2/1/99, R Clark, MD, PI); KO8-NS01946-05, Role of Neuroprotective Genes After TBI ($455,960 total direct costs over 5 years beginning12/1/96, R Clark, MD, PI; S Graham, MD, PhD. and P Kochanek, MD, Sponsors); P01-NS30318, PARP Activation After TBI, Project 4 of the BTRC Program Project ($595,000 total direct costs over 5 years beginning 6/1/00, R Clark, MD, PI).

4. Studies directed by Larry W. Jenkins, PhD

Larry Jenkins, PhD. Associate Professor of Neurological Surgery, University of Pittsburgh School of Medicine

A. Protein Synthesis, Memory and Pediatric Brain Injury

We have further examined the potential role of impaired protein synthesis in memory deficits after experimental pediatric TBI. There is extensive data suggesting that protein

synthesis is critical for the consolidation of hippocampal dependent learning and memory. Protein synthesis is involved in developmental synapse formation, long-term potentiation (LTP) and memory consolidation. Our initial study employing 2-D gel electrophoresis to examine global protein expression during the consolidation of spatial memory acquisition has been submitted for publication. Proteomic studies have potential to expand our understanding of neural injury and therapy but have yet to be applied to TBI. The purpose of this study was to examine global hippocampal protein changes in 17 PND rats 24 h after moderate CCI. Analysis was limited to a wide pH range (nonlinear pH 3-10) for isoelectric focusing with immobilized pH gradients (IPG strips) and large format (22 x 22 mm) SDS slab gels. We evaluated only the most soluble cellular protein fraction using hippocampal tissue protein lysates from sham and injured rats. About 1500 proteins spots were found in each gel with 40% spot matching. Of these 600 matched proteins 50% showed a 2-fold increase or decrease, 20%, a 5-fold increase or decrease, and 10%, a 10-fold decrease or increase. Limited spot matching with protein databases showed changes in some important cytoskeletal (actin, tubulin), and cell signaling (phosphatidylinositol transfer protein, superoxide dismutase) proteins suggesting that this approach is feasible and informative in the study of protein changes after pediatric TBI.

Our long-term goals are to also characterize some of the most important changes in neuronal signaling known to influence cognitive dysfunction after injury and determine if these changes can be normalized by delayed treatment with trophic factors. Protein synthesis may be altered after TBI by changes in the phosphorylation state of PKB. Phosphorylated PKB (p-PKB) alters protein synthesis by phosphorylating the target of rapamycin protein kinase (mTOR/FRAP) that in turn phosphorylates 4EBP (p-4EBP) the repressor binding protein (4EBP) of eukaroytic initiation factor 4E (eIF4E). p-PKB also activates eukaroytic initiation factor 2α(eIF2α indirectly by phosphorylating glycogen synthase kinase 3 (GSK-3) reducing the phosphorylation of eIF2α and activating p-eIF2α. Thus, PKB phosphorylation modulates the selection of translated mRNA by eIF4E and the global rate of protein synthesis by increasing p-eIF2α activity. We evaluated the level and distribution of brain p-PKB, p-4EBP, p-eIF4E, and p-eIF2α activity in injured or sham 17 PND rats at 6, 24 or 72 h after moderate CCI using immunohistochemistry. TBI increased the levels of all impacted hippocampal p-proteins at only 6 h except p-eIF4E suggesting an early but unsustained up-regulation of PKB linked protein synthesis activators after pediatric CCI. We are further expanding these studies.

Support: NIH-NINDS, Protein Synthesis, Memory and Pediatric Brain Injury, R21 NS-40049, ($186,250/yr, 5/1/00-4/30/04, Larry W. Jenkins, PhD, PI).

B. Protein Kinase B and C in Head Injury

The PKB and PKC enzyme families participate in many cellular functions including protein synthesis. Hippocampal protein synthesis after TBI is critical for neuronal survival, learning and memory, and synaptic plasticity. TBI alters hippocampal protein synthesis and while improved protein synthesis enhances recovery after cerebral ischemia, this has not been examined after TBI. Pathological changes in protein synthesis

mediated by dysfunction of eIF2 and eIF4 pathways after TBI may impair the initiation and fidelity of protein synthesis and injury related restorative and growth responses. Pathological changes in the phosphoinositide 3-kinase-protein kinase B (PI3K-PKB), PKC, GSK-3, mitogen activated protein kinase (MAPK) and mTOR pathways may all be involved in abnormal protein synthesis after TBI. Protein synthesis can be modified by cap-dependent (eIF4E), cap-independent (internal ribosome entry segment [IRES]), and 5'TOP-5' oligopyrimidine tract (mTOR) protein synthesis initiation. This project tests the hypothesis that improved functional recovery following TBI can occur by therapeutically activating beneficial stress related IRES protein synthesis after injury causing stress induced tolerance to secondary injury processes.

Thus, the aims of this proposal are to determine fundamental kinase and chaperone protein pathways that regulate protein synthesis in relation to hypothermia treatment after TBI by examining the control of three major initiation pathways, namely, cap-dependent, cap-independent (IRES) and 5' terminal oligopyrimidine tract (5'TOP) translation. We will further examine the expression of key protein products representative of these pathways involved in recovery from injury. Protein synthesis regulation is fundamental to most cellular processes. Recent advances in understanding the complexities of protein synthesis regulation contribute to the potential for therapeutic manipulation of protein synthesis. However, the manipulation of signals controlling protein synthesis after TBI may not only affect regional injury and restorative responses, but the normal function of relatively uninjured brain regions after TBI.

Control of protein synthesis primarily occurs at the rate-limiting step of initiation. Pathological changes in protein synthesis mediated by dysfunction of eIF2 (eIF2 - rate of translation - quantitative) and eIF4 (eIF4-mRNA selection-qualitative) pathways after TBI may impair the rate and fidelity of protein synthesis and injury repair. Protein kinases and phosphatases modulate many critical control steps in the initiation and fidelity of protein synthesis, especially the initiation steps mediated by eIF2 and eIF4 protein pathways and thus the activity of these kinase and eIF pathways can be determined in part by their phosphorylation status. Using a reproducible and clinically relevant model of controlled cortical impact (CCI) in the rat, (resulting in spatial memory dysfunction as occurs in humans, we have identified a number of important hippocampal signaling changes that affect protein synthesis initiation. Time dependent changes in PKB, PKC zeta, GSK-3B, 4E-BP, mTOR, p70S6K, eIF4E, and eIF2a phosphorylations after TBI have been documented and will be explored further in this project,

Support: NIH-NINDS, PKB and PKC in Head Injury, R01 NS42648-, ($ 231,250) yearly direct cost, 02/15/04-01/31/08, LW Jenkins, PhD, PI).

5. Studies directed by Anthony E. Kline, PhD

Anthony E. Kline, PhD, Assistant Professor, Department of PM&R, University of Pittsburgh School of Medicine

A. Protective Effects of Serotonin$_{1a}$ (5-HT$_{1A}$) Receptor Agonists Against TBI-Induced Cognitive Deficits and Histopathology

Serotonergic pathways originating in the raphe nuclei have extensive projections to brain areas involved in cognition and 5-HT receptor agonists and antagonists alter these processes. Of all the 5-HT receptors characterized thus far, the 5-HT$_{1A}$ is the most widely studied. 5-HT$_{1A}$ receptors (5-HT$_{1A}$R) are abundantly expressed in brain regions, such as the cortex and hippocampus, that play key roles in learning and memory and that are susceptible to neuronal damage by TBI. During the past three years, our laboratory has been investigating the effects of 5-HT$_{1A}$ receptor agonists on neurobehavioral, cognitive, and histological outcome. We first evaluated the high affinity 5-HT$_{1A}$R agonist Repinotan HCL (BAY x 3702), which was given (iv) as a 4-h continuous infusion commencing 5-min after TBI or sham injury. The data revealed that repinotan significantly attenuated spatial learning deficits as demonstrated by decreased latencies to locate a submerged (hidden) platform in a water maze task compared to the injured vehicle-treated group. Repinotan also attenuated histopathology as evidenced by more hippocampal CA$_1$/CA$_3$ neurons and smaller cortical lesion volumes vs. the vehicle group. This study, which was published in the journal *Neuroscience* in 2001, was the first investigation of 5-HT$_{1A}$R agonist interventions in any model of TBI. We then investigated whether the widely used 5-HT$_{1A}$R agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) would produce similar beneficial effects. Using our standard injury paradigm, we found that 8-OH-DPAT-treated rats exhibited significantly reduced latencies in locating the hidden platform vs. the vehicle-treated group over time, which is indicative of improved learning and memory. Significantly more CA$_3$ surviving neurons were observed in the group treated with 8-OH-DPAT vs. vehicle. This study was published in *Neuroscience Letters* in 2002. Because 5-HT$_{1A}$R agonists produce mild hypothermia, which may have contributed to the benefits observed, we are currently conducting temperature controlled studies in an effort to clarify this issue. We are also testing the potential efficacy of a delayed and chronic 5-HT$_{1A}$R agonist treatment paradigm. Our published and ongoing studies lend support for continued investigation of this therapeutic strategy. Collaborators include Drs. C. Edward Dixon, Amy Wagner, and Ross Zafonte from the Departments of Neurological Surgery, and PM&R.

B. Role of Environmental Enrichment (EE) after TBI

Enriched housing, which provides a complex, stimulatory, and social environment, and may be considered a rodent correlate of physiotherapeutic intervention, has been extensively studied in numerous experimental conditions. EE has been reported to increase brain weight, dendritic arborization, synaptogenesis, and to decrease apoptosis of neuronal precursor cells in the hippocampal dentate gyrus. Rats housed in EE for 30 days exhibit significantly higher levels of nerve growth factor mRNA in the rat visual cortex and hippocampus than rats housed in standard conditions. EE has also been shown to increase the expression of brain-derived neurotrophic factor mRNA in the rodent hippocampus. Furthermore, EE has been shown to improve spatial memory and reduce

contusion lesion volume. EE has also been demonstrated to improve motor performance on a beam walk task or sensory neglect after cortical lesions. In or laboratory we are comparing the effect of 28 days of EE with standard living conditions on functional and histological outcome after TBI. The data suggest that EE is superior to standard housing in facilitating functional recovery and suggests that this interventional strategy may be useful in a rehabilitative setting by augmenting pharmacotherapies. On-going studies in our laboratory are examining the role of EE coupled with the 5-HT_{1A} receptor agonists 8-OH-DPAT and buspirone on neurobehavioral and histological outcome after TBI. An R01 grant entitled "Novel Rehabilitative Approaches for Recovery from TBI" has been submitted to further examine the relationship between EE and 5-HT_{1A} receptor agonists on the recovery process after TBI. Collaborators include Drs. A Wagner, R Zafonte, and CE Dixon from the Departments of PM&R and Neurological Surgery.

C. Effects of Atypical Antipsychotics on Functional Outcome after TBI

Over 1 million survivors of TBI receive maintenance pharmacotherapy, of which a substantial number receive antipsychotic agents for the treatment of psychoses, agitation and aggression, and other maladaptive behaviors. The incidence of agitation after severe TBI varies from 11% to 50%. In spite of the common clinical use of antipsychotics, the motor and cognitive risks vs. benefits are unclear. Seminal studies by Feeney and colleagues have shown that treatment with antipsychotics (e.g., haloperidol) after TBI retard functional recovery. Moreover, the administration of such agents reinstates deficits in subjects appearing to be "recovered." More recent work has shown similar detrimental effects on motor function with haloperidol and clozapine after ablation-induced brain injury. Our laboratory is currently evaluating the effects of single (24 h after TBI or sham injury) and/or chronic (24 h–28 d) dministrations of the atypical antipsychotic risperidone on motor (beam-balance and beam-walk) and cognitive (spatial learning and memory) functioning in rats. Additionally, risperidone is being compared to the classical antipsychotic, haloperidol. The results from these studies should provide a clearer understanding of the effects of antipsychotic treatments in the recovering brain. An NIH grant is being prepared to further explore this important avenue. These studies are being conducted in collaboration with Drs. R Zafonte and CE Dixon.

Support: NIH-NICHD R03 HD043851-01, Interaction of serotonin and cholinergic systems after TBI, $144,233 for two years (04/01/03 – 03/31/05). AE Kline, PhD, PI. The Pittsburgh Foundation, Evaluation of the serotonergic$_{1A}$ receptor agonist, 8-OH-DPAT, on biochemical, functional, and histological outcome following TBI in rats, $19,096 for one year (2001-2002). AE Kline, PhD, PI. The Pittsburgh Foundation.

6. Studies Conducted by Amy K. Wagner, MD

Amy K Wagner, MD, Assistant Professor, Department of PM&R, University of Pittsburgh School of Medicine

A. Clinical Gender Differences in TBI Pathophysiology

There is conflicting evidence as to whether there are gender differences with TBI pathophysiology and outcomes. Some studies have reported that with brain injuries of equal magnitude, women sometimes fair worse. Previous work by Dr. Wagner shows that one year after hospitalization with TBI, women have more disability. Yet several animal studies show that female hormones are neuroprotective in attenuating aspects of secondary injury such as excitotoxicity, ischemia, and oxidative stress. We completed a retrospective clinical study using the NIH funded BTRC database identify if there are gender differences cerebrospinal fluid markers of traumatic brain injury and if hypothermia affects these markers in a gender specific manner. Multivariate regression modeling techniques were used to show that there are gender differences with the production and time-course of a cerebrospinal fluid marker of excitotoxic injury and a marker of ischemia early after injury. Females appear to have some neuroprotection against excitotoxic and ischemic injury. However, based on this study, hypothermia appeared to reduce excitotoxic injury primarily in males. This finding may be due to an apparent "floor effect" with hypothermia in reducing excitotoxic injury in females. Ischemic injury and excitotoxicity were also linked to a marker of oxidative stress. Again there were significant gender differences in the relationship of ischemia/oxidative stress & excitotoxicity/oxidative stress. Females have much lower oxidative stress loads than males for a given excitotoxic or ischemic insult. These findings indicate that there may be acute clinical correlates to the early neuroprotection previously reported in studies on experimental brain trauma. A manuscript reporting this work is currently submitted for review. Another manuscript has recently been published in *Journal of Neurotrauma*. Dr. Wagner has recently been funded by and R01 grant in the successful competitive renewal of the CDC center grant, the CIRCL. This grant is focusing on the role of sex hormones in mediating gender differences in CSF markers of TBI and evaluating the role of acute and chronic hormone levels on neuropsychological and functional outcome, and quality of life. Collaborators include the NIH funded Brain Trauma Research Center CSF Bank [(CE Dixon (Neurosurgery), Mary Kerr (Nursing), Ava Puccio (Neurosurgery)], Anthony Fabio (CIRCL), Ross Zafonte (PM&R, Hülya Bayır (CCM), and Sarah Berga (OB/GYN Emory University).

B. Gender Specific Effects of Environmental Enrichment on Dopamine (DA) Markers and Neurotrophin Production after Experimental TBI.

Environmental enrichment has been shown in a variety of animal models to improve behavioral performance and impact neural substrates affecting plasticity such as angiogenesis, neurotrophin production, gliogenesis, and dendritic sprouting. Enrichment of the housing environment has also been shown to improve spatial memory after experimental TBI in male rat models. Recently we reported that 3 weeks of environmental enrichment after experimental TBI improved cognitive recovery in male but not female rats. We then investigated the effects of gender and an enriched environment on dopaminergic markers and neurotrophin production after TBI. Using Western Blot techniques, we evaluated dopamine transporter (DAT) levels in the striatum and frontal cortex. Results showed significant injury related reductions in DAT protein

levels both in frontal cortex and striatum for males. Females did not have significant injury related reductions, with the exception of one striatal region. However, enriched housing post-injury did result in significant reductions in two additional regions for injured females.

In the second experiment, we used western blot to evaluate brain derived neurotrophic factor (BDNF) levels in the frontal cortex and hippocampus after TBI and housing in an enriched environment. In males, no significant enrichment or injury effects were observed with hippocampal BDNF expression, but there was a significant post-injury increase in frontal cortex BDNF expression that was not significantly augmented by EE. Neither injury nor EE significantly altered frontal cortical BDNF expression in females, but there was a trend for decreased BDNF expression in the hippocampus of injured females vs. sham. In contrast, there were robust increases in hippocampal BDNF expression for EE injured females compared to both sham and injured animals placed in standard housing. These results reveal significant, region-specific gender differences in chronic BDNF expression with both injury and EE that may impact enrichment-mediated improvements in cognitive recovery and responses to therapeutic interventions. Portions of the work were funded through Dr. Wagner's NIH K08 award. Portions of the work are going to be submitted to the journal *Neuroscience* for review. Future work will focus on the role of sex hormones on these findings as well as continuing to explore relevant neurotransmitter systems affecting a dimorphic response to environmental enrichment with cognitive recovery. This work was presented at the 2003 National Neurotrauma Society. Collaborators include Xiangbai Chen (PM&R), CE Dixon (Neurosurgery), A Kline (PM&R), and R Zafonte (PM&R).

C. DA Kinetics and TBI

Altered DA neurotransmission is hypothesized to play a role in neurobehavioral deficits after traumatic brain injury. DA enhancing agents (DA agonists) have been shown clinically to improve aspects of mental functioning after traumatic brain injury, and have been shown in multiple animal studies to improve behavioral performance. This laboratory has demonstrated reductions in striatal dopamine transporter (DAT) protein and increases in tyrosine hydroxylase (TH) chronically after TBI. These proteins play a critical role in DA release and reuptake. However, the effects of DAT reduction and TH increases on DA neurotransmission is unknown. Fast scan cyclic voltammetry (FSCV) permits real time in vivo evaluation of DAergic kinetics. The goal of this project was to assess striatal DA neurotransmission by evaluating presynaptic striatal DA kinetics in conjunction with neuroprotein and neurobehavioral correlates after experimental traumatic brain injury. We evaluated electrically evoked DA release and DA clearance kinetics 2 weeks after injury. Striatal dopamine release during bilateral electrical stimulation of the medial forebrain bundle was monitored in anesthetized rats by FSCV in conjunction with Nafion-coated carbon fiber microelectrodes. Prior to FSCV, we also evaluated rotational behavior. After FSCV, we evaluated a variety of striatal DA markers, including DAT, TH, Dopamine type 2 receptors (DRD2), and Vesicular Monoamine Transporter (VMAT). Striatal evoked overflow of DA was lower in injured

animals, compared to naïve. We also showed significant differences in zero and first order DA clearance for injured animals as well as an increase in DAT efficiency (function) after TBI. Decreases in DAT expression were noted post-injury, despite no changes in VMAT expression, indicating a regulatory change in DAT concentration. Behavioral data suggested a low incidence of rotational behavior in this injury model and correlated well with bilateral changes in presynaptic kinetics and DA marker expression. Increases in DAT efficiency post-TBI provide one explanation for the potential efficacy of DAT inhibitors (DA agonists) with improving cognitive recovery. A manuscript for this work has recently been submitted. In future work, we will investigate regional and post-injury time course differences in DA kinetics as well as response to acute and chronic pharmacotherapies. This work is being conducted in conjunction with Dr. A Michael in the Dept. of Chemistry, whose research focuses on electrochemical techniques and the measurement of neurotransmitters using microsensor technology. Other collaborators and students include CE Dixon (Neurosurgery). R Zafonte (PM&R), Joshua Sokoloski, (PM&R/Chemistry) and Zachary Repanshek (PM&R/Chemistry). This and other pilot work (see genetics section) were used to submit an NIH R01 application evaluating the role of DAT genotype in striatal Neurotransmission and responsiveness to treatment with methylphenidate in a clinical population with TBI

D. The Impact of Gender & Hormonal Status after Experimental TBI

Some studies have shown that sex hormones have neuroprotective qualities in the setting of acute traumatic brain injury. However, less is known about endogenously circulating sex hormones or particular hormone levels at the time of injury effect behavioral recovery. Recently, we reported that females appear to have a neuroprotective advantage with behavioral recovery on motor tasks performed early after injury. However, no gender differences were noted with spatial learning later after injury. A manuscript on this work was recently published in *Brain Research*. Currently, we are beginning to evaluate the role of physiological hormone replacement in female rats on behavioral recovery after TBI. Additional work will focus on how hormone manipulations affect histochemical markers of injury. Students and Collaborators include Xiangbai Chen (PM&R), Michael Wenger (PM&R/Neuroscience), Lauren Willard (PM&R/ Neuroscience), CE Dixon (Neurosurgery), A Kline (PM&R) and R Zafonte (PM&R).

E. Associations between DA Transporter Genotype, Outcome, & Cerebrospinal Fluid Dopamine Levels after Severe TBI: A Follow-up Analysis

DA pathways have been implicated in cognitive deficits after TBI. While not associated with alterations in protein structure, the DAT genotype is associated with differences in DAT protein density and development of DA mediated pathophysiological conditions. For instance, the DAT 10/10 genotype is associated with higher DAT protein levels and is implicated in the development of attention deficit disorder. Differential DAT expression presumably also affects both pre-synaptic DA release, via reverse transport, and DA reuptake. DAT regulation may have a role in DA mediated neurotoxicity acutely after TBI and play a compensatory role with DA neurotransmission chronically after TBI.

Catecholamines, including DA and its metabolites, are subject to auto-oxidation, resulting in the formation of reactive oxygen species that can contribute to oxidative stress associated with secondary injury. Prior work from this laboratory has shown reductions in DAT protein after experimental traumatic brain injury. The role of DAT genotype on injury and outcome has not been studied. We hypothesized that genetic & gender related differences in DAT density would affect CSF DA production & metabolism post-TBI, through reverse transport of DA via DAT. We genotyped & collected CSF for DA & metabolite (DOPAC & HVA) analysis via HPLC for 73 patients with acute severe TBI. Mixed effects multivariate regression analyses showed a significant impact of DAT genotype & a trend for female gender to increase CSF DA levels. Gender impacted CSF DOPAC & HVA production without affecting DA turnover, while DAT genotype impacted DA turnover. Further, preliminary analyses suggest acute CSF DA levels are linked to functional recovery curves. Data from this project was used as pilot data to submit an NIH R01 application evaluating the role of DAT genotype in striatal neurotransmission and responsiveness to treatment with methylphenidate in a clinical population with TBI. This work is being done in collaboration with the University of Pittsburgh BTRC, Dianxu Ren (Public Health), CE Dixon (Neurosurgery), Yvette Conley (Health Promotion and Development), Robert Ferrell (Human Genetics), Sue Beers (Psychiatry), R Zafonte (PM&R), and Mary Kerr (Nursing).

Support: NIH K08HD40833, AK Wagner, MD PI, *Dopamine Function and the Effects of Therapeutic Intervention* $622,258 beginning 2001 for 5 years (Sponsors: CE Dixon, PhD, AC Michael PhD, and RD Zafonte, DO); NIH R03HD41399, AK Wagner PI *Gender Differences in Dopamine Function after TBI* $145,535 beginning 2002; CDC R49/CCR323155-01-1---CIRCL, AK Wagner, MD Project PI (H Weiss PhD PI Center Grant), *Evaluating the Impact of Neuroendocrine Hormones on Pathophysiology and Outcomes after Traumatic Brain Injury* $772,948; CDC CCR310285-07---CIRCL, Small Grants Program AK Wagner, MD Project PI (H Weiss PhD PI Center Grant) $10,000 beginning 2002 for *Characterization of Alterations in the Female Rat Estrous Cycle after Experimental TBI*; NIH P50NS30318 Clinical Core--*University of Pittsburgh BTRC*, CE Dixon PI; NIH Loan Repayment Program; Department PM&R, University of Pittsburgh.

TBI Investigation by Safar Center Scientists and Visiting Scientists

7. Studies by P. David Adelson, MD

A. Severe TBI in Immature Rats

Dr. Adelson's laboratory has been examining the role of excitotoxicity and anti-excitotoxic therapies in experimental TBI in developing rats. He has studied both PND 7 and PND 17 rats and demonstrated important age-related differences in this pathway. He is also studying the impact of therapeutic hypothermia on outcome as it relates to age at injury in these same developmental paradigms. Dr. Adelson and his investigative team

presented work in both of these areas at the annual meeting of the National Neurotrauma Society. He has focused his recent efforts on the controlled cortical impact model of TBI.

Support: NIH Grant No. 1 R01 NS42298, Efficacy of Hypothermia in Pediatric TBI

B. Hypothermia for Severe TBI in Children

The major goal of this project is to test the safety and efficacy of therapeutic hypothermia in children after severe head injury. This program has been funded at an R01 level by the NIH/NINDS and seeks to investigate hypothermia as a treatment of TBI in children, with a special emphasis on the development of novel methods for the initial and outcome assessment. Dr. Adelson is the principal investigator of this important multi-center study that includes 8 centers. Dr. Harvey Levin, at the Baylor College of Medicine, is a co-investigator on that study, along with Drs Sue Beers and Tom Campbell, at the University of Pittsburgh, that is assessing long-term functional outcomes including language and speech acquisition, long-term effects of mild to moderate head injury, and a number of other collaborative and related efforts. Studies of the effect of therapeutic hypothermia on a variety of biochemical and molecular mediators of secondary injury and repair are ongoing from CSF samples obtained from patients enrolled at the Children's Hospital of Pittsburgh. PICU fellows H Bayır, and P Shore carried out those studies as previously described in Dr. Kochanek's report.

Support: NIH Grant No. 1 R21 NS043293, Hypothermia for Severe TBI in Children (planning grant) and NIH Grant NO. 1 R01 NS38448, Hypothermia for Severe TBI in Children.

Relevant to the area of child abuse, Dr. Adelson was the co-editor of an issue of *Neurosurgical Clinics of North America* that was devoted to child abuse and several Safar Center faculty and fellows were authors on review papers in that important issue that addressed a very underserved subgroup of pediatric TBI—inflicted childhood neurotrauma.

8. Studies by Rachel Berger, MD, MPH

Rachel Berger, MD, MPH. Assistant Professor of Pediatric, University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh

A. Use of Serum Biomarkers in the Detection of Silent Inflicted Childhood Neurotrauma

Infants who are victims of inflicted traumatic brain injury are often injured on multiple occasions or brought to care many hours to days after their injury. In addition, their injury is often not recognized since caretakers rarely provide a history of trauma and the infants often do not have any external signs of trauma. In the past year, Dr. Rachel Berger, a

general pediatrician working in the area of child abuse at Children's Hospital of Pittsburgh, has broadened the potential relevance of this project by studying the potential use of serum markers of brain injury with the hope of detecting otherwise unidentified brain injury in possible victims of child abuse. Rachel first showed that CSF levels of markers of neuronal (neuron specific enolase [NSE]) and glial (S-100B) death were massively increased versus control after severe TBI in infants and children—including child abuse victims. That work was published this year in the journal *Pediatrics*. That paper was selected as the most important paper in the field of child abuse at the Annual San Diego Conference on Child and Family Maltreatment. Dr. Berger also published an important report in the *Journal of Neurotrauma* showing that these markers of brain injury are increased in the serum in over one-third of infants and children with mild TBI—children that are often sent home from the emergency department. This study has set the stage for an assessment of the use of these biomarkers in a target population of infants in diagnostic categories that occasionally represent missed cases of inflicted traumatic brain injury - such as vomiting without diarrhea, a seizure without fever, unexplained bruising, etc. A positive serum test for such biomarkers would not confirm trauma as etiology of the increase, rather it would "point to the head" and suggest to the health care provider, the need to either obtain additional history, perform a careful fundoscopic examination, or perform a cranial imaging study. That important prospective study is the centerpiece of Dr. Berger's recently funded K-23 award—from NICHD, and the project of Drs. Berger and Kochanek that was funded in the renewal of the CDC-University of Pittsburgh CIRCL.

Support: 1K23HD43843-01 "Using Biochemical Markers to Detect Abusive Head Trauma," General Clinical Research Center (GCRC) M01RR00084 "Using Biochemical Markers to Detect Silent Brain Injury" and "Can We Detect Brain Injury by Looking in the Blood?" Children's Hospital of Pittsburgh of the UPMC Health System–Faculty Start-up Grant – "The Use of Biochemical Markers to Assess Accidental and Abusive Head Trauma in Infants and Young Children."

Collaborators: P Kochanek, Critical Care Medicine; P David Adelson, Neurosurgery; Mary Clyde Pierce, Emergency Medicine, John Leventhal, Department of Pediatrics, Yale University.

9. Studies by Steven DeKosky, MD

Steven T. DeKosky, MD. Professor and Chairman of the Department of Neurology and Director of the Alzheimer's Disease Research Center, University of Pittsburgh School of Medicine.

A. Antioxidant and Neurotrophic Response after TBI

Dr. DeKosky's laboratory studies the role of neural cells and their products in the brain's attempt at repair following TBI. The laboratory is particularly interested in the cytokine and antioxidant cascades that occur over the course of days to weeks after injury

(secondary injury processes), and their relationship with the upregulation of neuroprotective proteins such as neurotrophins. The goal is to elucidate the brain's injury response and provide insight into possible therapeutic interventions that could be used in clinical settings to treat human TBI patients.

Dr. DeKosky's group has examined the timecourse of changes in antioxidant activities (catalase, glutathione and superoxide dismutase) and neurotrophins (such as NGF) expression after experimental TBI. Close temporal relationships were observed between the upregulation of NGF protein and complex changes in antioxidant enzyme activities. To further investigate the relationship between NGF and the antioxidant enzyme response, Dr. DeKosky's group examined the effect of hypothermia on the post-injury level of NGF and on antioxidant enzyme activity, and demonstrated that in rats subjected to post-traumatic hypothermia, both NGF protein levels and catalase and glutathione peroxidase activity levels are suppressed. In an attempt to restore post-injury antioxidant enzyme activities in hypothermia-treated animals, NGF protein was infused immediately after injury, and during the course of hypothermia treatment. The study showed that NGF infusion was ineffective in restoring enzymes activities to post-injury levels. These results suggest that the low percentage of improved outcome in hypothermia-treated TBI patients may be due to blunted antioxidant response, and that infusion of exogenous NGF may not be sufficient to restore normal antioxidant enzyme activity after injury. The results of these studies have been accepted for publication in the *Journal of Neurotrauma* and the *Journal of Neurochemistry.*

B. Effects of TBI on Amyloid Precursor Protein (APP) Metabolism

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by neuronal loss in discrete brain regions and by formation of neurofibrillary tangles and beta-amyloid associated neuritic plaques. A major component of these plaques is the 42-43 amino acid amyloid beta (Aβ) peptide that is cleaved from the transmembrane region of amyloid precursor protein (APP).

One of the known risk factors for AD is TBI. Therefore, alterations in APP processing may play an important role in the pathogenesis of both TBI and AD. To better understand the relationship between TBI and AD, Dr. DeKosky's laboratory is conducting experiments using both mouse models and surgically excised tissue and CSF samples from patients with severe head injury. Collectively, these studies center on the cytokine-related molecular cascades involved in pathological alterations in APP and Aβ production and metabolism after TBI, and the effect of therapies designed to interrupt these cascades.

The humanized Aβ mouse model of TBI

In collaboration with Cephalon Inc., Dr. DeKosky's lab has developed a colony of mice that produce detectable levels of human Aβ (the "hAβ mouse"). This mouse represents a significant advance of previous transgenic mouse models of AD in that the APP gene is under its endogenous promoter, and APP itself is produced at normal levels. This mouse

is therefore particularly important for the studies of Aβ changes after TBI because 1) unlike in rats or wildtype mice that produce rodent Aβ, we are able to employ well characterized biochemical assays to detect *human* Aβ and 2) the continuous over-expression of APP as seen in transgenic mice is avoided, which is particularly important in our injury and intervention paradigms. Dr. DeKosky's laboratory is currently examining post-injury changes in APP and Aβ proteins, as well as components of a molecular cascade involving interleukin-1β, nuclear factor κB, and caspase-3 that are involved in post-injury upregulation and amyloidogenic processing of APP. Ultimately, the goals are twofold; 1) to define the pathways causing, and pathological effects of, Aβ overproduction after TBI, and 2) to assess the effect of therapies designed to prevent Aβ overproduction after TBI in mouse models, that could potentially be translated into therapeutic strategies to treat TBI patients.

Studies in TBI patients

To better understand the relationship between TBI and AD, Dr. DeKosky's laboratory is examining the distribution and levels of APP and Aβ protein in surgically resected temporal cortical tissue and serial CSF samples obtained from head-injured patients. This study is the first to demonstrate AD-like Aβ plaques in freshly resected brain tissue after severe TBI. Furthermore, within hours after TBI, human temporal cortex reacts to injury with a robust up-regulation of APP in pyramidal neurons, which are likely the main source of Aβ. This process is paralleled by increased neuronal accumulation of amyloidogenic APP fragments, as well as a marked up-regulation of apolipoprotein E in both neurons and glial cells. These observations are of particular importance for our understanding of TBI as a potential risk factor for later development of AD, suggesting a pathological cascade that involves neuronal overproduction of APP and Aβ, and glial upregulation of apoE, the latter of which has been known to facilitate Aβ deposition in AD brains. Of additional importance, the development of acute Aβ pathology after TBI is not paralleled by formation of neurofibrillary tangles (another pathological hallmark of AD), indicating that intracellular neurofibrillary changes and progression to dementia of AD can occur only after extended survival periods (i.e., months to years). This indicates that there is a large window of opportunity for therapeutic interventions after TBI before the onset of cellular pathology that could lead to AD dementia. Collectively, these studies convincingly demonstrate that increases in Aβ after injury result in acute AD-like pathological alterations that could be an important target for therapies that are being developed in our humanized Aβ mouse model. Co-investigators on these studies include Drs. Milos Ikonomovic, C Edward Dixon, Robert Clark and Patrick M Kochanek.

Support: Core C of 2 P50 NS30318-04A21, Project #3 in the University of Pittsburgh Head Injury Research Center (S DeKosky, MD, PI).

10. Studies by Steven Graham, MD, PhD

Steven Graham, MD, PhD. Associate Chief of Staff for Research, Geriatric Research Educational and Research Center, V.A. Pittsburgh Health System Professor and Vice-chairman, Department of Neurology, University of Pittsburgh School of Medicine

A. Bcl-2 Family genes in TBI

Dr. Graham's laboratory studies the molecular and cellular mechanisms of neuronal cell death. In collaboration with the Safar Center, Dr. Graham's laboratory investigates neuronal death in TBI. This work is part of the University of Pittsburgh BTRC funded by NINDS. The recent emphasis of the laboratory has been the genetic mechanisms that regulate neuronal cell death. In particular, the role of genes that regulate programmed cell death, the bcl-2 and the cysteine protease family of genes, is being investigated in trauma.

B. Role of COX-2 in TBI

Cyclooxygenase-2 (COX-2), the inducible isoform of the enzyme catalyzes the formation of prostaglandins. Dr. Graham's laboratory is investigating the role of COX-2 in both experimental cerebral ischemia and TBI. Expression of COX-2 is induced by neuronal excitation and COX-2 activity produces free radicals, so COX-2 may be an important mechanism whereby excitotoxicity is expressed. As discussed latter in this report, Dr. Graham also serves as a research mentor to Dr. Robert Hickey who is studying the age-related effects of COX-2 in cerebral ischemia and excitotoxicity.

Support: Core C of 2 P50 NS30318-04A21, Project #1 in the University of Pittsburgh BTRC (Steven Graham, MD, PhD, PI). Department of Veterans Affairs/Department of Defense Brain Trauma Initiative-Merit Review (SH Graham, MD, PhD, PI, 10/1/00 - 10/1/03, 20% of VA Time. Department of Veterans Affairs, The Role of Inducible Cyclooxygenase in Delayed Neuronal Death. Current Year Direct Costs: $143,000.)
Technician: Marie Rose

Peer-Reviewed Manuscripts: TBI Program

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Chapters, Editorials and Invited Papers: TBI Program

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CARDIOPULMONARY ARREST PROGRAM

Introduction to the Cardiopulmonary arrest program by Patrick M. Kochanek, MD

Last year, I named Dr. Clifton Callaway, Director of the Cardiopulmonary Arrest Program at the Safar Center. Although Dr. Callaway's bench and clinical research is carried out outside of the Safar Center, he is a disciple of the Safar Center, is conducting state-of-the-art work in this area at the University of Pittsburgh Center for Emergency Medicine, and graciously serves in that role. Dr. Callaway holds a cardiac arrest investigators meeting each month at the Safar Center that includes a broad spectrum of faculty and trainees interested in this area of research. I am optimistic that through Clif's role as director of the cardiopulmonary arrest program, a substantial body of research in this area will be unified at the University of Pittsburgh School of Medicine and even greater collaboration will develop between the Safar Center and the Center for Emergency Medicine.

A. Clifton Callaway and the Department of Emergency Medicine

Clifton W. Callaway, MD, PhD, Assistant Professor, Department of Emergency Medicine, University of Pittsburgh School of Medicine

We continue to emphasize the fact that resuscitation from cardiac arrest must attend to both heart and brain. About one-third of attempted resuscitations result in restoration of spontaneous circulation. Therefore, improved approaches to cardiac resuscitation are needed. Only about one-quarter of patients with restoration of circulation will regain consciousness. Therefore, therapies to improve neurological recovery are also required. Without attention to both of these organ systems, overall survival from cardiac arrest is unlikely to increase.

Work this year was devoted largely to expanding our understanding of the molecular mechanisms of neurological recovery after cardiac arrest using our rat model, and to expanding our commitment to clinical cardiac arrest research. Additional funding was secured for the molecular studies, and an out-of-hospital investigation was initiated with the City of Pittsburgh Emergency Medical Services. Because induced hypothermia after cardiac arrest appears to be an effective therapy for improving brain recovery, we have advocated its acceptance as therapy rather than as research.

1. Altered Intracellular Signaling in Brain after Resuscitation

As previously described, the activity of two mitogen-activated protein kinases (MAPKs) increase in hippocampus over the 24 hrs period after resuscitation from cardiac arrest: the p42/p44 MAPK (extracellular-signal regulated kinase, ERK) and the Jun-N-terminal kinase (JNK). Induction of mild hypothermia (33°C) between 1 and 23 hrs after reperfusion, further increases activity of ERK relative to normothermic (37°C) controls.

The same regimen of hypothermia also decreases histological and behavioral signs of brain damage, prompting us to speculate that some of the beneficial effects of induced hypothermia are mediated via increased ERK activation.

As planned last year, we established tools for manipulating ERK activation after cardiac arrest. We conducted a dose-response and time course study of the ERK kinase inhibitor U0126. This drug prevents ERK phosphorylation and activation. We have previously found that this drug does not cross the blood-brain barrier and produced no appreciable inhibition of ERK activation when injected intravenously at doses up to 2 mg/kg. Therefore, naïve rats (n=2-3 per group) were anesthetized with halothane, placed in a stereotaxic device and injected over 5 minutes into one lateral ventricle with doses of U0126 ranging from 10 μg to 500 μg dissolved in 50%:50% DMSO:phosphate-buffered saline.

This experiment revealed partial reduction of ERK activation after 10 μg U0126, with robust reductions after 100 μg U0126. There was no inhibition or perhaps activation of ERK after 500 μg U0126, probably reflecting nonspecific effects or the effects of the large volume of injection required for this dose. The reduction of ERK activation was evident in both the left and right hippocampus, indicating good distribution of the drug from the injection site. Based upon this series of experiments, we selected 100 μg of U0126 for further study.

When rats (n=2-3 per group) were sacrificed at 2, 4, 9, 12 and 24 hours after injection of 100 μg U0126, immunoblots of hippocampal tissue revealed near complete inhibition of ERK activity bilaterally for 12 hours. ERK activity had returned to near normal levels by 24 hours. This study confirmed that we could use a single injection of U0126 to block ERK activation in bilateral forebrain structures for at least 12 hours, with partial inhibition lasting almost 24 hours.

Using the information derived in the dose-response and time-course studies described above, we have examined the effect of inhibiting ERK activation on neurological recovery after cardiac arrest. Rats (n=32) were subjected to eight minutes of asphyxia. Thirty minutes after resuscitation, each rat was randomly assigned to receive an intracerebroventricular injection of either U0126 (100 μg/40 μl) or vehicle. Sixty minutes after resuscitation rats were randomly assigned to either normothermia (37°C x 23 hours) or hypothermia (33°C x 23 hours).

This study confirmed that induced hypothermia improved neurological recovery after cardiac arrest and resuscitation. Neurological deficit scores were persistently better in the hypothermia group, with all rats achieving a grossly normal status (score=26) by day 4 (Table 2). Most normothermia rats achieved a normal status only after day 7. All rats exhibited a weight loss over the first 5 days after resuscitation, with weight gain resuming thereafter (Table 3). There was no significant difference between the U0126-treated and vehicle-treated rats on these measures. These data suggest that the gross improvement in

neurobehavioral recovery afforded by induced hypothermia is not dependent upon forebrain ERK activation.

2. Altered Neurotrophic Factor Signaling in Brain after Resuscitation

We have previously reported that brain-derived neurotrophic factor (BDNF) increases in hippocampus at 24 hours after resuscitation from cardiac arrest. BDNF levels are further increased by the beneficial regimen of induced hypothermia. We did not detect any increase in neurotrophin-3 or in nerve growth factor. These data were published in the *Journal of Cerebral Blood Flow and Metabolism.* The association between induced hypothermia and increased BDNF levels suggests that this neurotrophic factor may participate in the beneficial effects of post-cardiac arrest, induced hypothermia. It is also tempting to speculate that BDNF is the upstream signal that triggers increased ERK activation after cardiac arrest and hypothermia.

To supplement these observations, we have also examined the expression of glial-cell derived neurotrophic factor (GDNF) in brain after resuscitation. Immunoblots were used to measure GDNF in brain tissue from rats resuscitated from 8 minutes of asphyxial cardiac arrest. Sixty minutes after resuscitation rats were randomly assigned to either normothermia (37°C x 23 hours) or hypothermia (33°C x 23 hours). These experiments revealed that GDNF increased in hippocampus and cortex 24 hours after resuscitation. This increase was less evident in the cerebellum. Induced hypothermia appears to accelerate the expression of GDNF in hippocampus and cerebellum. These data suggest that induced hypothermia increases GDNF levels as well as BDNF levels in vulnerable brain regions.

Our immediate plans are to continue assessing the role of ERK and BDNF signaling in the beneficial effects of induced hypothermia. (1) We will develop a pharmacological strategy to block BDNF and GDNF expression in brain using either intracranial injections of neutralizing antibodies or antisense oligonucleotides. The most successful regimen will be used to assess the contribution of these factors on neurobehavioral outcome after resuscitation with or without hypothermia. (2) We will examine the pattern of new gene expression after resuscitation and hypothermia using DNA arrays. The influence of ERK-dependent pathways on the patterns of gene expression will be assessed using U0126 injections. We anticipate that these approaches will better elucidate the temperature-dependent molecular events after global brain ischemia.

3. Vasopressin in Cardiac Arrest

We believe that chest compressions, augmented by vasoactive drugs, are one of the most important determinants of restoration of circulation after cardiac arrest. With Dr. Menegazzi, we have noted that vasopressin is superior to epinephrine for increasing coronary perfusion pressure during chest compressions in swine. Also, several case series from Europe suggest that vasopressin is a superior vasoconstrictor for treating human cardiac arrest. Based on this background, we initiated the necessary steps to

conduct a clinical trial of vasopressin use by paramedics for resuscitation of cardiac arrest.

Vasopressin is a generic drug with no corporate backing. It is packaged in a manner that does not resemble epinephrine. Furthermore, we are aware that there is a large multicenter trial in Europe that is examining the use of vasopressin versus epinephrine as the first-line drug for treatment of cardiac arrest. For these reasons, we designed a study to examine the effect of adding vasopressin to standard treatment for cardiac arrest. Subjects in cardiac arrest receive all standard care. If epinephrine is required, these subjects receive also a vial of study drug that is either vasopressin (40 IU) or saline placebo.

This study employs an Exception from the Requirement from Informed Consent for Emergency Research. During the year, we consulted with our own Institutional Review Board, and set in motion the steps to meet the requirements for this waiver. An Investigation New Drug application was submitted to the Food and Drug Administration. The protocol was reviewed by the Local and State Department of Health. We made press releases, and conducted interviews with local media to publicize the trial. A public forum was held to solicit comments from the community. Groups representing the community were also consulted. All approval was obtained, and the first subjects were enrolled in May 2003.

We hope that this prospective, blinded trial of a drug therapy administered by paramedics will pave the way for more clinical research to improve resuscitation. The clinical data acquired during this study will provide an invaluable baseline against which to gauge future progress.

Support: Brain Ischemia and MAP Kinase Activation, (#K02 NS02112) National Institute of Neurological Disorders and Stroke (07/99 – 06/04) total award $573,480 ($101,854 direct costs + $8,148 indirect costs per year) Clifton W. Callaway, MD, PhD, PI. Hypothermia and Gene Expression after Cardiac Arrest, (#R01 NS046073) National Institute of Neurological Disorders and Stroke (07/99 – 06/04) total award $848,032 ($166,250 direct costs + $80,631 indirect costs per year) Clifton W. Callaway, MD, PhD, PI. Vasopressin in Cardiac Arrest, Pittsburgh Emergency Medicine Foundation, total award $1525, Clifton W. Callaway, MD, PhD, PI.

B. Pediatric Cardiopulmonary Resuscitation

There is an expanding pediatric cardiac arrest program at the Safar Center that now has both bench and clinical components. Dr. Robert Clark (see prior report in TBI), Associate Professor in the Department of Critical Care Medicine, Associate Director of the Safar Center and Pediatric Critical Care Medicine specialist at Children's Hospital, has received funding from Children's Hospital of Pittsburgh to initiate laboratory studies in a new model of asphyxial cardiopulmonary arrest in rats. This research is off to a spectacular start. In addition, Dr. Robert Hickey in the Department of Pediatrics,

Division of Emergency Medicine at Children's Hospital of Pittsburgh has ongoing mechanistic studies in the area of developmental brain injury and has played a key role in the national guidelines committees in resuscitation. Finally, Dr. Howard Ferimer of the Mercy Hospital Department of Pediatrics is carrying out studies in asphyxial cardiopulmonary arrest.

1. Laboratory Research in Pediatric Resuscitation

A. Asphyxial Cardiopulmonary Arrest in the Developing Rat (Robert Clark, MD)

In 1995, Drs. Larry Katz and Peter Safar published a seminal paper in the *Journal of Cerebral Blood Flow and Metabolism* describing a clinically relevant model of asphyxial cardiopulmonary arrest in adult rats. Based on that work, and with special talents of senior laboratory technician, Henry Alexander, Dr. Robert Clark developed an important pediatric analog of that asphyxial cardiopulmonary arrest model using post-natal-day (PND) 17 rats. This is an important development in that the PND 17 rat models a toddler or young child—the population most commonly afflicted by cardiopulmonary arrests resulting from asphyxiation (i.e., near drowning, trauma, child abuse, choking, SIDS). Although there are models of perinatal ischemia, there are no small animal models mimicking cardiopulmonary arrest. Equally important is the fact that this is a clinically relevant model that includes a global insult to the entire organism and all of the standard clinical components of resuscitation as guided by contemporary pediatric advanced life support (i.e., mechanical ventilation, chest compressions, epinephrine). PICU fellow Dr. Ericka Fink presented the initial report of the successful development of this model at the 2003 meeting of the Society for Pediatric Research. The full manuscript of this work is in press in *Pediatric Critical Care Medicine*. Important therapeutic trials including the use of mild hypothermia and novel mechanism-based pharmacological approaches are underway under the direction of Dr. Clark at the Safar Center. In addition, Dr. Clark is pursuing studies of the effect of gender on histopathological and functional outcome in this model.

Support: Children's Hospital of Pittsburgh. The Laerdal Foundation for Acute Medicine.

B. Developmental aspects of COX-2-mediated brain injury (Robert Hickey, MD)

Dr. Robert Hickey continued work on his KO-8 award from NICHD to study developmental aspects of the role of COX-2 in brain injury. This research is being carried out under the mentorship of Dr. Steven Graham in the department of Neurology at the VA Hospital. Dr. Kochanek is a co-sponsor of the grant. COX-2 plays an important role in secondary injury in models of stroke, trauma, and cardiac arrest in adult investigation. Its role in pediatric brain injury remains to be defined. Dr. Hickey Presented a paper at the 2003 meeting of the National Neurotrauma Society on Differential age at injury effect on COX-2 expression after TBI in immature rats. Studies are planned to evaluate the effects of COX-2 inhibitors in the developing rat subjected to

asphyxial cardiopulmonary arrest. Drs Graham and Hickey also co-authored a review article on COX2 published in *Archives of Neurology*. Finally, Dr. Hickey published a paper in the journal *Critical Care Medicine* entitled "Induced hyperthermia exacerbates neurological neuronal histological damage after asphyxial cardiac arrest in rats" which provided further insight into the importance of avoiding fever after cardiopulmonary arrest. This study embellishes upon a prior clinical report by Dr. Hickey and associates (*Pediatrics*, 2000) demonstrating that fever is remarkably common after cardiopulmonary arrest in infants and children.

Support: COX-2 and Injury in the Immature Brain, KO-8 (#HD40848) National Institute of Health, National Institute of Child Health and Development, (7/01-7/06), total award $623,430 ($115,450 direct + $9,236 indirect per year), Robert W. Hickey, MD, PI, Steven Graham, MD, Patrick Kochanek, MD, Co-Investigators; Robert Clark, MD, C. Edward Dixon, PhD, Peter Safar, MD, Consultants. COX-2 and Excitotoxicity in Developing Rat Brain, Competitive Medical Research Fund (CMRF), University of Pittsburgh, (7/1/03-6/30/05), total award $25,000. Robert W. Hickey MD, PI: Steven H Graham MD, PhD, Co-investigator.

C. Role of Adenosine after Asphyxial Cardiac Arrest (Howard Ferimer, MD)

Adenosine is produced by the breakdown of ATP during ischemia. It is neuroprotective via multiple mechanisms; reduced free radical production, associated hypothermia, improved cerebral blood flow, and reduced metabolic demands. Systemic administration of adenosine is limited by its short half-life, inability to cross the blood brain barrier and adverse cardiovascular side effects (hypotension, bradycardia). The beneficial effects of augmenting adenosine levels locally in the brain have been documented in experimental TBI and stroke. Augmenting adenosine levels in the brain after asphyxial cardiac arrest is the focus of our work. In collaboration with Dr. Edwin Jackson, Dr. Ferimer is continuing to study the effects of adenosine modulating drugs on interstitial levels of purines in the brain of rats subjected to asphyxial cardiac arrest using microdialysis and HPLC. This work is also tests pharmacological strategies to increase brain adenosine levels early after resuscitation. Ultimately, our studies may improve therapy in this all-to-common problem in the pediatric population.

2. Public Education and National Guidelines Committee

Dr. Robert Hickey is the current Vice-Chair of the American Heart Association Emergency Cardiovascular Care Committee (ECC) and the immediate past-chair of the American Heart Association subcommittee on Pediatric Resuscitation. The ECC is responsible for overseeing the American Heart Association's pediatric advanced life support (PALS), advanced cardiovascular life support (ACLS) and basic life support (BLS) courses. The AHA has approximately 250,000 instructors that train over 7 million people annually. In his capacity as Vice-Chair of the ECC, Dr. Hickey also serves as a representative to the international liaison committee on resuscitation (ILCOR) and has recently participated in meetings in Australia, Italy and Brazil to develop international

consensus on new developments in resuscitation science. Dr. Hickey was co-author on important guidelines manuscripts that addressed therapeutic hypothermia and automated external defibrillators in children (see publication list below).

3. Pediatric Cardiopulmonary Arrest: Clinical Studies

Dr. Hickey has initiated the assembly of a multidisciplinary team to evaluate children resuscitated from cardiac arrest. The team has representatives from the entire continuum of care including pre-hospital, emergency medicine, critical care, neurology, neuroimaging, behavioral pediatrics, and rehabilitation medicine. The team will, 1) characterize early molecular markers of HI brain injury, 2) evaluate strategies for prognosis of neurologic recovery, 3) identify patterns of functional deficits in long-term survivors, and 4) develop targeted strategies for rehabilitation of patients with HI brain injuries. This information will facilitate comprehensive evaluation and treatment for individuals suffering from HI brain injury and also develop a profile of the natural history of injury and recovery that can be used for evaluation of anticipated neuroprotective therapies.

Peer-Reviewed Manuscripts: Cardiopulmonary Arrest Program

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3. Graham SH, Hickey RW. Controversies in neurology. Cyclooxygenases in CNS diseases: a special role for COX-2 in neuronal cell death. Arch Neurol 60:628-629, 2003.

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Chapters, Editorials and Invited Papers: Cardiopulmonary Arrest Program

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3. Kochanek PM: World Congress on Drowning, 2002: Task- Force on "Brain Protection" Pediatric Considerations (in press).

Abstracts: Cardiopulmonary Arrest Program

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SHOCK AND SUSPENDED ANIMATION PROGRAM

The hemorrhagic shock (HS) and suspended animation program consists of project I on hemorrhage shock (HS) in rats and pigs (P.I., Dr. Tisherman; Co-P.I., Dr. Safar); and project II on suspended animation (SA) in dogs (P.I., Dr. Safar; Co-P.I., Dr. Tisherman). The funding since 1997 was made possible through special "plus-up" funds from Congress initiated by former Navy Commander Lyn Yaffe, M.D. During 2001/2003, the HS studies were funded separately by the Office of Naval Research. For the two programs combined, we received total funds (including 50% institutional "indirect costs") of approximately $1,182,649 during 2002/2003.

Our research ICU for large animals, initiated in the 1970s, is still considered a unique resource for the documentation of novel CPCR methods. It must be maintained continuously to be cost-effective, with at least four technicians, two full-time MD research fellows with CCM experience, and about 80 long-term dog experiments per year. Maintaining this ICU program alone requires over $0.5M per year. In 2002/2003, the research fellows were Dr. Nozari (in his second year) and Dr. Wu (in his fourth year); Mr. William Stezoski has continued as lab coordinator. The co-investigators or consultants included Drs. Kochanek, Klain, Jackson, Dixon, Clark, Kagan, Jenkins, and Radovsky (pathologist).

The objective of the HS-SA program has been to help maximize the reversibility of presently lethal traumatic hemorrhage. The HS studies in rats and pigs were designed to extend the golden hour of HS tolerance; HS (low blood flow), with viscera as the most vulnerable organs, is the prevalent cause of death in soldiers "dying of wounds" (DOW). Exsanguination cardiac arrest (CA) (no blood flow), with the brain as the most vulnerable organ, is the prevalent cause of death in soldiers "killed in action" (KIA). SA is a totally new approach for presently unresuscitable conditions. While SA has been considered science fiction, colleagues are now increasingly using this term seriously, as representing rapidly induced preservation of the organism for delayed resuscitation. This idea was initiated in the 1980s by Drs. Bellamy and Safar. For HS and SA we have explored mainly hypothermic strategies – specifically mild hypothermia (33-36°C) for HS and profound hypothermia (5-15°C) for SA. Dr. Tisherman is planning clinical feasibility studies for both in selected trauma centers. Devices needed for such studies are being developed concurrently with additional laboratory studies and preliminary plans for clinical trials.

The HS models in rats and SA models in dogs used in 2002/2003 had been initiated and further developed over the years by our group. They have several unique features, the most important being clinical relevance in terms of insult, resuscitation strategy, ICU management, and outcome.

1. Hemorrhagic Shock (HS) Studies (Tisherman)

The HS studies of academic year 2002/2003 were completed under year 6 of funding by the Office of Naval Research (PI: Samuel A. Tisherman, MD; Co-PI: Peter Safar, MD). Fellow Xianren Wu, MD supervised all studies. The rat studies were completed by technician Jason Stezoski. The pig studies utilized the ICU team led by S. William Stezoski, with technicians Jeremy Henchir, Sherman Culver, Alan Abraham, Jason Stezoski, Scott Kostelnik, and Murugan Subramanian. Fellow Ala Nozari, MD, also assisted with the pig studies.

Hypothermia and Prolonged HS

Previously, we had demonstrated, using models of uncontrolled HS or pressure-controlled HS, that a mean arterial pressure (MAP) of 50 mmHg was insufficient to allow long-term survival after very prolonged (6 h) HS. Even a MAP of 60 did not consistently allow survival. With this background, we explored the potential for mild hypothermia (34°C) to improve survival after prolonged HS. Mild hypothermia, started at 10 min HS or 1 h HS, improved survival time compared to normothermia after 6 h HS at MAP 60 mmHg. Survival to 72 h was achieved in 2 of 14 rats at normothermia, 7 of 14 if cooling began at 1 h, 9 of 14 if cooling began at 10 min. This study was presented as a poster at the 26th Annual Conference of the Shock Society in Phoenix, Arizona 2003.

Solutions and Prolonged HS

The optimal fluid for hypotensive (limited) resuscitation during very prolonged HS has not been explored. Hypertonic saline (7.2%) has potential immunologic and practical (less volume) advantages over isotonic fluids, such as lactated Ringer's (LR). Hetastarch (6%) may have similar advantages in terms of less volume requirement. We tested these fluids using a model of volume controlled HS (30 ml/kg) followed by limited resuscitation (with the test fluid) for 6 h. Compared to LR, both 6% Hetastarch and 7.2% Saline reduced the volume requirement for hypotensive fluid resuscitation during prolonged HS. Hypertonic saline decreased survival compared to both LR and Hetastarch. Hetastarch may be the superior fluid for trauma victims with long transport times, such as in military and rural trauma. This study was presented as a poster at America Association for the Surgery of Trauma 2003 Annual Meeting in Minneapolis, Minnesota.

Hypothermia and Poikilothermia

In previous animal studies that demonstrated improved outcome from HS with mild hypothermia, anesthesia was utilized to produce poikilothermia and prevent shivering. Clinically, particularly in the prehospital setting, anesthesia may not be available. Pharmacologic induction of poikilothermia may facilitate induction of hypothermia while preventing deleterious side effects such as shivering and catecholamine surge. Suggested by a study by former fellow Larry Katz, MD, we tested a new neurotensin analog (NT-69L), which he had found to induce rapid and sustained mild hypothermia in rats following asphyxial cardiac arrest. Using a model of volume-controlled HS and limited

fluid resuscitation with Hetastarch in awake rats, we compared 1) normothermia, 2 spontaneous cooling to 34°C, and 3) spontaneous cooling with NT-69L. Survival was significantly prolonged in both hypothermia groups compared to normothermia. NT had no further beneficial effect on survival. This suggests that, unlike asphyxial cardiac arrest, amelioration of stress with NT-69L during the induction of hypothermia in HS (i.e., production of a more poikilothermic state than the use of hypothermia alone) did not confer additional benefit. This highlights the fact that one must carefully determine the optimal application conditions for hypothermia (target temperature, duration, re-warming rate, sedation/analgesia, and associated pharmacological agents) in each disorder that it used. This study was presented as a poster in the Society of Critical Care Medicine 33rd Annual Meeting in Orlando, Florida.

Large Animal Outcome with Mild Hypothermia

Previous studies of mild hypothermia during HS have been performed in small animals. Clinically, there is great concern that hypothermia is associated with worse outcomes in trauma patients. Prior to making final plans for clinical studies of mild hypothermia during HS in trauma patients, we felt that a large animal study using a clinically-relevant model of HS plus trauma, with prolonged life support, was needed. Also, we wanted to test the safety and efficacy of ice-cold fluid infusion for induction of hypothermia during HS. Studies have suggested benefit in patients after cardiac arrest. Consequently, we developed a pig HS model with controlled continuous bleeding (75 ml/kg over 3 h) and trauma induced by laparotomy and splenic transection (delayed splenectomy). At HS 40 min (simulating arrival of paramedics) pigs were randomized into 3 groups: Group-1, normothermia (38°C) with warmed saline, Group-2, hypothermia (34°C) induced with 2°C i.v. saline and surface cooling, and Group-3, hypothermia (34°C) with 24°C i.v. saline and surface cooling. Resuscitation fluids were given when MAP was <30 mmHg until HS 3 h. Use of ice-cold fluid increased blood pressure and lactate. This study was initiated in the spring or 2003, but not completed until the fall.

Dr. Wu presented posters on the effect of temperatures and NT-69L on outcome from very prolonged HS at the Society of Critical Care Medicine meeting and the study on hypothermia during prolonged HS at the Shock Society meeting.

Dr. Tisherman presented "When is it Enough? Endpoints of Resuscitation" at the American College of Surgeons Spring Meeting, and the effects of Hetastarch, hypertonic saline and LR in the prolonged HS model at the American Association for Surgery of Trauma 2003 annual meeting.

2. Suspended Animation (SA) in Dogs (Safar et al)

Addition of tissue trauma to the SA model: Effect of plasma exchange

In previous SA experiments, we have demonstrated that induction of profound cerebral hypothermia (tympanic membrane temperature 10°C) can allow intact survival after 90 min exsanguination cardiac arrest. The potential benefits of drugs or specialized solutions have been disappointing. The anti-oxidant Tempol and a specially developed fluid (by

Michael Taylor, PhD) for organ preservation with hypothermia (Unisol) seem promising. The addition of tissue trauma (thoracic incision, laparotomy, splenectomy) causes extra-cerebral organ system dysfunction, although brain histopathology is normal after 60 min SA. In children with multiple organ system dysfunction and thrombotic microangiopathic anemia, use of plasma exchange has resulted in significant clinical improvement. Thus, we hypothesized that plasma exchange might help alleviate some of the extra-cerebral complications seen after trauma and SA. After 120 min SA in dogs, plasma exchange decreased the coagulopathy and improved overall performance, without affecting neurologic deficits and brain histopathology. These studies support the potential use of 2 h of SA even in the setting of exsanguination cardiac arrest that is accompanied by considerable tissue trauma. This is an important study toward the potential clinical application of this agent. Plasma exchange may be needed as a clinical adjunct. However it must be recognized that our studies in dogs have been carried out without the resources of a canine blood bank (i.e., we are limited by lack of therapies such as platelets, cryoprecipitate, and fresh-frozen plasma).

Dr. Nozari presented posters at the Society of Critical Care Medicine meeting on coagulopathy and multiple organ failure after traumatic exsanguination and suspended animation, as well as on the use of mild hypothermia induction during cardiopulmonary resuscitation during 40 min cardiac arrest.

3. Suspended Animation: Proteomic Studies in Rats (Jenkins and Safar)

In the 2002/2003 academic year, Drs. Larry Jenkins and Peter Safar initiated a project linked to the SA program that seeks to probe into the mechanisms of cellular (neuronal) degradation at prolonged global cerebral ischemia during profound hypothermia—at levels of cooling that are successfully used in our SA experiments. An intriguing question is–during prolonged (1-2 h or more) complete global cerebral ischemia (at profound hypothermia, 10°C), what cellular derangements occur. Is degradation during prolonged periods of hypothermia occurring, does it set the stage for damage during reperfusion, or is reperfusion and re-warming the key? Although mechanisms involving lipid degradation, or DNA or RNA damage, may be important, a key initial focus of our work in this area has been on proteolytic damage. Dr. Jenkins has used proteomics to begin to study protein degradation and post-translational modification in TBI (please see the 2001/2002 annual report and the TBI section of this annual report). This year, Dr. Jenkins, and PICU fellow Dr. Mandeep Chadha, used 2-D gel electrophoresis to examine the effect of 30 min of complete global brain ischemia (at either normothermia or profound hypothermia, 10°C) on the proteome of the isolated rat hippocampus. In these initial studies, ischemia was produced by decapitation. Their initial work suggests that 30 min of complete global brain ischemia produced only modest changes in the proteome of the rat hippocampus. Obviously, the limitations of the sensitivity of 2-D gel electrophoresis for low copy proteins and protein fragments must be taken into consideration. Nevertheless, these initial studies are provocative. Longer ischemia durations and the effect of reperfusion will be studied in future experiments in the next funding year. The latter (reperfusion) will require the development of a complete SA

model in rats, including miniaturized cardiopulmonary bypass in our center. This will be required to resuscitation rats from prolonged cardiopulmonary arrest at profound hypothermia. Finally, Dr. Chadha presented an abstract of this initial work at the SCCM meeting .

4. Device Development (Safar et al)

During the 2002/2003 academic year, Safar Center investigators (Drs. Safar, Tisherman, and Kochanek, and Mr. William Stezoski) working on the SA project provided consultation to Dr. Lyn Yaffe and his "Smart Catheter" group working on the development of novel catheters for the clinical and experimental implementation of SA. We evaluated several catheter prototypes for aortic insertion. In addition, this same group of Safar Center investigators provided consultation to the Ardiem Medical Company in the development of cooling devices for use in induction of hypothermia both in SA and HS paradigms. We met with the development team of Ardiem Medical at the Safar Center on several occasions to aid them in formulating plans for the initial prototypes for both laboratory and clinical use.

5. Emergency Hypothermia, Clinical planning

At the annual meeting of the American Association for the Surgery of Trauma meeting in Orlando (9/26/02), Dr. Tisherman held a meeting with representatives from several other centers to begin discussions on clinical trials of therapeutic hypothermia in exsanguination cardiopulmonary arrest and hemorrhagic shock. Future meetings of this consortium group of potential investigators are planned.

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A Fond Farewell

On August 3, 2003, after a 15-month fight against cancer, the Safar Center for Resuscitation Research lost its Founding Director, a collegial colleague, and a loyal friend -- Peter J. Safar, MD. Now that we can no longer walk into his office and ask for his advice, we must accept the challenge to continue his work and preserve his legacy for future generations of researchers and scientists.

Dr. Safar received his MD degree in 1948 from the University of Vienna. He came to the United States permanently in 1954 along with his wife, Eva Kyzivat Safar. In 1961 at age 37, he became the founding chairman of the Department of Anesthesiology and Critical Care Medicine at the University of Pittsburgh, until 1979 when he founded the International Resuscitation Research Center (later renamed Safar Center for Resuscitation Research). Over the course of his career Dr. Safar earned many awards and honors, as well as the trust and respect of his colleagues. You can read about his many accomplishments and view his extensive publication list on the Safar Center website.

Not only was Dr. Safar our leader, mentor, and colleague for many years, but he was also a personal friend to many of us. Though he is greatly missed, the way he lived life to its fullest continues to inspire us to make the world a better place for all.

Tisherman SA and Sterz F (eds), Kluwer
(in press, October 2004)

THERAPEUTIC HYPOTHERMIA

Patrick M. Kochanek, Robert S.B. Clark, P. David Adelson, Larry Jenkins, C. Edward Dixon, Hülya Bayır, Xianren Wu, Paul Shore, Samuel A. Tisherman

Introduction

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." Having been asked to "update" that article for *Trauma Care* 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 *N Engl J Med* 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 Europe and Bernard, et al in Australia reported significant beneficial effects on outcome when hypothermia was initiated after restoration of spontaneous circulation. In the Sterz study, 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 or 24 hours in the study by Bernard. 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 Sterz study (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 –

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 – cyctochrome 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 VF CA 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 a study in 22 adults, Bernard, et al (10) reported that 30 mL/kg bolus over 30 min of an ice cold (4°C) lactated Ringer's solution is safe and reduces care 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 available several liters of ice cold fluid readily available. More recently in an experimental laboratory model of CA in dogs simulating field resuscitation, Nozari, et al (11) 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 felt 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 vs 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 to a number of other brain-oriented therapies in TBI which 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, gender may be an important factor in determining the efficacy of hypothermia in TBI. Bayır, et al (19) recently reported that lipid peroxidation (assessed by CSF levels of F_2-isoprostane) after severe TBI in adults was markedly increased on day 1 in males, but not in females. Hypothermia was only able to affect this mechanism in males. 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. 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 his group (20), our investigators at the Safar Center have performed a comprehensive assessment of the effect of therapeutic hypothermia (32-33°C) applied for 48 h 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 (21). 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, hopefully 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 have lead the way in the investigation of this potential use of mild hypothermia.

In a series of studies in rats (23-28), mild cooling during shock was found to increase survival in both uncontrolled and pressure-controlled models. 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). He 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 CA

Finally, our group has been intensely studying a very novel approach to the treatment of victims of exsanguination cardiac arrest. 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 min after established exsanguination CA in a dog model that includes 72 hrs 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 min. 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 post-resuscitation 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 h) 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 cardiac arrest from penetrating trauma (30).

Acknowledgement

This brief review is written in honor of Dr. Peter Safar who passed away on August 3, 2003.

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Mild Hypothermia Improves Survival after Prolonged, Traumatic Hemorrhagic Shock in Pigs

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Disclosure Statement

The following authors of this manuscript, entitled, "Mild Hypothermia Improves Survival after Prolonged, Traumatic Hemorrhagic Shock in Pigs", from the University of Pittsburgh, have no financial or proprietary interest in the subject matter or materials discussed in the manuscript. This includes (but is not limited to) employment, consultancies, stock ownership, honoraria, and paid expert testimony.

ABSTRACT

Introduction: The American Heart Association recommends therapeutic hypothermia for comatose survivors of cardiac arrest. For hemorrhagic shock (HS), laboratory studies suggest that mild hypothermia (34°C) prolongs the golden hour for resuscitation. Yet, the effects of hypothermia during HS are unclear since retrospective clinical studies suggest that hypothermia is associated with increased mortality. Using a more clinically relevant, large animal model with trauma and intensive care, we tested the hypothesis that hypothermia, induced with intravenous cold saline (ice cold or room temperature) and surface cooling, would improve survival after HS in pigs.

Methods: Pigs were prepared under isoflurane anesthesia. After laparotomy, venous blood (75 ml/kg) was continuously withdrawn over 3 h (no systemic heparin). At HS 35 min, the spleen was transected. At HS 40 min, pigs were randomized into 3 groups (n=8, each): 1) Normothermia (Norm)(38°C) with warmed saline, 2) Mild hypothermia (34°C) induced with i.v. infusion of 2°C saline (Hypo-Ice) and surface cooling, and 3) Mild hypothermia (34°C) with room temperature (24°C) i.v. saline (Hypo-Rm) and surface cooling. Fluids were given when mean arterial pressure (MAP) was <30 mmHg. At HS 3 h, shed blood was returned and splenectomy was performed. Intensive care was continued to 24 h.

Results: At 24 h, there were 2 survivors in Group Norm, 4 in Group Hypo-Ice and 7 in Group Hypo-Rm ($p<0.05$ vs Group Norm, Log Rank). Time required to achieve 34°C was 17±9 min in Group Hypo-Ice and 15±4 min in Group Hypo-Rm (NS). Compared to Group Hypo-Rm, Group Hypo-Ice required less saline during early HS (321±122 vs 571±184 ml, $p<0.05$). Group Hypo-Ice also had a transiently higher MAP (NS) and higher lactate levels ($p<0.05$). Hypothermia did not cause any increase in bleeding.

Conclusion: Mild Hypothermia improves survival in a clinically relevant model of HS and trauma. However, administration of ice-cold resuscitation fluid may have detrimental effects, possibly due to induced vasoconstriction. During HS, infusion of room temperature saline and surface cooling are safe and effective.

INTRODUCTION

After cardiac arrest, 2 large, randomized, controlled clinical trials[1,2] demonstrated that induction of mild hypothermia (33-34°C) in comatose survivors of cardiac arrest could improve survival and neurologic dysfunction. Based on these findings, the American Heart Association and the International Liaison Committee on Resuscitation recommended cooling all cardiac arrest victims who remain comatose to 32-34°C for 12-24 h.[3]

Hypothermia's effect on survival from trauma and hemorrhagic shock (HS) is more controversial. Clinical retrospective analyses have suggested that hypothermia is associated with poor outcome in trauma patients. [4,5] This supports the recommendations of the Advanced Trauma Life Support Course[6] that hypothermia should be avoided in trauma patients. In contrast with the clinical data, animal experiments have consistently showed that mild hypothermia improves survival during and after HS in models of volume-controlled, [7,8] pressure-controlled,[9] and uncontrolled HS.[10,11] To understand these differences, it is critical to consider the difference between secondary hypothermia (from exposure, administration of cold fluids, shock, anesthetics, etc) and therapeutic, induced hypothermia with prevention of shivering and sympathetic response by anesthetics and muscle relaxants.[12]

Previous laboratory studies, however, did not include significant tissue trauma, nor did they include clinically relevant prolonged intensive care. Therefore, to explore the effects of mild hypothermia with a more clinically-relevant insult and resuscitation, we established a large animal HS model with trauma via laparotomy and splenectomy followed by intensive care life support to 24 h.

Although a recent cardiac arrest study showed that hypothermia remained effective even if patients were cooled to the target temperature over 8 h,[2] it is generally believed that the faster

hypothermia is induced, the more effective it will be. Kuboyama *et al* reported that cooling initiated 15 min after return of spontaneous circulation had almost no effect in a canine cardiac arrest model.[13] Ice-cold saline has recently been used after cardiopulmonary resuscitation (CPR) to facilitate induction of hypothermia. Infusing 30 ml/kg 4°C saline over 30 min rapidly decreased the body temperature by 1.7°C in 20 CPR patients and increased blood pressure.[14] No severe side effects, such as arrhythmia or pulmonary edema were found. It is logical to assume that ice-cold saline, if well tolerated, may thus be an ideal solution for both induction of hypothermia and volume replacement during initial resuscitation during HS. Indeed, Norio *et al* reported that infusion of a fixed volume (500 ml) of 4 °C saline over 20 min decreased the core temperature by 2°C, and significantly prolonged the short-term survival time in pigs with uncontrolled bleeding from aortomy.[15]

In the current study, we developed a clinically-relevant HS model in pigs with the following features: 1) controlled continuous hemorrhage during HS simulating uncontrolled bleeding over 3 h; 2) laparotomy and spleen transection; 3) limited fluid resuscitation (simulating field conditions), and 4) full resuscitation and 24 h life support. Normothermia was compared to mild hypothermia (34°C) (induced with surface cooling and intravenous infusion of either room temperature or ice-cold saline during HS) in terms of physiologic parameters, survival time, and long- term survival rate.

We hypothesized that, compared to maintenance of normothermia, mild hypothermia would improve survival from prolonged, traumatic HS in a clinically relevant large animal model with intensive care life support. We also hypothesized that infusion of ice-cold saline during resuscitation would facilitate cooling and further improve survival.

MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Design of the Study [Fig 1]

Thirty-one Yorkshire/Landrace crossbred swine (Whippo Farms Enon Valley, PA), age 9-11 weeks, weighing 20.0-33.2 kg were used. The HS model incorporated continuous stepwise bleeding via a catheter placed in the right external jugular vein. The hemorrhage phase lasted 3 h. At HS 35 min, the spleen was transected. At HS 40 min, limited (hypotensive) fluid resuscitation was started, simulating arrival of paramedics. Pigs were randomized into 3 groups: 1) Normothermia (38°C) with warmed saline (Norm), 2) Hypothermia (34°C) induced with infusion of 2°C saline and surface cooling (Hypo-Ice), and 3) Hypothermia (34°C) with room temperature (24°C) saline and surface cooling (Hypo-Rm). Resuscitation fluids were given when MAP was <30 mmHg. After the targeted temperatures were achieved, the resuscitation fluid was switched to warmed lactated Ringer's (LR, standard resuscitation fluid) to prevent temperature overshoot. At HS 3 h, shed blood was returned, and splenectomy was performed. Life support and intensive care were continued to 24 h.

Anesthesia and Surgical Preparation

The pigs were fasted overnight with free access to water. They were premedicated with intramuscular injection of ketamine 20 mg/kg, xylazin 2 mg/kg, and atropine 0.5 mg. Following administration of 1.5- 2% isoflurane via a cone mask for 5 min, endotracheal intubation was performed, and mechanical ventilation was started with a tidal volume of 10 ml/kg and a frequency of 14-16 breaths/min (Piston Ventilator Model 613, Harvard Apparatus, South Natick, MA), adjusted to maintain an arterial PCO_2 of 35-45 mmHg. An 18-G cannula (Angiocath,

Becton Dickinson, Infusion Therapy Systems Inc. Sandy, Utah) was inserted into the ear vein for fluid infusion. The maintenance fluid (0.45% NaCl in 5% Dextrose) was infused at a rate of 4 ml/kg/h to assure normovolemia and normoglycemia. Electrocardiogram (EKG) was continuously monitored with standard lead II.

A sterile cutdown was performed in the right groin, and a PE 90 catheter was inserted into the right femoral artery for blood pressure monitoring. Through a sterile cutdown on the right side of the neck, a 16 G catheter was inserted 20 cm into the external jugular vein for continuous blood withdrawal. A PE 60 catheter was inserted into the blood withdrawal catheter for infusion of citrate solution during blood withdrawal for maintenance of catheter patency and preservation of shed blood. The tip of the citrate catheter was 3 cm from the tip of the blood withdrawal catheter. A pulmonary artery catheter was inserted via the right cephalic vein into the inferior vena cava to measure the core body temperature without contamination from the resuscitation fluid administered via the superior vena cava system. A sterile cutdown was performed on the left side of the neck and a PE 90 catheter was inserted into the cephalic vein for fluid infusion. A cystostomy was performed through a sterile 5 cm lower midline laparotomy, and a balloon catheter was placed for urine drainage. Esophageal and rectal temperatures were all monitored.

Core temperature (blood temperature at the inferior vena cava) was maintained at 38.0°C with heating blankets and heating lamps prior to the insult.

Twenty min was allowed for stabilization before baseline hemodynamics and blood samples were collected.

Laparotomy and Induction of HS

A sterile 12 cm midline laparotomy was performed and the spleen was gently exposed for transection at HS 35 min. The wound was temporarily closed with towel clips.

Just prior to induction of HS, the heating and fluid infusion were stopped. The FiO_2 was set at 0.25 with 75% N_2. The isoflurane was kept at the baseline level. It was decreased to 1% when MAP was 50 mmHg, to 0.5% at MAP 40 mmHg, and to 0.2% at MAP less than 15 mmHg. Starting from HS 40 min, isoflurane was set at 0.5%. Pancuronium 0.2 mg/kg was given at the beginning of HS and repeated as needed. Pancuronium was avoided in the late HS phase (HS >1.5 h) because its adverse circulatory effects[16,17] may artificially shorten the survival time.

Venous blood withdrawal was in a continuous and graded fashion: 1) 68.6 ml/kg/h for the first 35 min, 2) 20 ml/kg/h from HS 35-95 min, and 3) 10 ml/kg/h from HS 95-180 min. At HS 35 min, the spleen was transected at the mid point. The splenectomy was delayed until the animals were hypotensive to avoid large amounts of blood loss that could not be replaced without a blood bank during resuscitation. The transected spleen remained in the abdomen, untouched until the end of HS.

Pigs that developed cardiac arrest (ventricular fibrillation, pulseless electrical activity, or asystole) prior to 40 min were excluded from further evaluation. At HS 40 min, the pigs were randomized into 3 groups: 1) Group Norm, in which the core temperature was maintained at 38.0±0.5°C. Warmed (38°C) saline was infused when MAP decreased below 30 mmHg for limited fluid resuscitation. 2) Group Hypo-Ice, in which the core temperature was decreased to 34°C with surface cooling. Ice-cold (2°C) saline was used for limited fluid resuscitation. 3) Group Hypo-Rm, similar to Group Hypo-Ice except that room temperature (20°C) saline was

utilized. When the target temperatures were achieved, warmed LR was used for hypotensive fluid resuscitation if needed.

Resuscitation and Splenectomy

At HS 180 min, the shed blood from the first 30 min was reinfused. Additional LR was given to restore MAP >70 mmHg. The splenectomy was performed and the abdominal wound was closed. The quantity of blood loss from the spleen was measured.

Intensive Care

Analgesia and mechanical ventilation. Morphine 15 mg IV was administered for signs of distress (midriasis, tachycardia, movement). Pancuronium 0.2 mg/kg was administered to facilitate mechanical ventilation after sufficient opiate was given.

Temperature. The temperature in the hypothermia groups was maintained at 34°C until resuscitation time (RT) 12 h, followed by a slow rewarming (1°C/h) to 38°C. Group Norm was maintained at 38°C throughout the experiment.

Hemodynamics and Fluid balances. LR was administered when MAP was less than 70 mmHg and CVP was less than 8 mmHg. Infusion of norepinephrine was started when hypotension was accompanied by an elevated CVP (>8 mmHg).

Electrolytes and acid-base balance. Potassium chloride (20 mEq) was added to the maintenance fluid when plasma potassium was lower than 3 mmol/L. If plasma calcium was less than 1 mmol/L, 200 mg $CaCl_2$ was slowly injected. If base deficit (BD) was greater than 6 mmol/L, sodium bicarbonate ($NaHCO_3$) (bodyweight x BD/6) was administered.

At 24 h, all pigs were euthanized with an overdose of isoflurane and KCl. A thorough necropsy was performed.

Statistic Analysis

Data are presented as mean ± standard deviation unless otherwise stated. During HS 40-60 min (the time for cooling in the hypothermic groups), the requirements for fluids were analyzed with analysis of variance (ANOVA) followed by Tukey-Kramer post-hoc test. Changes in MAP during induction of hypothermia (HS 40-60 min) were analyzed separately using one way ANOVA for repeated measurements. The Student t-test was used in the analysis of arterial lactate levels at HS 2 h and 3 h in the two hypothermia groups, because there were only 2 surviving pigs in Group Norm at HS 2 and 3 h. The survival rates were analyzed with Fisher's exact test, and the survival time by Log-Rank life table analysis.

RESULTS

Of the 31 pigs initially studied, 7 (23%) died before HS 40 min and were excluded from analysis. Their survival time was median of 39 min (range: 35-40 min).

There were no significant differences in the baseline variables amongst the 3 groups (Table 1).

Hemorrhagic shock phase

Hemodynamics. Hemodynamics and physiological parameters were not different between groups before randomization at HS 40 min (Table 1). MAP was numerically higher in Group Hypo-Ice than the other two groups during induction of hypothermia (HS 40-60 min) (NS). After this, MAP was similar in all groups (Fig. 2). The heart rates were significantly lower in both hypothermia groups ($p<0.01$, vs Group Norm) (Fig 3). The amount of resuscitation fluid required during induction of hypothermia was 507±93 ml in Group Norm, 571±184 ml in Group Hypo-Rm, and 321±122 ml in Group Hypo-Ice ($p<0.05$, Group Hypo-Ice vs Group Hypo-Rm). The total fluid requirement over 3 h of HS was not significantly different between groups. The total blood loss from the spleen was <30 ml in all pigs.

Temperatures. The core temperatures increased slightly during the initial HS phase (HS 0-40 min). The temperature in Group Norm was then maintained at 37.5-38.5°C throughout the remaining HS phase. It required 17±9 min in Group Hypo-Ice and 15±4 min in Group Hypo-Rm (NS) to reach 34°C (Fig. 4).

Physiologic parameters. There were no significant differences in pH, PCO_2, BD, hematocrit, glucose or plasma potassium levels at HS 1, 2 or 3 h. At HS 2 and 3 h, the lactate levels in Group Hypo-Ice were significantly higher than Group Hypo-Rm ($p<0.05$) (Table 1).

Resuscitation and ICU phase

Two of 8 pigs in Group Norm survived the HS phase, compared to 5 of 8 in Group Hypo-Ice and 7 of 8 in Group Hypo-Rm. There were no significant differences in MAP (Fig. 2) or HR (Fig. 3) amongst groups. The lactate levels were higher in Group Hypo-Ice vs Group Hypo-Rm during the early resuscitation phase; however, lactate levels in both groups rapidly fell into the normal range. The remaining physiologic parameters were not significantly different between groups (Table 1).

One pig in Group Hypo-Ice died at RT 10 min. One pig in Group Hypo-Rm died at RT 12 h of a tension pneumothorax caused by a ventilator malfunction. The pig had stable hemodynamics and normal blood gas and lactate levels up to that point and most likely would have survived to 24 h. At necropsy there was no gross organ damage.

Final outcome

Survival to RT 24 h was achieved by 7 of 8 Hypo-Rm pigs (1 animal in the Hypo-Rm Group was censored at 12 h), 4 of 8 Hypo-Ice pigs, and 2 of 8 Norm pigs ($p=0.01$. Hypo-Rm vs Norm) The survival time (Fig. 5) was significantly longer in Group Hypo-Rm compared to Group Norm ($p<0.01$).

At 24 h, there were no significant differences in cardiac enzymes, liver injury tests, or renal function between groups (Table 2).

In necropsy, there was no gross organ damage found in any survivors.

DISCUSSION

This study demonstrated that mild hypothermia improves survival in a clinically relevant pig HS model that includes significant tissue trauma, as well as resuscitation and intensive care similar to clinical situations. This is an important first. In addition, we found that induction of hypothermia using ice-cold fluid may have back-fired, since use of room temperature fluid lead to a similar cooling rate with improved survival.

The finding that mild hypothermia improves survival from HS corroborates our previous hypothermia studies in rat HS models, which consistently demonstrated that hypothermia, induced either during HS or during fluid resuscitation, was associated with improved survival.[8,9,11,18] Other investigators also reported various beneficial effects of hypothermia during HS in animal experiments.[19-22] The hemorrhage insult in this study was very severe. Twenty-three percent of all subjects died before HS 40 min. In a previous rat study[23], in which we allowed spontaneous cooling to occur during HS, continuing mild hypothermia during resuscitation improved survival compared to active rewarming, particularly with a more severe, highly lethal insult. Deaths in these studies occurred relatively early during resuscitation and intensive care, with cardiovascular collapse unresponsive to aggressive resuscitation, not delayed multiple organ system failure. The main benefit of hypothermia during HS and resuscitation may be protective effects on the heart and peripheral vasculature, though this will need further study. These results may indicate that those with very severe HS may benefit most from hypothermia.

Our HS model with continuous, controlled bleeding in pigs was established based on Healey's[24] and Alam's[25] rat HS models. The model was designed to study prolonged hypotensive resuscitation, simulating medical support when transportation or evacuation is delayed as in rural and military settings. Using large animals, we can make the model more clinically relevant by

avoidance of systematic heparin, inclusion of trauma (laparotomy and spleen transection) and life support during the post-resuscitation phase.

One surprising finding in this study was that the method of induction of hypothermia with IV fluids produced markedly different physiologic effects and impact on survival, despite similar temperature curves. The fact that the infusion of ice-cold fluid was associated with increased MAP and blood lactate in Group Hypo-Ice suggests that vasoconstriction with decreased tissue perfusion may have played a role in worsening outcome. Two questions then arise. First, could ice-cold saline further stimulate a cold response, such as vasoconstriction, after animals had already been in shock and had been fully exposed to surface cooling? Second, is the vasoconstriction effect responsible for the worsened outcome?

Ice-cold saline appears to be a very potent stimulus to the thermoregulation center. Infusion of 40 ml/kg of 4 or 20°C saline to awake human volunteers decreased the core temperatures by 2.5 or 1.4°C, respectively.[26] Infusion of 30 or 60 ml/kg cold (4°C) saline over 30 min increased plasma norepinephrine by 220 to 700 %,[27,28] while epinephrine levels remained unchanged until a threshold (decrease in core temperature of 1°C) was reached.[28] Cheng *et al*[29] found that changes in the surface temperature contributed only about 20% to the cold response. Therefore, it seems that changes in core temperatures more readily trigger cold responses, such as vasoconstriction and shivering. Based on the above evidence, it is possible that Group Hypo-Ice had a more potent cold stimulus resulting from a lower temperature of resuscitation solution.

Among the major cold responses, shivering and vasoconstriction are most likely to affect the course of HS. Because of the use of muscle relaxants in the study, shivering was prevented, leaving vasoconstriction as the major cold-induced physiological response. Since the 1950s when Close *at al*[30] demonstrated that infusion of norepinephrine during HS increased mortality in a

dog model, vasoconstriction is believed to be detrimental for resuscitation from HS. However, physiologically, vasoconstriction is a life-saving response that redistributes limited blood flow to vital organs after trauma and hemorrhage. In certain situations, exogenous vasopressors are complementary to the insufficient or exhausted physiological vasoconstriction. Recently, it has been reported that vasoconstriction induced pharmacologically during HS appeared to improve acute survival.[31-33] Morales *et al*[34] reported that infusion of vasopressin to dogs that were not responsive to norepinephrine late in HS dramatically increased arterial blood pressure. In general, however, the enhanced vasoconstriction induced by drugs or hypothermia is a double edge sword. Accompanying improved acute survival, Alspaugh *et al*[32] found a marked increase in brain lactate/pyruvate ratio, a marker of adequate perfusion that was determined by microdialysis, when animals were treated with a vasopressor during HS.

Studies of volume-controlled or uncontrolled HS have shown that hypothermia increases MAP during shock.[8,10] With less severe HS than that studied here, we previously found that controlling for blood pressure during HS did not negate the beneficial effects of hypothermia.[9]

Another possible explanation for the lack of benefit of the ice-cold fluid may have been related to the model itself. The volume of fluid administered during HS was dependent upon MAP. The Hypo-Ice group received less fluid during the early phase of limited fluid resuscitation since the MAP increased quickly, in part because of the impact of hypothermia on MAP. This question deserves further study.

In addition to the above vascular effects of ice-cold saline, the possible cardiac effects of ice-cold saline deserve additional attention. In our HS model, most pigs had a MAP around 25 mmHg (range 12-32 mmHg) immediately before the start of limited fluid resuscitation. When fluid was given at the speed of ~50 ml/min, MAP usually increased steadily. However, one pig

in Group Hypo-Ice had a MAP of only 13 mmHg at HS 40 min, accompanied by a decelerating HR from 200 bpm at HS 35 min to 165 bpm. Within 2 min of infusion of ice-cold saline the heart went into asystole. We have noticed that deceleration of heart rate is a sign of decompensation, often followed by severe bradycardia and cardiac arrest in a few minutes. However, this may not always be the case. There was an almost identical pig in Group Norm that responded immediately after infusion of warmed fluid with increased MAP and the pig survived for another 75 min. We believe that rapid infusion of ice-cold fluid during profound hypovolemic hypotension may risk causing cardiac arrest.

One rationale for infusion of ice-cold saline is the belief that the faster hypothermia is induced, the more effective it will be. The need for ice-cold fluid to increase the rate of cooling may be less of an issue during HS than it is after cardiac arrest. First, patients in HS tend to become hypothermia spontaneously because of exposure and administration of room temperature fluids, as well as a decreased ability to maintain normothermia because of shock itself, anesthetics/sedatives, alcohol and drug use. Second, unlike normovolemic cardiac arrest victims,[14] HS patients need a copious amount of fluid for resuscitation, which, if stored at room temperature, will add to the cooling.[35] Third, we have found that hypothermia has similar benefit when induced at 10 min or 1 h in rats;[36] thus, the therapeutic window may be substantial.

Our study is limited in several ways. First, unlike Norio *et al*'s study[15], we did not use a fixed volume of ice-cold saline in the resuscitation protocol. Fixed volume resuscitation regardless of response may be relevant in military or certain civilian pre-hospital settings. However, ideally, resuscitation should always be guided by certain endpoints. In our study, we took MAP as an endpoint, which is important in order to avoid increased bleeding and mortality.[37]

The model is different from clinical reality for a number of reasons. Use of anesthesia, muscle relaxants, endotracheal intubation and mechanical ventilation before and during HS is not what happens clinically. However, at the time of induction of hypothermia, we needed to prevent shivering and a sympathetic response to hypothermia by making the organism poikilothermic using anesthetics and muscle relaxants. Takasu *et al*[38] found that ineffective cooling during HS actually shortened the survival time in pigs after aortic injury.

The laparotomy was performed prior to the splenic injury out of necessity. Obviously, in the clinical situation, the trauma to the spleen would have occurred first. We did perform the laparotomy as close to the beginning of hemorrhage as we could.

Another issue is the use of whole, autologous blood for transfusion during resuscitation. Clinically, the effects of donated blood that has been separated into packed cells and other components, and then stored for a prolonged period of time are significant.

One of the biggest issues in hypothermic trauma patients is coagulopathy. This may be one of the critical reasons for the discrepancy between the clinical and laboratory findings related to hypothermia and HS/trauma. In this study and a previous one,[39] we have not found that cooling to 34°C in pigs leads to clinically significant bleeding from the liver or transected spleen. Even in patients, tests of the coagulation system and platelet function do not seem to demonstrate clinically relevant changes until temperature is below 34°C.[40] The fact that cooling head injured patients did not cause any increase in intra-cranial hemorrhage also demonstrates this point.[41]

In conclusion, in a model of continuous bleeding in pigs, we found that mild hypothermia induced with surface cooling and infusion of room temperature fluids during HS improved survival. Infusion of ice-cold saline may induce excessive vasoconstriction or cause cardiac arrest, undermining hypothermia's beneficial effects. Clinical safety and feasibility studies of

mild hypothermia for resuscitation of trauma victims with evidence of HS should be conducted, followed by randomized clinical trials.

Table 1. Physiologic data during HS and resuscitation

	Group	BL	HS 40 min	HS 1h	HS 3h	RT 6h	RT 24h
pH	Norm	7.58±0.04	7.56±0.05	7.47±0.05	7.13±0.01	7.51, 7.54	7.54, 7.54
	Hypo-Ice	7.57±0.04	7.55±0.06	7.45±0.05	7.20±0.08	7.4±0.0	7.5±0.1
	Hypo-Rm	7.55±0.02	7.50±0.04	7.38±0.05	7.24±0.06	7.4±0.1	7.5±0.0
PCO_2 (torr)	Norm	34.0±5.4	24.0±7.6	26.4±5.8	27.0±1.8	35.7, 32.5	30.7, 36.2
	Hypo-Ice	35.8±3.5	22.1±5.8	27.6±5.8	28.2±4.6	40.8±3.3	37.1±3.1
	Hypo-Rm	35.4±4.3	25.1±5.3	32.4±3.8	29.0±3.1	41.3±3.4	34.5±3.0
PO_2 (torr)	Norm	206±25	92±21	103±20	170±55	183, 93	182, 138
	Hypo-Ice	199±26	112±15	132±18	191±53	201±71	209±47
	Hypo-Rm	205±23	111±16	133±14	175±45	230±77	263±24
Base deficit (mmol/L)	Norm	-10.6±3.1	-0.3±4.3	2.9±5.1	17.5±1.1	-6.2, -3.1	-4.8, -8.4
	Hypo-Ice	-10.9±2.9	1.6±2.9	3.1±4.0	15.0±2.0	-2.7±2.3	-8.4±2.3
	Hypo-Rm	-9.0±2.5	1.9±3.5	4.2±3.7	12.8±1.6	-3.2±3.7	-7.8±3.0
Glucose (mg/dl)	Norm	118±29	184±116	181±90	319	338, 153	132, 92
	Hypo-Ice	125±26	200±117	160±82	397±59	309±81	103±15
	Hypo-Rm	125±30	170±90	209±73	511±110	391±116	126±43
SvO_2 (%)	Norm	79.6±6.0	9.4±3.9	13.6±9.3	21.4,10.2	81.2, 79.0	82.8, 84.0
	Hypo-Ice	78.8±4.7	19.2±9.8	21.4±18.8	15	79.4±11.9	79.8±5.3
	Hypo-Rm	75.0±8.7	19.3±9.8	25.3±18.2	25.1±12.9	77.8±8.0	82.4±8.4
Lactate (mmol/L)	Norm	1.2±0.6	6.9±1.6	9.0±2.2	16.5	2.7, 1.7	0.5, 1.0
	Hypo-Ice	0.8±0.4	7.2±1.1	8.4±1.4	18.4±2.3*	5.3±3.0	0.7±0.3
	Hypo-Rm	0.5±0.3	6.3±1.2	7.6±1.9	15.2±1.3	4.2±1.8	0.4±0.4
Hematocrit (%)	Norm	29.3±1.8	28.5±3.2	24.1±4.1	11.0,10.0	26, 26	29, 23
	Hypo-Ice	30.0±1.9	29.9±4.1	26.0±4.5	9.7±2.5	33.3±2.4	26.3±2.8
	Hypo-Rm	29.4±2.7	28.8±4.8	21.4±3.2	11.5±2.3	34.3±3.3	27.8±2.2

Data are presented as mean ±standard deviation. Individual data are presented if n<3. BL=baseline, HS=hemorrhagic shock, RT=resuscitation time, SvO2=Oxygen saturation of central venous blood. *: $p<0.05$, vs Group Hypo-Rm

Table 2. Cardiac, hepatic and renal damage in survivors

		Baseline	RT 24 h
Bilirubin (mg/dl)	Hypo-Ice	<0.1	<0.1
	Hypo-Rm	<0.1	<0.1
Aspartate aminotransferase (IU/L)	Hypo-Ice	32±5	67±11
	Hypo-Rm	34±7	108±36
Alanine aminotransferase (IU/L)	Hypo-Ice	63±20	71±20
	Hypo-Rm	54±14	69±12
γ-glutamyl transpeptidase (IU/L)	Hypo-Ice	45±21	44±16
	Hypo-Rm	36±19	41±28
Alkaline phosphatase (IU/L)	Hypo-Ice	171±40	193±79
	Hypo-Rm	139±26	156±37
Troponin-I (ng/mL)	Hypo-Ice	0.51, 0.76	4.9, 18.1
	Hypo-Rm	0.41±0.18	18.76±12.72
Creatinine (mg/dL)	Hypo-Ice	1.2±0.1	1.1±0.1
	Hypo-Rm	1.2±0.3	1.7±08

Data are presented as mean±standard deviation. N=3 in Hypo-Ice Group, and N=6 in Hypo-Rm Group. Only 2 animals had values for troponin in the Hypo-Ice group. RT=Resuscitation time

FIGURE LEGENDS

Figure 1
Experimental protocol. LR=lactated Ringer's; MAP=mean arterial pressure; FR=fluid resuscitation.

Figure 2
Mean arterial pressure (MAP) during hemorrhagic shock (HS) and early resuscitation. Groups are normothermia (Norm), mild hypothermia with ice-cold flush (Hypo-Ice), and mild hypothermia with room temperature flush (Hypo-Rm).

Figure 3
Heart rate (HR) during hemorrhagic shock (HS) and early resuscitation. Groups are normothermia (Norm), mild hypothermia with ice-cold flush (Hypo-Ice), and mild hypothermia with room temperature flush (Hypo-Rm).

Figure 4
Core temperature during hemorrhagic shock (HS) and early resuscitation. Groups are normothermia (Norm), mild hypothermia with ice-cold flush (Hypo-Ice), and mild hypothermia with room temperature flush (Hypo-Rm).

Figure 5
Survival following prolonged hemorrhagic shock and resuscitation. Groups are normothermia (Norm), mild hypothermia with ice-cold flush (Hypo-Ice), and mild hypothermia with room temperature flush (Hypo-Rm). *One pig in the Hypo-Rm group died of a tension pneumothorax at 12 h.

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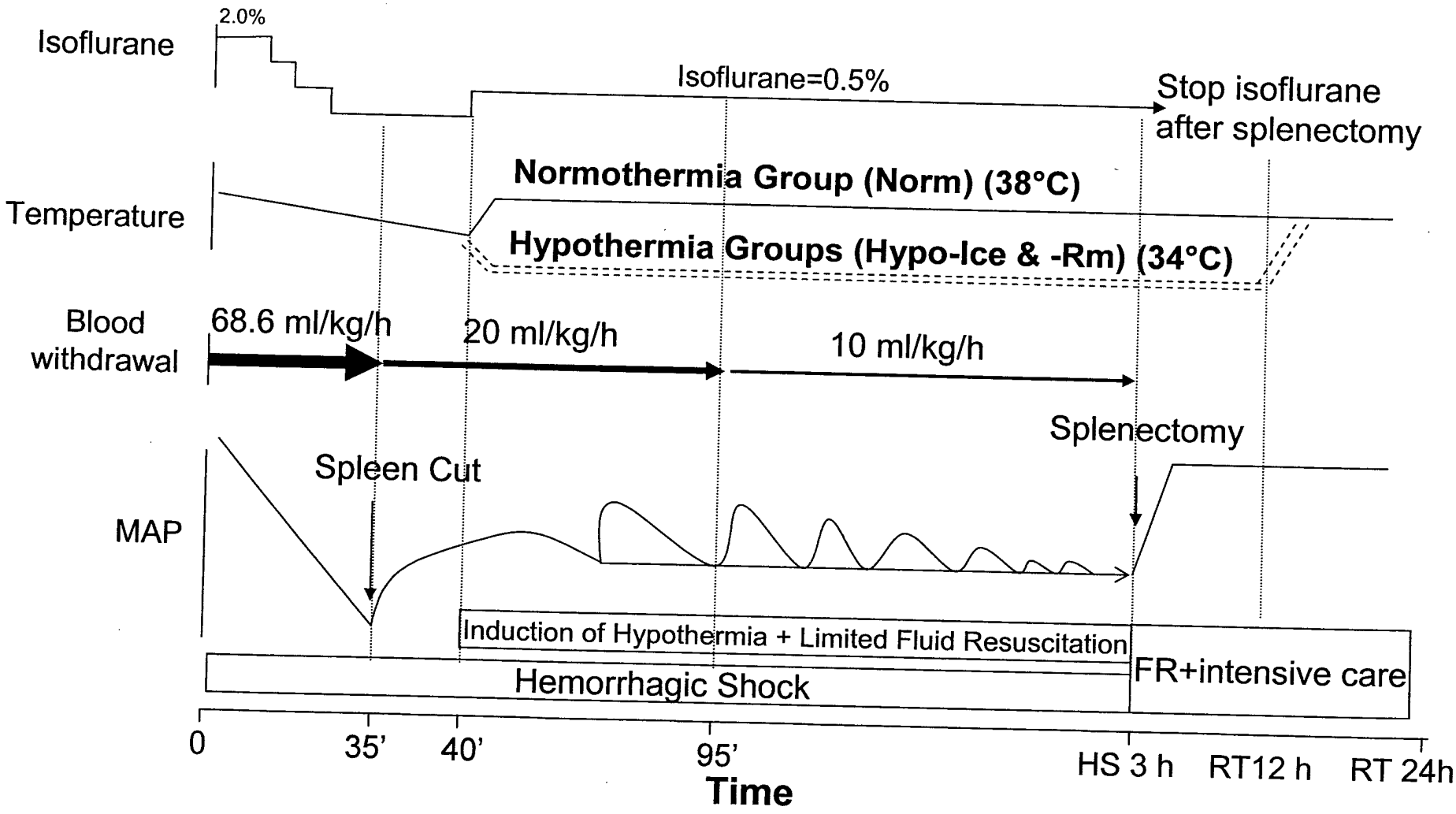
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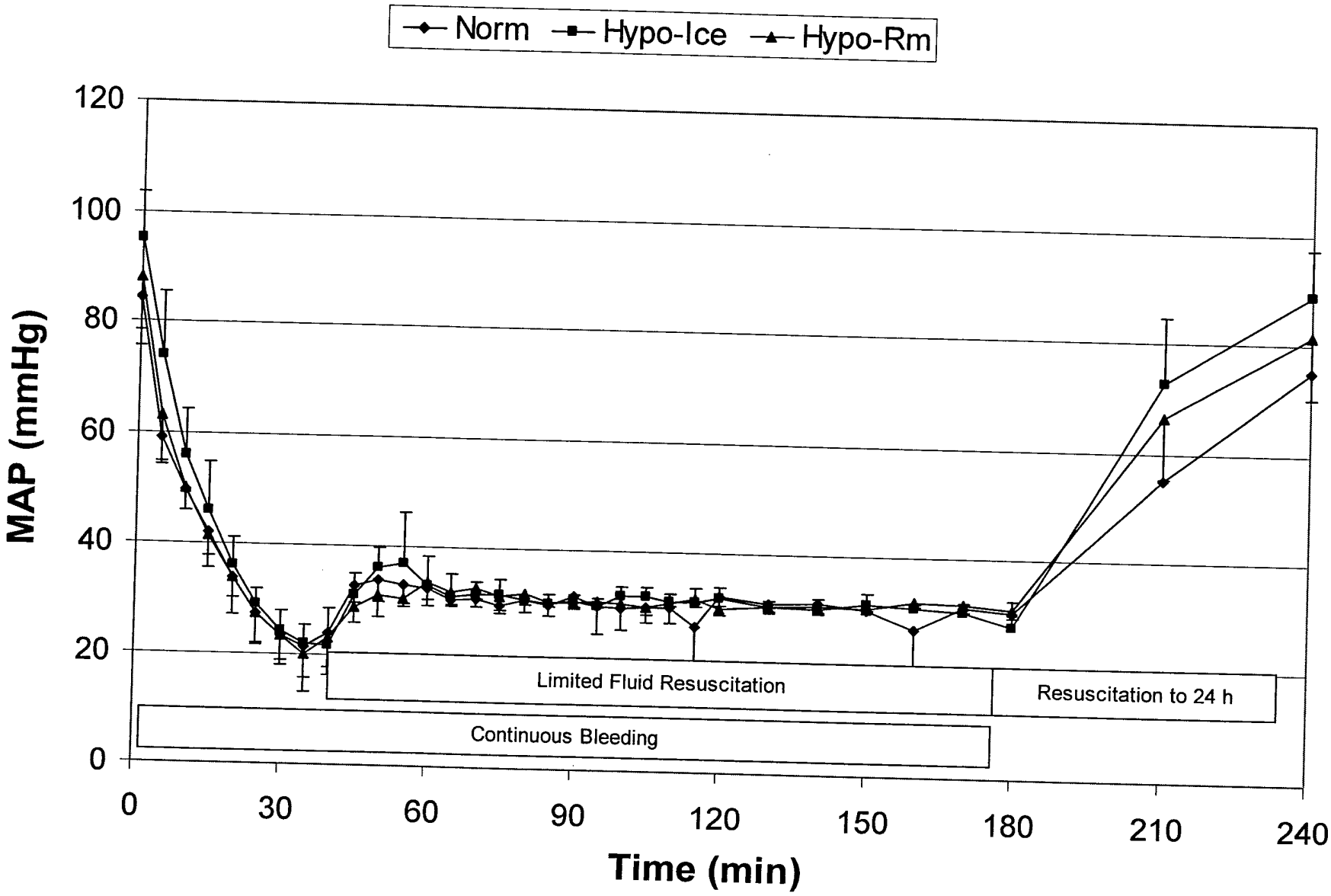
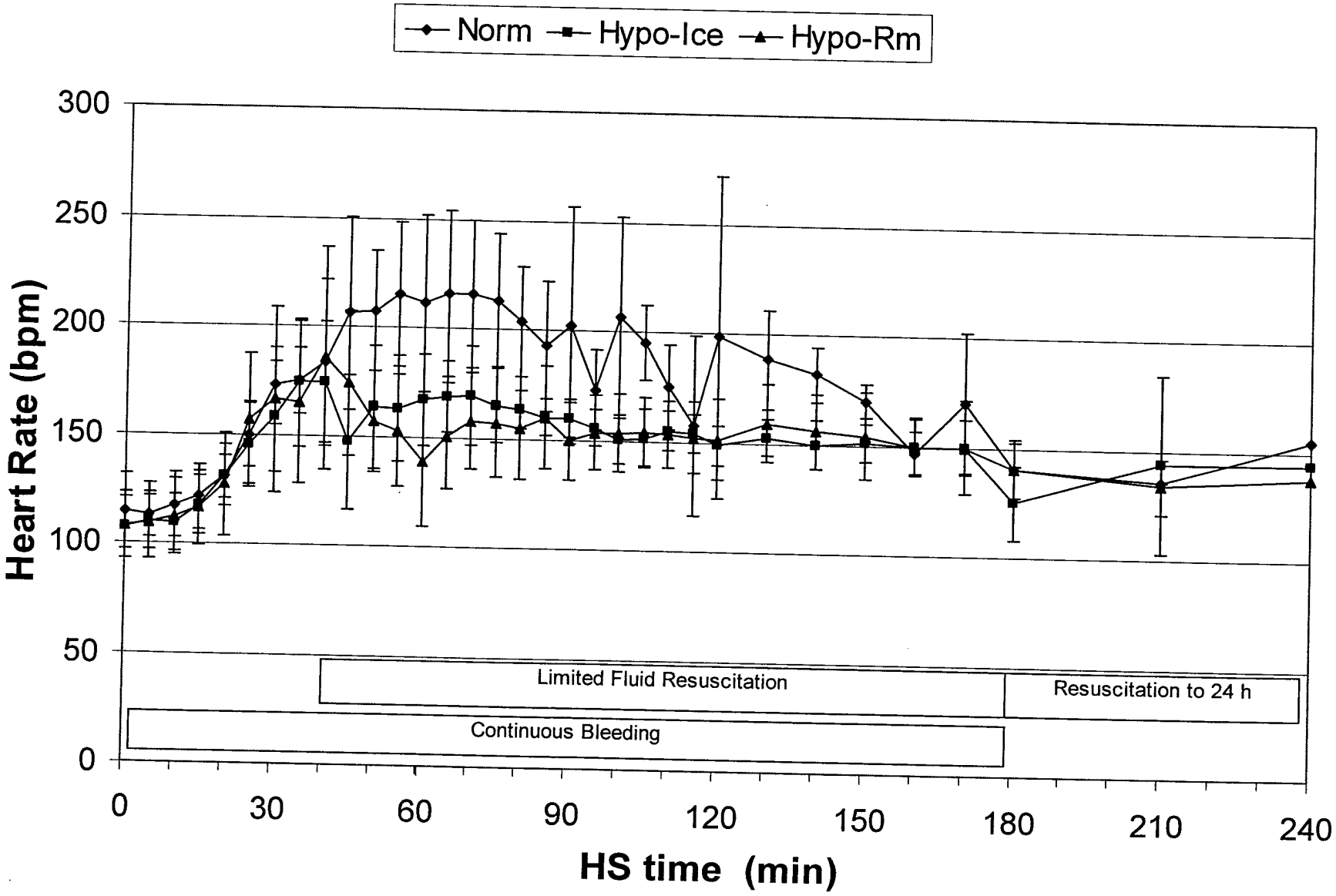
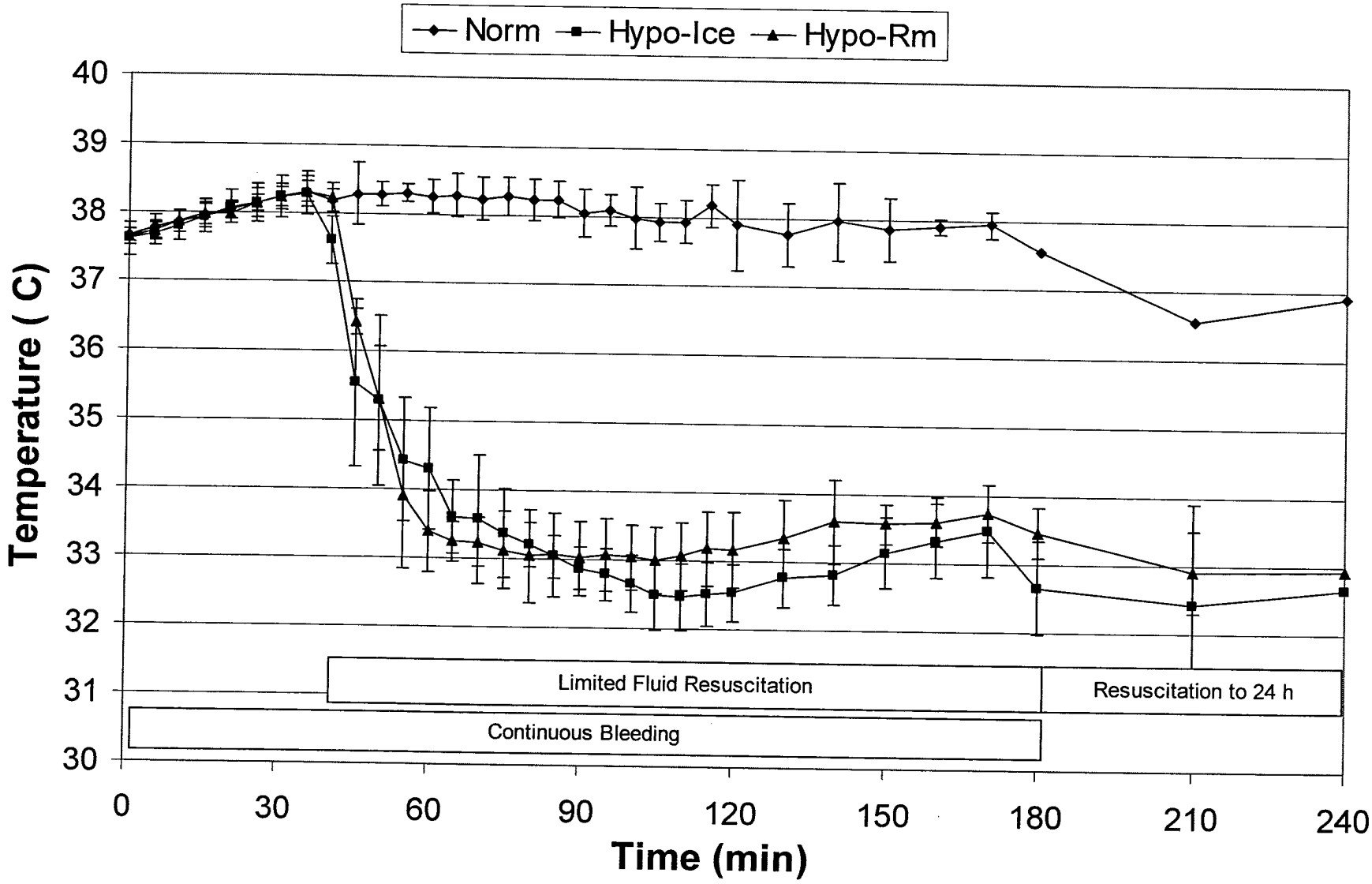
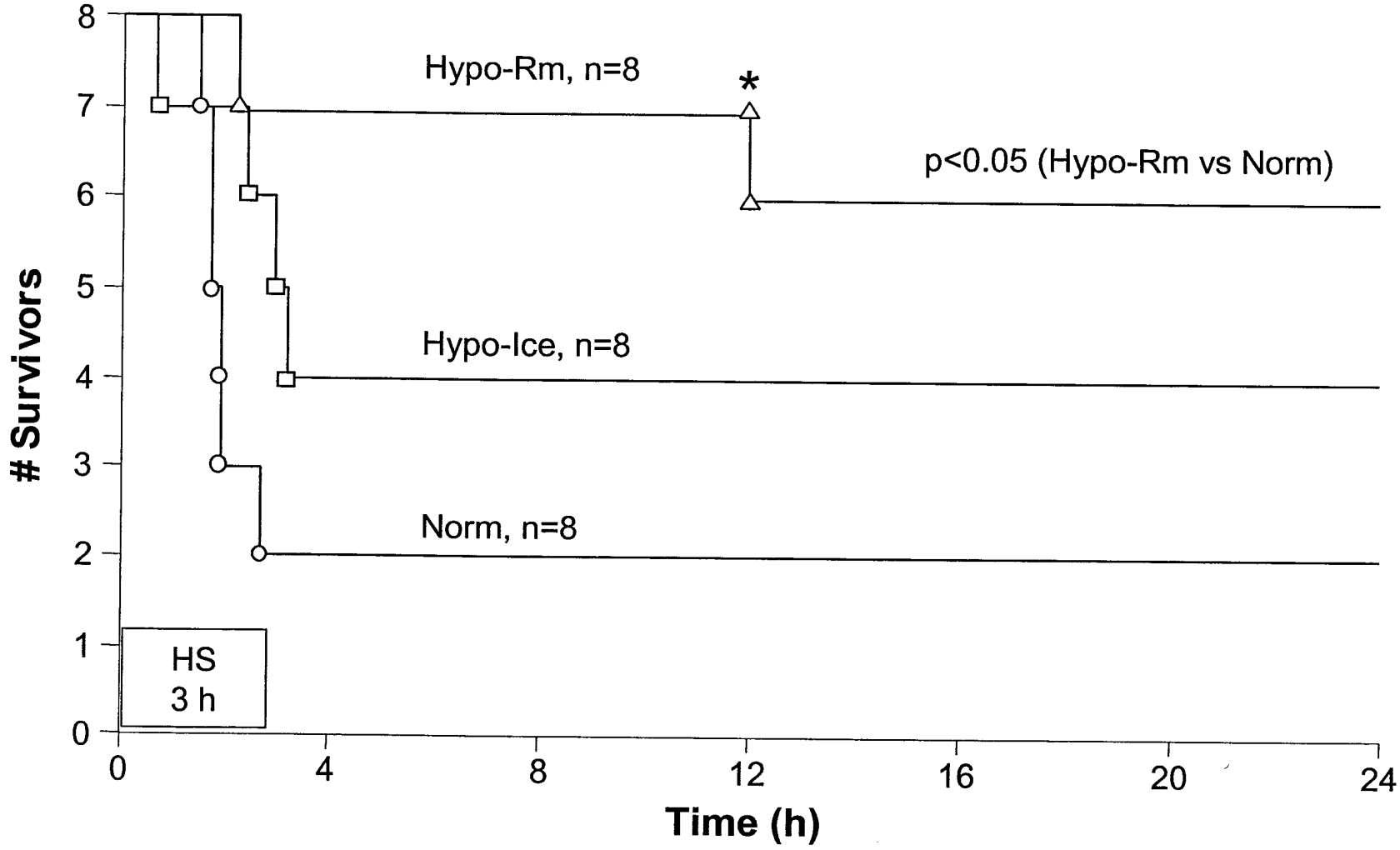
Isoflurane=0.5%
Stop isoflurane after splenectomy
Temperature
Normothermia Group (Norm) (38°C)
Hypothermia Groups (Hypo-Ice & -Rm) (34°C)
Blood withdrawal
68.6 ml/kg/h
20 ml/kg/h
10 ml/kg/h
Splenectomy
Spleen Cut
MAP
Induction of Hypothermia + Limited Fluid Resuscitation
Hemorrhagic Shock
FR+intensive care
0
35'
40'
95'
HS 3 h
RT12 h
RT 24h
Time


Norm
Hypo-Ice
Hypo-Rm
120
100
80
60
40
20
0
MAP (mmHg)
0
30
60
90
120
150
180
210
240
Time (min)
Limited Fluid Resuscitation
Resuscitation to 24 h
Continuous Bleeding


Norm
Hypo-Ice
Hypo-Rm
300
250
200
150
100
50
0
Heart Rate (bpm)
Limited Fluid Resuscitation
Resuscitation to 24 h
Continuous Bleeding
0
30
60
90
120
150
180
210
240
HS time (min)


Norm
Hypo-Ice
Hypo-Rm
Temperature (C)
40
39
38
37
36
35
34
33
32
31
30
Limited Fluid Resuscitation
Resuscitation to 24 h
Continuous Bleeding
0
30
60
90
120
150
180
210
240
Time (min)


Hypo-Rm, n=8
*
p<0.05 (Hypo-Rm vs Norm)
Hypo-Ice, n=8
Norm, n=8
HS
3 h
Survivors
Time (h)
0
1
2
3
4
5
6
7
8
0
4
8
12
16
20
24