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Is Hypothermia in the Victim of Major Trauma Protective or Harmful?

A Randomized, Prospective Study

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Objective
The purpose of this randomized, prospective clinical trial was to determine whether hypothermia during resuscitation is protective or harmful to critically injured trauma patients.

Summary Background Data
Hypothermia has both protective and harmful clinical effects. Retrospective studies show higher mortality in patients with hypothermia; however, hypothermia is more common in more severely injured patients, which makes it difficult to determine whether hypothermia contributes to mortality independently of injury severity. There are no randomized, prospective treatment studies to assess hypothermia's impact as an independent variable.

Methods
Fifty-seven hypothermic ($T \leq 34.5$ C), critically injured patients requiring a pulmonary artery catheter were randomized to a rapid rewarming protocol using continuous arteriovenous rewarming (CAVR) or to a standard rewarming (SR) control group. The primary outcome of interest was first 24-hour blood product and fluid resuscitation requirements. Other comparative analyses included coagulation assays, hemodynamic and oxygen transport measurements, length of stay, and mortality.

Results
The two groups were well matched for demographic and injury severity characteristics. CAVR rewarmed significantly faster than did SR ($p < 0.01$), producing two groups with different amounts of hypothermia exposure. The patients who underwent CAVR required less fluid during resuscitation to the same hemodynamic goals (24,702 mL *vs.* 32,540 mL, $p = 0.05$) and were significantly more likely to rewarm ($p = 0.002$). Only 2 (7%) of 29 patients who underwent CAVR failed to warm to 36 C and both died, whereas 12 (43%) of 28 patients who underwent SR failed to reach 36 C, and all 12 died. Patients who underwent CAVR had significantly less early mortality ($p = 0.047$).

Conclusion
Hypothermia increases fluid requirements and independently increases acute mortality after major trauma.

Hypothermia has two well-known clinical effects: 1) to preserve life and 2) to kill. Which of these two effects takes precedence in severely injured trauma patients currently is unknown. Current trauma care guidelines call for active efforts at preventing hypothermia and for aggressively treating it once it has occurred.[1] These recommendations are based on retrospective studies that document an extraordinarily high association between hypothermia and mortality.[2–5] However, hypothermia is more common and more severe in more seriously injured patients. Therefore, it is unclear whether the increased mortality is caused by the hypothermia itself or by the underlying injuries.

Studies have attempted to address this question by controlling injury severity using the Injury Severity Score (ISS).[6] These studies show that patients in whom hypothermia develops have a higher mortality than do patients with a similar ISS who remain warm.[5,7] However, the process of dying is characterized by a progressive extinction of oxygen consumption and consequent heat production. In these studies, the development of hypothermia may simply have identified patients within each ISS category who were dying from their injuries, with hypothermia not being the cause, but the result. These factors make it difficult to prove a cause-and-effect relation between hypothermia and mortality using retrospective studies.

Only a prospective treatment study using hypothermia as an independent variable can determine whether hypothermia is protective or harmful to severely injured patients. There have been significant constraints toward the performance of such a study. Hypothermia is notoriously difficult to treat with standard methods and generally takes several hours to resolve.[8] Therefore, a comparative study to assess the effects of treating hypothermia would result in both treated and control group subjects being exposed to a prolonged period of hypothermia. Cardiopulmonary bypass has the potential to rapidly rewarm patients, but its complexity, frequent need for heparin, and introduction of other variables would confound the results of such a study.

Continuous arteriovenous rewarming (CAVR) is a recently described technique that uses percutaneously placed femoral arterial and venous catheters and the patient's own blood pressure to create an arteriovenous fistula that diverts a portion of the cardiac output through a compact, heparin-bonded heat exchanger (Fig. 1). The procedure is analogous to arteriovenous hemofiltration, produces a rewarming rate similar to that of cardiopulmonary bypass, and provides a means of rapidly correcting hypothermia in trauma patients.[8–11] This rewarming technology provides an opportunity to study the effects of hypothermia on injured patients by allocating subjects to receive either standard (slow) rewarming methods or CAVR, producing two groups with significantly different durations of hypothermia exposure. To test the hypothesis that hypothermia is protective in critically injured trauma patients, we conducted this randomized, prospective trial comparing outcome of hypothermic trauma patients treated with standard rewarming (SR) methods or CAVR.

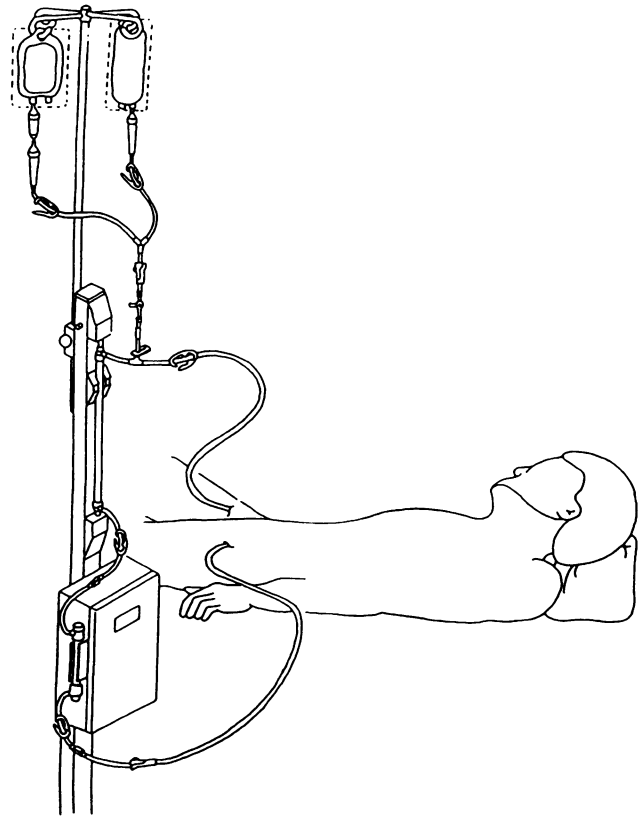

Figure 1. Schematic depiction of continuous arteriovenous rewarming.

METHODS

This study was conducted at Harborview Medical Center, University of Washington, School of Medicine, between September 1993 and October 1995. Given the known association between hypothermia and blood loss, the prospectively chosen primary study endpoint was a significant difference in the first 24-hour total blood and fluid resuscitation requirements. The sample size projection was estimated on the basis of differences in fluid requirements found in our previously published study

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comparing 16 hypothermic patients treated with CAVR with 18 historic control subjects.[11] Using those differences, we determined that 28 patients in each group would provide a 90% chance of identifying a difference in fluid requirements with an alpha of 0.05. Based on that same study, detecting differences in survival to hospital discharge with similar power would require 160 patients in each group and would only be pursued if there were no significant differences in resuscitation requirements at our initial stopping point.

The study population consisted of patients 18 years of age or older admitted to the intensive care unit (ICU) after injury. Patients were considered eligible if a pulmonary artery catheter was required to guide initial resuscitation and the initial core temperature reading was ≤34.5 C. Patients with an injury that precluded access to the femoral artery or with a nonsurvivable brain injury were not eligible for randomization. Consent for use of study data was obtained retrospectively from the patient or next of kin. After determination of eligibility, patients were randomly assigned to the SR or CAVR group using a code generated from a table of random numbers, which was concealed until after study entry. Standard trauma resuscitation protocols were used for all other components of care, and resuscitation endpoints were identical for both groups. Statistical analysis was by intention to treat, and all randomized patients are included. The principal investigators did not participate in rewarming procedures. The study protocol was approved by the University of Washington Institutional Review Board.

Rewarming Technique

Rewarming was initiated immediately after randomization. The SR group received simultaneous administration of warm intravenous fluids (Sims Level 1 Technologies, Rockland, MA), airway rewarming (Concha Therm II; Hudson Respiratory Care, Inc, Temecula, CA), a convective air blanket (Augustine Medical, Eden Prairie, MN), and an aluminized Therma Drape Hat (OR Concepts, Dallas, TX).

The CAVR group received the above SR methods plus CAVR. CAVR was performed by percutaneously cannulating the femoral artery and contralateral femoral vein with a specially designed 8.5-French catheter using Seldinger technique. In three cases, femoral arterial access already had been obtained to perform angiography, and guidewire exchange was performed to insert the CAVR catheter. The catheters were connected to the heparin-bonded CAVR tubing circuit (Sims Level 1 Technologies, Rockland, MA). Patients who underwent CAVR who were hypotensive had additional fluids administered by piggyback into the CAVR circuit to maintain fistula flow rate until hypotension was corrected, as shown in Figure 1.

The heat exchanger consists of an inner chamber through which hot water (40 C) is pumped (9 L/minutes) and an outer chamber through which the patient's blood flows under arterial pressure in a countercurrent direction. The two chambers are separated by a thin layer of corrugated, anodized aluminum. A 170-μm blood filter with a gas eliminator was located between the heat exchanger and the venous catheter. The total volume of the extracorporeal system was 83 mL. Warming was continued in both groups until a core temperature of 36 C was attained.

Study Variables

Baseline data included age, gender, height–weight, medical history, vital signs, serum lactate level, injury mechanism, significant injuries, and initial ICU temperature. Severity of injury was classified using ISS. Core temperature, fluid requirements, vital signs, lactate level, hemodynamics, and oxygen transport parameters were recorded hourly for the first 4 hours, then daily. Coagulation was measured using the prothrombin time and activated partial thromboplastin time at baseline and hourly for 4 hours. The assays were performed at the patient's measured core temperature using a fibrometer modified to permit assays at temperatures other than the clinical laboratory standard of 37 C, as described previously by our group.[12]

Follow-up evaluation included duration of mechanical ventilation, length of ICU stay, total hospital stay, and survival to hospital discharge. The incidence of organ failure between groups also was compared. The definition of acute lung injury required the presence of all of the following: ≥5-cm water positive end-expiratory pressure; inspired oxygen concentration (FiO_2) ≥ 40%; PaO_2/FiO_2 ≤ 200; and diffuse bilateral infiltrates on chest roentgenogram. Hepatic dysfunction was considered present if serum bilirubin increased by 3 mg/dL over baseline for 2 or more days in the absence of hemolysis or biliary tract obstruction, and serum glutamic oxalotransaminic level was greater than twice normal.

Central nervous system dysfunction was defined by inability to follow simple commands when this condition was not related to head injury or neuromuscular blocking agents. Myocardial dysfunction was defined by a cardiac index <2.5 L/minutes per m^2, or new myocardial infarction. Renal dysfunction was considered present if creatinine clearance was <30 mL/minutes and serum creatinine level was >1.5 mg/dL for 2 or more days, or if oliguria persisted for >24 hours despite adequate volume status. Gastrointestinal dysfunction was noted by inability to tolerate enteral feeding or gastric bleeding with changes in vital signs or hematocrit.

Infectious complications also were recorded. The definition of pneumonia required a sputum gram stain with leukocytes and a predominant organism, a culture positive for a known pathogen, leukocyte count >12,000/mm^3, a

Table 1. DEMOGRAPHIC INFORMATION*

	SR	CAVR	p Value
n	28	29	—
Age (yr)	45.6	47.5	0.85
ED temperature (C)	33.92 (±1.4)	34.05 (±1.5)	0.76
ICU temperature (C)	33.3 (±1.3)	33.6 (±1.1)	0.10
Injury Severity Score	32 (±8.3)	31 (±9.3)	0.39
Gender (male)	18 (64%)	16 (55%)	0.48
Severe head injury	15 (52%)	15 (52%)	0.89
Severe chest injury	20 (71%)	17 (59%)	0.31
Severe abdominal injury	10 (36%)	10 (35%)	0.92
Severe extremity injury	16 (57%)	19 (66%)	0.52
Laparotomy	10 (36%)	20 (69%)	0.01
Systolic blood pressure at start of warming (mmHg)	112 (±43)	120 (±28)	0.18
Blunt mechanism (%)	86	83	0.75

SR = standard rewarming; CAVR = continuous arteriovenous rewarming.
* Severe injuries were those classified as having Abbreviated Injury Severity Score ≥3. Pearson chi square for categorical data and Mann-Whitney U test for continuous data.

core temperature ≥38 C, and a new or changed infiltrate on chest roentgenogram. Bacteremia was defined as a blood culture positive for a standard pathogen or two cultures positive for *Staphylococcus epidermidis*. A diagnosis of sepsis required a positive blood culture, fever, leukocytosis, and two organ system abnormalities not otherwise explained, or systemic vascular resistance <800 dyne-second/cm^5. Patients were considered to have sepsis syndrome if they met these criteria, but blood cultures were negative.

Complications were classified as inability to gain vascular access, hematoma or loss of pulses at the catheter insertion site, pseudoaneurysm formation, or compartment syndrome.

RESULTS

A total of 62 patients with hypothermia who required a pulmonary artery catheter were admitted to the ICU during the study period. Five patients were not randomized: three because of presence of a nonsurvivable head injury and two because of enrollment in competing studies. Of the remaining 57 patients, 28 were randomized to the SR group and 29 were randomized to receive CAVR. Age, gender, and ISS were similar between the two groups (Table 1). Severe chest injuries were slightly more common among patients who underwent SR (71% *vs.* 59%, p = 0.31), and patients who underwent CAVR were more likely to have undergone laparotomy (69% *vs.* 36%, p = 0.01).

Total fluid resuscitation requirements during the first 24 hours in the ICU was significantly less in patients who underwent CAVR (24,702 *vs.* 32,540, p = 0.05). This was most marked during the 0- to 8-hour period (12,548 ± 9641 mL *vs.* 8380 ± 8391 mL, p = 0.06). These increased volume requirements were reflected in all categories of infused products (Table 2). At 24 hours, circulating hemoglobin levels were slightly but not significantly greater in patients who underwent SR (11 g/dL *vs.* 10.3 g/dL, p = 0.56), suggesting an equivalent resuscitation endpoint. Two patients who underwent CAVR died in each of the 0- to 8- and 8- to 24-hour periods as compared to 8 and 5 of the patients who underwent SR in the same periods, respectively. The effect of these deaths on fluid requirements cannot be determined, but it is likely that fluid requirements in control group subjects were reduced by early death. As evidence, control subjects who died within 24 hours received more than five times as much fluid in the first hour (5771 ± 3407 mL *vs.* 1034 ± 750 mL) as did control subjects who survived 24 hours.

As shown in Figure 2, patients who underwent CAVR reached 36 C more rapidly and consistently than did the conventionally warmed patients, with most achieving 36 C within 3 hours (Mann–Whitney U = 96, p = 0.002). Rewarming was much less consistent in the SR group, with seven requiring more than 5 hours to reach 36 C. As patients who underwent CAVR were slightly warmer at the start of rewarming (33.2 C *vs.* 33.6 C), analysis of covariance was used to adjust for the potentially confounding effects of initial temperature. After adjustment, patients who underwent CAVR still were found to rewarm more rapidly (F = 16.6, p ≤ 0.001). The differences in

Table 2. VOLUME REQUIREMENTS

	SR	CAVR	p Value
Crystalloid 0–8 hr	9844 (±7039)	6289 (±4623)	0.04
Crystalloid 0–24 hr	23,916 (±14,446)	17,872 (±14,734)	0.08
Red blood cells 0–8 hr	5341 (±4824)	4179 (±4052)	0.34
Red blood cells 0–24 hr	6002 (±4935)	4941 (±4293)	0.48
FFP 0–8 hr	1412 (±1291)	1123 (±1507)	0.44
FFP 0–24 hr	2120 (±1622)	1669 (±1598)	0.23
Cryoprecipitate 0–8 hr	208 (±205)	139 (±194)	0.27
Cryoprecipitate 0–24 hr	387 (±419)	280 (±400)	0.16
Platelets 0–8 hr	449 (±514)	353 (±398)	0.49
Platelets 0–24 hr	535 (±537)	392 (±401)	0.32
Total volume 0–8 hr	12,548 (±9641)	8380 (±8391)	0.06
Total volume 0–24 hr	32,960 (±20,607)	25,154 (±20,723)	0.05

FFP = fresh frozen plasma; SR = standard rewarming; CAVR = continuous arteriovenous rewarming.

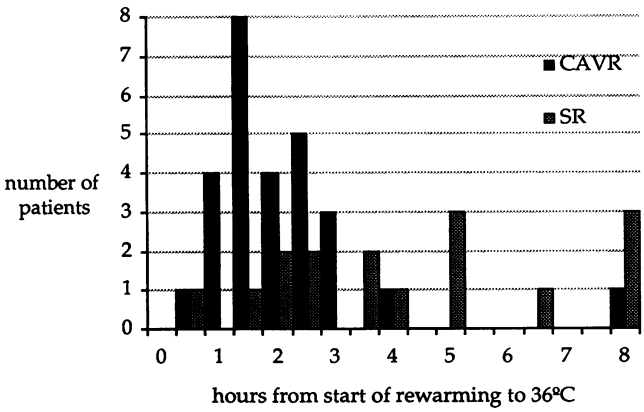

Figure 2. Time to rewarming to 36 C for standard rewarming and for patients who underwent continuous arteriovenous rewarming. Twelve patients who underwent standard rewarming and 2 patients who underwent continuous arteriovenous rewarming failed to rewarm to 36 C and are not included in the above graph.

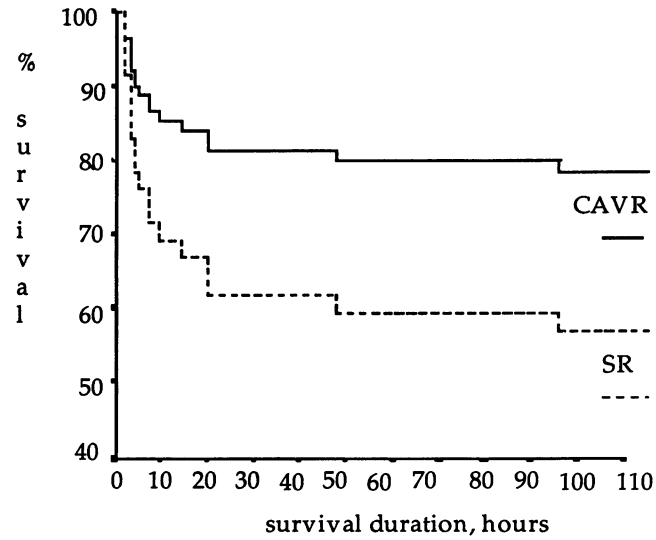

Figure 3. Adjusted cumulative survival (Kaplan–Meier), continuous arteriovenous rewarming *vs.* standard rewarming, p = 0.047.

rewarming rate were most noticeable during the initial 1.5 hours, at which time mean temperature was 35.6 C for patients who underwent CAVR and only 33.9 C for control subjects.

Of 57 patients, 43 were warmed successfully to a temperature of 36 C. The remaining 14 patients remained hypothermic, and all died within 8 hours of the start of rewarming. Patients who underwent CAVR were significantly more likely to be rewarmed successfully to 36 C (chi square = 9.94, p = 0.002), including after using logistic regression to control for the difference in initial temperature (odds ratio = 9.32, 95% confidence interval = 1.83–47.5). The ability to rewarm had a marked effect on mortality. Only 2 (7%) of 29 patients who underwent CAVR failed to warm to 36 C, and both died, whereas 12 (43%) of 28 conventionally warmed patients failed to reach 36°C, and all 12 died. Patients who underwent SR were less likely to die if they survived to reach 36 C, as only 2 of 14 deaths in this group were late deaths. In contrast, eight of ten deaths in the CAVR group occurred after successful warming to 36 C. This raised the possibility that rewarming predisposes to late deaths. However, it is likely that the higher early mortality rate in patients who underwent SR resulted in two groups that no longer had equivalent risk factors for late complications and death.

The survival curves of the two groups were significantly different. Kaplan–Meier survival analysis showed less early mortality in patients who underwent CAVR when compared to that in the SR group (p = 0.059). To control for the possible effects of additional factors on survival, Cox proportional hazards regression was used (Fig. 3). After controlling for the effects of head and abdominal injuries, CAVR was associated with a significant improvement in Kaplan–Meier survival (HR = 0.41, p = 0.047). No other clinical or demographic factors, including laparotomy, were identified as confounders or independent predictors of survival and were, therefore, excluded from the model.

Late deaths reduced the overall survival to discharge advantage in patients who underwent CAVR (CAVR 19/29, 66%, *vs.* 14/28, 50%; chi square = 1.41; p = 0.24). As expected with prolonged survival, the CAVR group had a longer ICU stay (16 *vs.* 9 days, p = 0.03) and a longer length of hospital stay (26 *vs.* 16 days, p = 0.02). Patients who underwent CAVR also were more likely to have ARDS develop (28% *vs.* 14%, p = 0.06), whereas remaining organ system failures and infectious complica-

Table 3. OUTCOMES*

	SR	CAVR	p Value
Time to 35 C (hr)	2.4 (±1.3)	1.4 (±1.0)	0.003
Time to 36 C (hr)	4.2 (±2.4)	2.3 (±2.5)	0.002
Survival to discharge	14 (50%)	19 (66%)	0.24
Hospital stay (days) (median)	7.5 (±17.1)	25 (±18.9)	0.018
Mechanical ventilation (days) (median)	4.5 (±10.3)	6.0 (±16.4)	0.031
ARDS	3 (11%)	9 (31%)	0.06
Sepsis	3 (11%)	4 (14%)	0.72
Pneumonia		8 (28%)	0.83
Acute renal failure	1 (4%)	1 (4%)	0.98
Hepatic failure	1 (4%)	1 (4%)	0.98

SR = standard rewarming; CAVR = continuous arteriovenous rewarming; ARDS = adult respiratory distress syndrome.

* Twelve of 28 control patients and two CAVR patients died before rewarming occurred, and are not included in rewarming times. Chi square for categorical data, Mann-Whitney-U test for continuous data.

Table 4. COAGULATION VALUES CONDUCTED AT PATIENT CORE TEMPERATURE (MANN-WHITNEY U TEST)

Time (hr)	SR		CAVR		p Value	
	PTT	PT	PTT	PT	PTT	PT
1	42.0	19.8	38.9	16.8	0.99	0.09
2	35.6	16.9	35.7	16.1	0.91	0.23
3	34.2	19.8	33.6	17.9	0.62	0.35
4	34.9	16.4	30.8	17.8	0.89	0.95

SR = standard rewarming; CAVR = continuous arteriovenous rewarming; PTT = partial thromboplastin time; PT = prothrombin time.

tions occurred at a similar frequency between groups (Table 3).

Comparison of coagulation parameters during the initial 4 hours did not show a difference between groups at any hourly interval (Table 4). However, patients who underwent SR received a greater amount of fresh frozen plasma and cryoprecipitate (1620 mL *vs.* 1262 mL), which may have affected these results. There were no differences in cardiac output or other hemodynamic parameters, although significant differences in oxygen transport and utilization were apparent (Table 5). This was most marked on the second postinjury day, with patients who underwent SR showing both higher oxygen consumption (157 *vs.* 136 mLO_2/m^2 per minute, $p = 0.04$) and oxygen delivery (641 *vs.* 526 mLO_2/m^2 per minute, $p = 0.02$). By 72 hours postinjury, both oxygen delivery and consumption were similar in the two treatment groups. As listed in Table 5, lactate levels increased during the initial 4 hours in control subjects and decreased in patients who underwent CAVR, although there were frequent missing values at 4 hours, preventing meaningful statistical comparison. Despite similar initial arterial pH, the CAVR group showed normal pH at 4 hours, whereas patients who underwent SR had continued acidosis pH (7.39 *vs.* 7.33, $p = 0.09$).

Weekly duplex examinations were obtained on patients who underwent CAVR while in the ICU. There were no venous complications identified. There were five complications in the CAVR group. A stopcock inadvertently was left closed on the CAVR tubing circuit in one patient, which resulted in clotting within the tubing. The procedure was abandoned, and the patient was rewarmed conventionally over 18 hours. In two patients, the femoral arterial catheter was left in place for 24 and 48 hours, in one for pressure monitoring and in the other for undetermined reasons. Both patients had small pseudoaneurysms develop. One resolved without treatment, and the other was taken to the operating room for arteriorrhaphy. In the patient requiring repair, the catheter was found to have been placed in the superficial femoral rather than in the common femoral artery. One patient had disseminated intravascular coagulation and had hemorrhage from both venous and arterial access sites after catheter removal, totaling an estimated 500 mL. One patient underwent arteriography after CAVR through the same femoral artery site using guidewire exchange and bleeding developed in this patient after removal of the angiography catheter, which required suture repair.

DISCUSSION

The protective effects of hypothermia during periods of low blood flow have been known since antiquity. Hippocrates advocated packing hemorrhaging patients in

Table 5. CARDIOPULMONARY DATA

	SR	CAVR	p Value
Lactate, start of warming	6.28 (±3.18)	6.04 (±3.26)	0.85
Lactate at 4 hr*	7.85 (+4.21)	4.02 (+2.75)	0.55
pH, start of warming	7.30 (±0.12)	7.33 (±0.13)	0.41
pH, 4 hr	7.33 (±0.13)	7.39 (±0.07)	0.09
Day 1 VO_2I†	153 (±42)	137 (±32)	0.26
Day 2 VO_2I†	157 (±28)	136 (±45)	0.04
Day 1 DO_2I‡	515 (±137)	468 (±117)	0.21
Day 2 DO_2I‡	641 (±79)	526 (±141)	0.02
Day 1 cardiac index	3.5 (±0.9)	3.4 (±1.0)	0.36
Day 2 cardiac index	4.4 (±0.9)	4.2 (±1.3)	0.51

SR = standard rewarming; CAVR = continuous arteriovenous rewarming.
* Based on six patients in each group.
† Oxygen consumption index.
‡ Oxygen delivery index.

snow and ice.[13] Napolean's chief battlefield surgeon, Baron de Larrey, noted that injured soldiers who sat closest to the fire usually were the first to die, and Bazzett[14] remarked on the increased survival of injured soldiers left in the snow compared to those treated with warm blankets and heated drinks. Contemporary surgeons were ambivalent about rewarming hypothermic injured soldiers during both World Wars, and the clinical application of cold even extended to battlefield casualties in Vietnam, where it was induced deliberately by French military surgeons.[15,16]

A number of animal studies have shown a beneficial effect of hypothermia on outcome from hemorrhagic shock.[17–20] Hypothermia allows up to 30 minutes of circulatory arrest with full neurologic recovery, whereas exsanguinating cardiac arrest while normothermic is universally lethal.[21] Even when induced after an ischemic insult, hypothermia results in benefits after experimental brain contusion, significantly improves neurologic outcome after prolonged ventricular fibrillation, and ameliorates experimental ischemic renal failure.[22,23] Hypothermia also has been shown to diminish capillary permeability associated with ischemia–reperfusion injury.[24–26] As a result of these laboratory findings, there has been some concern that attempts to aggressively rewarm severely injured hypothermic trauma patients are misguided.[27–29]

This randomized, prospective study refutes the hypothesis that hypothermia has a protective effect in adult trauma victims during resuscitation from major injury and showed that rapid rewarming improves the likelihood that resuscitation will be successful. It also supports our previous study, done in nonrandomized fashion, which noted a similar reduction in fluid requirements (20.4%) to that observed in this trial (21.6%). The differences in group mortality of trauma patients in that study (CAVR 36% *vs.* SR 58%) also were very similar to those observed in the current study (CAVR 34%, SR 50%). These consistent results suggest that mortality during initial resuscitation is increased by the concomitant presence of hypothermia. The fact that patients who underwent SR had a higher mortality rate than did patients who underwent CAVR while they still were hypothermic, but not after rewarming, adds further support to the presence of an adverse effect of hypothermia on survival during trauma resuscitation.

More late deaths occurred in the CAVR group, and the incidence of ARDS also was higher, which raises the potential that rewarming predisposes to late complications and death. However, it is likely that the increased early mortality in patients who underwent SR (43% *vs.* 7%) did not occur randomly, but occurred selectively in "sicker" patients, resulting in two groups that no longer had equivalent risk factors for complications and death after resuscitation. This would make subsequent comparisons suspect because of selection bias, as patients who died early may have been at higher risk for late complications and death. The increased early death rate in patients who underwent SR also may have affected comparisons of 24-hour fluid and blood product requirements, coagulation tests, arterial pH, and length of ICU and hospital stay. Time to rewarming also was influenced, as 43% of control group subjects died while still hypothermic, precluding meaningful comparison of rewarming times.

The lack of statistical significance in mortality to hospital discharge also raises the possibility that rewarming postpones, but does not prevent, death. However, this study could not test the effect of rewarming on survival to hospital discharge with a reasonable degree of power, despite a reduction in mortality of 32%. This would require a sample size of 132 patients in each group, and our prospectively defined stopping point required termination of the study if one group showed greater blood product and fluid requirements after 28 patients were included in each group. The finding that patients who underwent SR were more difficult to resuscitate and had higher overall mortality in both of our clinical trials provides consistent evidence that hypothermia during resuscitation increases mortality, although clinicians still are faced with subsequent complications due to infections and organ failure.

We attempted to determine the mechanism by which hypothermia affected mortality. One potential mechanism is its inhibitory effect on platelet aggregation and the clotting cascade. We previously showed that the effect of hypothermia on coagulation is more severe when superimposed on clotting factor depletion.[12] For this reason, differences in blood product and fluid resuscitation requirements were chosen as our primary outcome variable. However, we could not accurately determine whether the increased early mortality in patients who underwent SR was because of coagulopathic bleeding, despite greater blood loss, as patients who underwent SR also received a greater amount of transfused platelets and clotting factors, which may have offset some of the effects of hypothermia on clotting. The fact that coagulation assays were similar in both groups suggests that treatment with additional coagulation factors corrected for any effect of hypothermia on clotting.

There were no significant differences in cardiac output between groups; however, patients who underwent SR had consistently higher levels of oxygen delivery and consumption than did patients who underwent CAVR, which persisted for a 48-hour study period. The reasons for this were unclear. One potential explanation is that hypothermia during initial resuscitation resulted in an increase in physiologic stress, and changes in oxygen delivery and consumption were a compensatory reaction to added circulatory and metabolic demands. A metabolic defect that has been shown consistently in clinical studies of hypothermia is excess production of lactic acid.[30,31] The persistence of metabolic acidosis in patients who underwent SR but not patients who underwent CAVR suggests that restoration of oxidative me-

tabolism was delayed or prevented by hypothermia. Nevertheless, we could not detect a significant defect in cardiopulmonary function as an underlying cause for the early deaths in patients who underwent SR.

The increase in fluid requirements in patients who underwent SR was contrary to what has been reported in acute animal experiments, in which rewarming after ischemia has been associated with an increase in capillary permeability, which presumably augments fluid requirements. However, clinical studies have shown that edema is a frequent complication of prolonged hypothermia.[32]

Although hypothermia has been used therapeutically during open heart, transplant, and neurologic surgery, a potential benefit in trauma victims has not yet been identified. Perhaps the most interesting area for the use of hypothermia in the trauma victim lies in the realm of traumatic brain injury. However, preliminary studies investigating the use of moderate hypothermia in brain-injured patients excluded patients with hypoxia, hypotension, or severe injuries, and hypothermia (33 C) typically was not achieved until 10 or more hours after ICU admission.[33,34] The clinical application of hypothermia may therefore not be applicable to the severely injured trauma patient and may require methods to selectively cool the brain in patients with multiple injuries.

One of the potential weaknesses of this study design is that it did not enable us to assess the effect of hypothermia on patients before their arrival to the ICU. It is possible that hypothermia provides some benefit in the field, before the performance of necessary surgical procedures to stop blood loss. Testing this hypothesis would require an effective means of rapidly rewarming patients before hospital arrival or in the emergency department or during operative intervention. However, it is unlikely that the benefits associated with rewarming were caused by delaying its performance until procedures for stopping surgical blood loss already had been completed. Mean erythrocyte transfusion requirements for the entire study sample during the first 8 hours after ICU arrival was 4736 mL, corresponding to >15 units of packed erythrocytes. This ongoing blood loss, along with continued acidosis, suggests that patients continued to have ongoing bleeding and still were in shock when rewarming was initiated.

In conclusion, this randomized, prospective trial showed that persistent hypothermia in critically injured trauma patients increases fluid resuscitation requirements and increases the risk of early death. Decreasing the duration of hypothermia in the ICU by aggressive core rewarming decreased overall fluid requirements and increased the likelihood of successful resuscitation.

Acknowledgments

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Discussion

DR. FRANK R. LEWIS (Detroit, Michigan): I want to congratulate Dr. Gentilello and his colleagues on doing a very difficult study.

Studying patients this severely injured is always difficult and being able to randomize them and measure the multiple variables is a challenge. Their group has had a long and continuing interest in hypothermia and trauma and has contributed significantly to the therapeutic advances with the development of the passive arteriovenous (AV) rewarming circuit that was illustrated here. I think many others may begin to use that in coming years. The effects of hypothermia on patients have always been double-edged. Metabolic and oxygen demands are effectively reduced but multiple temperature-dependent enzymatic reactions are simultaneously disrupted.

In previous studies Dr. Gentilello has shown a major increase in trauma mortality with moderate hypothermia. Criticism of these studies, as he has pointed out here, is that they are retrospective and not well controlled. The present study was designed to correct this and provide randomized prospective data. To some extent it has succeeded, though not as positively as one would have hoped. I have several comments and questions.

In the present manuscript, the hypothesis is that hypothermia causes decreased survival. If so, it appears the hypothesis must be rejected because the difference in survival, 66% *versus* 50%, was not significantly different by chi square analysis. The caveat is that these were very severely injured patients and the underlying severity of injury may have obscured the effects of hypothermia.

In both groups the requirement was for around 10 units of transfusion, plus another 6 to 10 L of crystalloid in the first 8 hours. These were massively injured and massively resuscitated patients, a group that had a mortality of 50%, as can be seen. Would the effects of hypothermia have been more evident had patients been studied with lesser degrees of injury in which the injury itself was not so overwhelming? Second, the rapidly rewarmed group had longer intensive care unit (ICU) and hospital stay and a greater incidence of adult respiratory distress syndrome (ARDS), indicating generally more negative effects of rapid rewarming. These results are difficult to interpret because the severely injured patients in the conventional group had a much higher early mortality. The authors imply this was responsible for the difference. I would think they might segregate this out by some analysis of Injury Severity Score (ISS) in the groups that survived through the early period and by a comparison using ISS stratification in the later groups. Could they provide us with any information about that? A number of details regarding the patients that I would have liked to know in the study were not described. What were the actual causes of death and how many of the patients were basically nonsalvageable? How were the deaths causally related to the hypothermia? Finally, the authors made a point of the greater early fluid requirements in the conventionally warmed group as an outcome measure, but it is not clear that this is relevant or free of bias. They have not specified the end-point measures of resuscitation and have noted only in the manuscript that they were using standard protocols.

In a study of this type it is impossible for those participating in the study to be blinded to the study group, so the possibility of unintended bias in resuscitation end point exists.

Thus, can you specify the end points that were used and the degree to which they were followed? Why do you feel that the increase in resuscitative volume is an important end point measure?

DR. TIMOTHY C. FABIAN (Memphis, Tennessee): I would like to compliment the authors on a thought-provoking concept and manuscript. They have made an important contribution. The title of their paper is certainly appropriate: "Is Hypothermia in the Major Trauma Patient Protective or Harmful?" The question is valid but I don't believe it can yet be answered.

There are indeed three possible conclusions from the study. One, there are no differences in outcome between the treatment groups. Two, CAVR improves outcome. Or three, CAVR harms outcome. I believe the data can be used to support all three of these conclusions.

When evaluating a comparative study, I think it is helpful to look at the differences.

The significant differences in this study are higher laparotomy rate with CAVR, 69% *versus* 36%. Is this a bias against CAVR? I am not sure. There were lower 24-hour fluid requirements with CAVR, the major end point and hypothesis for the study. Lengths of hospitalization and mechanical ventilation were greater for CAVR and adult respiratory distress syndrome