PAPER

Delayed Fluid Resuscitation of Head Injury and Uncontrolled Hemorrhagic Shock

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Objective: To evaluate the effects of delayed vs early fluid resuscitation on cerebral hemodynamics after severe head injury and uncontrolled hemorrhagic shock.

Design: Prospective, randomized, controlled experimental trial.

Setting: Surgical research laboratory.

Participants: Immature swine (N=16) weighing 40 to 50 kg.

Interventions: Twelve swine were subjected to cryogenic brain lesion and hemorrhage to maintain a mean arterial pressure (MAP) of 50 mm Hg. Animals were randomized to receive 1 L of Ringer lactate solution in 20 minutes, starting 20 minutes after injury and hemorrhage, followed by 1 L of Ringer lactate solution in 30 minutes (ER group) (n=6), or no fluid resuscitation (DR group) (n=6). The 4 control animals underwent instrumentation only. The study ended 70 minutes after head injury and hemorrhage.

Main Outcome Measurements: Measurements of MAP, bilateral regional cerebral blood flow, serum hemoglobin level, systemic and regional cerebral oxygen delivery, and intracranial pressure performed at baseline and 20 (phase 1), 50 (phase 2), and 70 minutes (phase 3) after head injury and hemorrhage. Lesion size (percentage of ipsilateral cortex) was measured post mortem.

Results: All animals survived the experimental period. Systemic cerebral oxygen delivery in the DR group was significantly lower at phase 3 compared with that of the ER group (31.5% vs 53.1% at baseline) (P=.03). However, bilateral regional cerebral oxygen delivery was significantly greater in the DR group at phase 3 compared with that of the ER group (71.5% vs 47.0% at baseline in the injured side; 72.9% vs 48.4% at baseline in the noninjured side) (P=.02). Bilateral cerebral blood flow was similar in all groups at all times. The ER group showed a trend toward a greater intracranial pressure elevation (6.8 vs –0.25) (P=.07) and lesion size (37.0% vs 28.6%) (P=.07). Hemoglobin level became significantly lower in the ER group at phase 2 (7.0 vs 10.7) (P=.03) and remained lower at phase 3 (6.9 vs 11.7) (P=.01).

Conclusions: Early fluid resuscitation with Ringer lactate solution following head injury and uncontrolled hemorrhagic shock worsens cerebral hemodynamics. Cerebral pressure autoregulation is sufficiently intact following head injury to maintain regional cerebral oxygen delivery without asanguineous fluid resuscitation.

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DATA FROM a recent clinical prospective randomized trial have suggested that prehospital fluid administration in hypotensive trauma patients reduces survival when compared with delayed resuscitation (DR).[1] Confirmatory laboratory work has shown that aggressive fluid resuscitation of uncontrolled hemorrhage results in an increase in blood pressure and dilution of coagulation factors, leading to clot disruption at the site of bleeding and continued blood loss.[2] Although these studies are interesting and have challenged conventional thinking about resuscitation of hemorrhagic shock, none has addressed the issue of concomitant head injury—the leading cause of traumatic death in the United States.[3] When combined with severe head injury, hypotension doubles mortality by creating a secondary ischemic injury.[4] Thus, aggressive resuscitation with rapid elevation of blood pressure has been advocated in patients with head injury.[5] In fact, the recent guidelines for the management of head injury categorically state that "the concept of delayed resuscitation cannot be considered applicable in head injury."[6] We undertook this investigation to study the effect of DR on cerebral hemodymanics in a

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SUBJECTS AND METHODS

Mature swine weighing 40 to 50 kg were fasted overnight, but allowed free access to water. On the morning of the experiment, animals were sedated with intramuscular ketamine hydrochloride (20 mg/kg) and given intramuscular gentamicin sulfate (80 mg) and penicillin G potassium (1 million U). Animals were administered 3% halothane through a face mask, and an 18-gauge intravenous (IV) catheter was placed in an ear vein. Animals were then orotracheally intubated in the prone position and connected to a ventilator (Narkomed AVE; North American Drager, Telford, Pa). Halothane dose was decreased to 1.5% and then titrated to maintain constant jaw tension throughout the experiment. Respiratory rate was adjusted to keep end tidal carbon dioxide levels between 35 and 45 mm Hg using an end tidal carbon dioxide monitor (Datex 223; Puritan-Bennett Corp, Wilmington, Mass).

A cruciate scalp incision was made, and the calvarium was exposed. An area of the calvarium 3 cm in diameter was prepared to create a cryogenic lesion by removing the outer table of the skull using a power drill fitted with an engraving bit. The inner table of the skull was left intact. A copper reservoir fitted with a spout and a ventilation port was then attached using epoxy resin over the lesion site. A platinum electrode (Grass Electronics, West Warwick, RI) for measurement of CBF using the hydrogen clearance method was inserted through a burr hole positioned 1 cm anterior to the lesion site. A similar electrode was inserted in a topographically similar position in the right hemisphere. The burr holes were then sealed with epoxy resin. A fiberoptic intracranial pressure (ICP) transducer (Camino model 420; Camino, San Diego, Calif) was placed through a 2-mm twist bit hole in the right occipitoparietal region (**Figure 1**). Probes to measure CBF were connected to a polarimeter with a reference voltage of +0.6 V. The outputs of the polarimeter and ICP monitor were recorded on a strip chart recorder (Gould Instruments, Cerritos, Calif).

Animals were turned to the supine position and, under aseptic conditions, commercially available polyethylene catheters (PE200) were placed in the left axillary and femoral arteries and veins and in the right femoral artery for blood pressure monitoring, blood sampling, hemorrhaging, and IV fluid administration. A pulmonary artery catheter (American Edwards, Irvine, Calif) was placed for determination of central venous pressure (CVP), mean pulmonary artery pressure, cardiac output (CO), and core body temperature. Catheters were connected to pressure transducers; the readout was displayed on a monitor terminal (HP 78534B; Hewlett-Packard, Hartford, Conn). Through a small midline laparotomy, the ureters were exposed for cannulation with silicone rubber catheters for measurement of urine output. All incisions were closed in layers. Instrumentation was then allowed to equilibrate undisturbed for 45 minutes. Serial blood gas analysis ensured that arterial P_{O_2} was maintained at more than 100 mm Hg and P_{CO_2} was kept between 35 and 45 mm Hg for the duration of the experiment. Maintenance fluid (Ringer lactate solution [RL]) was delivered at 4 mL/kg per hour during instrumentation.

PHYSIOLOGIC MEASUREMENTS

After equilibration, the following measurements were made at baseline: mean arterial pressure (MAP), CVP, mean pulmonary arterial pressure, pulmonary artery wedge pressure, CO via thermodilution (model 9520A cardiac output monitor, American Edwards), CBF, ICP, fluid administered, urinary output, arterial and venous blood gas analysis using a pH-gas analyzer (model 170; Ciba-Corning, Medfield, Mass), levels of serum lactate, serum hemoglobin, and hematocrit, and intravascular blood volume (BV) via the Evan blue dye (EBD) method.

STUDY PROTOCOL

After the baseline measurements, we continued maintenance IV fluid in the control group only. The cryogenic brain lesion was made in the experimental groups by applying liquid nitrogen through the copper reservoir to the exposed inner table of the skull for 3 minutes. Simultaneous with the brain lesion, hemorrhage began via femoral artery catheters to reduce MAP to 50 mm Hg within 5 minutes. Hemorrhage was continued as necessary to maintain MAP at 50 mm Hg for the remainder of the study. Animals with lesions were then randomized to early fluid resuscitation (ER) or DR groups. Clinically relevant time frames were used to simulate traumatic injury and emergency medical response. Injury and hemorrhage occurred at zero time.

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model of simulated uncontrolled (pressure-driven) hemorrhage combined with cryogenic brain injury. We hypothesized that early (prehospital) fluid resuscitation would improve cerebral blood flow (CBF) and regional cerebral oxygen delivery (COD) compared with DR (operating room).

RESULTS

SYSTEMIC VARIABLES

There were no significant differences between the groups in MAP, CVP, pulmonary artery wedge pressure, mean pulmonary arterial pressure, CO, DO_2, or SVR at baseline (**Table**). Mean arterial pressure decreased from baseline in both experimental groups at phase 1 and remained significantly lower than that of controls. There was no significant difference between experimental groups in MAP during the study. Cerebral venous pressure decreased significantly in both experimental groups at phase 1 and remained lower than that of controls. At phase 3, CVP in the DR group was significantly lower than that in the ER group. Systemic vascular resistance was similar among all groups until phase 3, when it became significantly elevated in the DR group compared with controls. Pulmonary artery wedge pressure and mean pulmonary arterial pressure decreased significantly in both experimental groups at phase 1 and remained significantly below that of controls, but no differences occurred between groups.

Resuscitation volumes in the ER group averaged 1021±105 mL during phase 2 and 1091±60 mL during phase 3. Cumulative hemorrhage volume was similar between experimental groups until phase 3, when it became significantly greater in the ER group. Blood volume was similar in both experimental groups at baseline

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Phase 1 simulated ongoing hemorrhage for 20 minutes, during which MAP was maintained at 50 mm Hg. No fluids were administered to either group during this phase. Study variables were measured at the end of phase 1 (20 minutes). Phase 2 simulated emergency medical services arrival, stabilization, and transport to the emergency department. The ER animals received 1 L of RL via 18-gauge ear vein catheter in 30 minutes. The DR animals received no fluid. Hemorrhage continued in both groups to maintain MAP at 50 mm Hg. Study variables were measured at the end of phase 2 (30 minutes). Phase 3 simulated arrival at the emergency department, large-bore IV resuscitation, diagnosis of intra-abdominal hemorrhage, and operating room preparation. The ER animals received 1 L of RL in 20 minutes via femoral vein catheter. The DR animals received no fluid. Study variables were measured at the end of phase 3 (20 minutes). After phase 3, animals were killed using exsanguination in accordance with the 1993 recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. This protocol was approved by the Institutional Animal Care and Use Committee of the University of Vermont, Burlington.

BRAIN PREPARATION

Brains were retrieved immediately after exsanguination and set in agar. Thin (6-mm) slices were made beginning 1 mm anterior and ending 1 mm posterior to the lesion. Slices were incubated in 2% 2,3,5-triphenyltetrazolium chloride, which is taken up by viable mitochondria, staining viable tissue red while leaving nonviable tissue white.[7] Incubation lasted 30 minutes. Lesions were imaged with a camera (Chromachip II model JE3462RGB; Javelin Electronics, Tokyo, Japan) and sized less than 60 minutes after brain retrieval, using digital imaging analysis software (Optimas, Bioscan Inc, Edmonds, Wash), by measuring the area of nonviable tissue and dividing by the area of the ipsilateral cerebral cortex. Lesion size was reported as percentage of ipsilateral cortex.

INTRAVASCULAR BLOOD VOLUME MEASUREMENT

Evan blue dye (0.8%) was used for plasma volume measurements at baseline and phases 1 and 3. A blood sample was drawn from a femoral vein catheter before dye injection. Evan blue dye was drawn into a syringe and weighed. Approximately 2.5 mL was injected into a femoral vein catheter followed by 15 mL saline solution, so that no dye was visible in the catheter. The syringe was reweighed, and the volume of injected dye was calculated from the difference in weight. At 10 minutes after injection, 10 mL of blood was drawn from an arterial catheter. Blood samples were centrifuged at 2550 revolutions per minute for 30 minutes, and the plasma fraction was drawn off. A plasma blank and a calibration standard were made by adding 7.5 mL 0.9% normal saline solution and 7.5 mL EBD, respectively, to 2292.5 mL plasma obtained before dye injection. All samples were analyzed for absorbance at 620 nm and 740 nm on a spectrophotometer (Spectronic 1001; Bausch & Lomb, Rochester, NY). Since EBD absorbs maximally at 620 nm and minimally at 740 nm, absorbance of EBD was taken to be the difference between absorbance at 620 and 740 nm. Actual absorbance for the calibration standard was obtained by subtracting EBD absorbance of the plasma blank from that of the calibration standard. Actual absorbance for the BV measurements at phases 1 and 3 were obtained by subtracting EBD absorbance before dye injection from EBD absorbance after dye injection. At least 1 hour elapsed between each measurement. Plasma volume was calculated using the formula of Gibson and Evans.[8] Corrections were made for trapped plasma (0.91) and whole body hematocrit (Hct) measurements (0.96). Blood volume was then calculated using the formula BV=plasma volume×[100/(100−Hct)].

DATA MANAGEMENT AND ANALYSIS

Continuous variables are reported as mean±SEM. Differences between groups were evaluated using analysis of variance. Multiple comparisons against the control group were performed using the Dunnett test. Differences within groups were evaluated using the paired Student *t* test. Systemic cerebral oxygen delivery (DO_2) was calculated using the formula $DO_2=CO\times O_2$ content. Regional cerebral oxygen delivery was calculated using the formula $COD=CBF\times O_2$ content. Systemic vascular resistance (SVR) was calculated using the formula SVR=(MAP−CVP)/CO. Significance was attributed to $P<.05$.

and decreased significantly below baseline in both at phase 1. Blood volume remained significantly below baseline in both experimental groups at phase 3. Although the BV was higher in the ER group at phase 3, this difference was not statistically significant ($P=.07$).

Cardiac output in both experimental groups was significantly less than that of controls at phase 1. However, CO in the ER group increased at phases 2 and 3 such that there was no significant difference from controls. Cardiac output in the DR group remained significantly less than that of controls (**Figure 2**). Systemic cerebral oxygen delivery decreased significantly in both experimental groups in phase 1, and did not change in the ER group through phases 2 and 3. In the DR group, DO_2 continued to decrease such that at phase 3 it was significantly lower than in the ER group (**Figure 3**). Serum hemoglobin level was unchanged in the control and DR groups during the entire study. Serum hemoglobin levels decreased in the ER group at phase 2 and were significantly less than in the control and DR groups at phases 2 and 3. Serum lactate levels increased slightly in the DR group. In the ER group, lactate levels increased substantially such that at phase 3, they was significantly greater than at baseline and in controls. Arterial pH was similar between all groups at baseline. In both experimental groups, arterial pH decreased significantly compared with baseline at phases 2 and 3. No differences in pH occurred among groups at any time (Table 1).

CEREBRAL VARIABLES

There were no significant differences between groups in ICP, cerebral perfusion pressure (CPP), CBF, or COD at baseline. Intracranial pressure in the control and DR groups did not change from baseline during the study. Intracranial pressure increased steadily in the ER group

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and was significantly greater than baseline at phase 3. The difference in ICP between the experimental groups at phase 3 approached but did not reach statistical significance (P=.07). Cerebral perfusion pressure in controls did not differ from baseline during the study. Cerebral perfusion pressure decreased at phase 1 in both experimental groups and remained significantly lower than that in controls for the remainder of the study. No differences in CPP occurred between experimental groups at any time (**Figure 4**). Cerebral blood flow and COD did not differ from baseline in the control group at any time. Cerebral blood flow in the lesioned and nonlesioned hemispheres in both experimental groups decreased significantly from baseline at phase 1, but did not differ statistically from that of controls. Cerebral blood flow remained significantly below baseline in both experimental groups (**Figure 5**). Regional cerebral oxygen delivery decreased significantly from baseline in both experimental groups at phase 1. At phase 2, COD in the DR group reached its lowest point and began to improve at phase 3. No significant differences in COD existed between the DR and control groups during the study. Regional cerebral oxygen delivery in the ER group continued to decrease at phases 2 and 3. At phase 3, COD in the ER group was significantly less than that of the DR and control groups (**Figure 6**). Lesion size was greater in the ER animals (37.0%±3.1% vs 28.6%±2.7%), but the difference did not quite reach statistical significance (P=.08).

COMMENT

Crystalloid solutions are routinely administered to hypotensive trauma patients in the prehospital setting. However, recent clinical and laboratory studies have shown that early asanguineous fluid resuscitation of trauma victims in hemorrhagic shock actually decreases survival.[1,2] A prospective, randomized clinical trial of patients with penetrating torso trauma compared standard prehospital fluid resuscitation to no resuscitation until operative intervention.[1] The study showed that patients who received prehospital resuscitation had a greater incidence of coagulopathy, lower serum hemoglobin levels, and decreased survival to discharge. The selective patient population, however, prevented the results of that study from being extrapolated to hypotensive patients with severe head injury. In fact, caution has been recommended in applying the results of that study to patients with head injury, since aggressive prehospital resuscitation has been advocated to prevent secondary ischemic injury.[6]

The injured brain is vulnerable to secondary ischemic injury when persistent hypotension allows ongoing cerebral ischemia.[9] Viable cells in the ischemic penumbra may be salvaged with prompt return of cerebral oxygen delivery.[10] It has been asserted that early resuscitation would improve CPP, thereby decreasing ischemia time. Cerebral perfusion pressure is dependent on MAP and ICP by the relationship in the formula CPP=MAP−ICP. Recent experimental models of uncontrolled hemorrhagic shock show that MAP elevation is not sustained after resuscitation with standard crystalloid solutions. Attempts to restore MAP with crystalloid

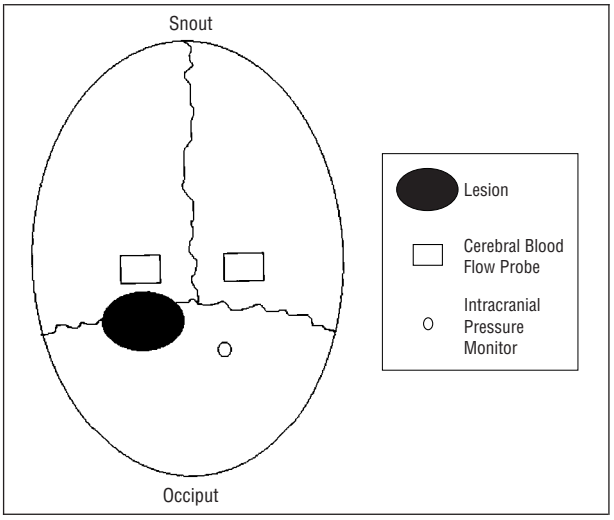

Figure 1. *Schematic of cranial instrumentation showing relationship of probes to lesion site.*

have resulted in greater hemorrhage volumes and only transient elevations in MAP.[2,11] In addition, animals resuscitated with standard crystalloid solutions after head injury and shock have significant elevations in ICP as a result of increased cerebral water content.[10] These observations predict that CPP would not be elevated, despite fluid resuscitation in uncontrolled hemorrhagic shock. However, we are unaware of any studies that have measured CPP after hypotension and head trauma in a model of uncontrolled (pressure-driven) hemorrhage.

The model we designed results in similar physiologic perturbations as those observed in aortotomy or organ injury models of uncontrolled hemorrhage. The MAP was rapidly brought to 50 mm Hg and then kept constant in both treatment groups. We chose to keep the MAP at 50 mm Hg because models of uncontrolled hemorrhagic shock have shown that, regardless of resuscitation, MAP remains approximately 40 to 60 mm Hg after a very transient elevation in the treated group.[2,9,12] The hemorrhage volumes of 1077±96 mL (22.9 mg/kg) in the DR group and 1415±113 mL (30 mg/kg) in the ER group are similar to results obtained by Matsouka et al[11] in their murine model of uncontrolled liver hemorrhage (21.5 mg/kg in the untreated group and 26.9 mg/kg in the treated group). Bickell et al[1] demonstrated much larger differences in hemorrhage volume between groups (783 mL in the untreated group vs 2142 mL in the treated group) in a swine model of aortic laceration, but their resuscitation volume (80 mL/kg in 9 minutes) was much larger than ours (42 mL/kg in 50 minutes). We used resuscitation volumes that were similar to those reported in clinical trials of resuscitation from hemorrhagic shock.[1,13]

Although MAP was kept constant between experimental groups, CO improved with resuscitation in the ER group. This was most likely due to increased filling pressures and decreased blood viscosity from hemodilution.[14,15] Hemodilution can also cause direct vasodilatation in the microcirculation,[14] which may have contributed to the lower SVR in the ER group. Despite the improved CO, DO_2 failed to increase with resuscitation. The failure of DO_2 to improve can be explained by the offsetting ef-

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Systemic and Cerebral Hemodynamics*

Variable	Study Interval			
	Baseline	Phase 1	Phase 2	Phase 3
MAP, mm Hg				
Controls	96.0 ± 4.7	94.3 ± 3.6	84.5 ± 2.7	85.5 ± 2.3
ER	84.7 ± 3.2	50.8 ± 1.2†‡	53.0 ± 1.6†‡	53.2 ± 3.9†‡
DR	90.5 ± 2.1	51.2 ± 0.5†‡	50.3 ± 0.8†‡	48.8 ± 2.3†‡
CVP, mm Hg				
Controls	15.8 ± 1.3	16.0 ± 1.2	16.3 ± 0.6	16.3 ± 1.0
ER	16.7 ± 2.6	10.0 ± 2.1†‡	10.0 ± 0.7†‡	11.6 ± 0.9‡§
DR	12.6 ± 2.1	7.8 ± 1.6†‡	8.6 ± 1.6†‡	6.6 ± 1.1†‡
SVR, dynes/s per cm^2				
Controls	1011.0 ± 52.3	977.1 ± 231.0	872.9 ± 55.3	815.2 ± 56.3
ER	1134.0 ± 141.0	1363.0 ± 266.0	1240.0 ± 193.0	1225.0 ± 212.0
DR	1140.0 ± 49.0	1492.0 ± 231.0	1521.0 ± 251.0	2373.0 ± 552.0‡
MPAP, mm Hg				
Controls	28.5 ± 1.7	28.3 ± 2.3	25.5 ± 2.5	28.9 ± 2.6
ER	25.4 ± 2.4	18.4 ± 2.3‡	18.1 ± 1.7‡	20.1 ± 1.1‡
DR	25.4 ± 1.7	17.3 ± 1.2‡	18.8 ± 1.1‡	19.7 ± 1.9‡
PAWP, mm Hg				
Controls	17.3 ± 2.1	18.8 ± 1.3	16.3 ± 0.5	17.5 ± 1.2
ER	15.2 ± 1.9	9.8 ± 1.0‡	10.0 ± 1.0‡	9.8 ± 0.8‡
DR	17.0 ± 2.0	10.0 ± 2.1‡	8.4 ± 1.4‡	7.6 ± 0.9‡
ICP, mm Hg‖				
Controls	0.0	2.5 ± 1.6	3.3 ± 1.4	3.8 ± 1.6
ER	0.0	1.2 ± 1.0	5.3 ± 2.2	6.8 ± 2.2†
DR	0.0	0.0 ± 3.2	−0.3 ± 2.6	−0.3 ± 2.4
CPP, mm Hg‖				
Controls	0.0	−4.3 ± 2.5	−14.8 ± 5.2	−14.0 ± 4.9
ER	0.0	−35.0 ± 4.5†‡	−37.0 ± 3.5†‡	−37.3 ± 4.4†‡
DR	0.0	−40.3 ± 4.8†‡	−41.5 ± 2.5†‡	−41.3 ± 4.6†‡
HgB, g/L				
Controls	92 ± 1	92 ± 2	92 ± 2	91 ± 1
ER	97 ± 5	92 ± 6	70 ± 3†‡§	69 ± 5†‡ SM §
DR	104 ± 3	99 ± 4	107 ± 6	117 ± 8
pH				
Controls	7.41 ± 0.01	7.42 ± 0.01	7.43 ± 0.01	7.44 ± 0.01
ER	7.41 ± 0.02	7.44 ± 0.03	7.33 ± 0.05†	7.31 ± 0.05†
DR	7.43 ± 0.01	7.42 ± 0.02	7.32 ± 0.04†	7.37 ± 0.02†
Lactate level, mmol/L				
Controls	1.50 ± 0.12	1.53 ± 0.11	1.30 ± 0.09	1.38 ± 0.10
ER	1.74 ± 0.12	1.84 ± 0.16	4.40 ± 1.30	5.82 ± 1.00†‡
DR	1.92 ± 0.23	2.20 ± 0.41	3.14 ± 0.71	3.96 ± 0.86
Hemorrhage volume, mL				
ER	. . .	824 ± 99	1222 ± 97	1415 ± 113§
DR	. . .	950 ± 97	1055 ± 92	1077 ± 96
Blood volume, mL				
ER	3718 ± 154	2926 ± 321†	. . .	2728 ± 298†
DR	3450 ± 202	2504 ± 204†	. . .	2374 ± 219†

*MAP indicates mean arterial pressure; ER, early resuscitation group; DR, delayed resuscitation group; CVP, central venous pressure; SVR, systemic vascular resistance; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; HgB, serum hemoglobin level; and ellipses, not applicable. Phases are described in the "Study Protocol" subsection of the "Subjects and Methods" section.

†P<.05 vs baseline.

‡P<.05 vs control group.

§P<.05 vs DR group.

‖Given as change from baseline.

fects of hemodilution. In addition to decreasing blood viscosity, hemodilution decreases oxygen-carrying capacity by diluting serum hemoglobin levels, thereby worsening DO_2. The continued decrease in CO and DO_2 in the DR group reflects the ongoing state of severe hemorrhagic shock characterized by a high SVR and a low CVP. However, despite the significantly lower DO_2, the DR group showed a trend toward a lower serum lactate level and higher pH than the ER group at phase 3; this suggests better oxygen use or lower oxygen requirements at the cellular level. Others have shown that oxygen consumption changes little in untreated hemorrhagic shock, but it becomes impaired when asanguineous fluids are administered as treatment.[2] Unfortunately, we were unable to evaluate oxygen consumption due to technical difficulties with venous blood gas measurements. This difficulty, however, is not unique to our study, as another group has reported similar difficulty.[12]

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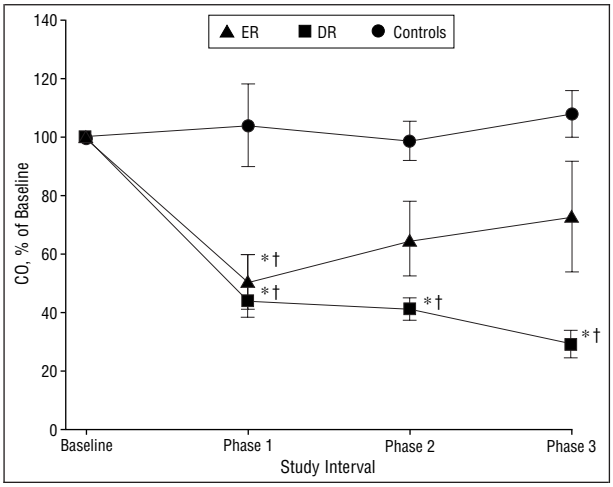

Figure 2. *Changes in cardiac output (CO) during study. ER indicates early resuscitation group; DR, delayed resuscitation group; asterisk,* P<*.05 compared with baseline; and dagger,* P<*.05 compared with control group. Phases are described in the "Study Protocol" subsection of the "Subjects and Methods" section.*

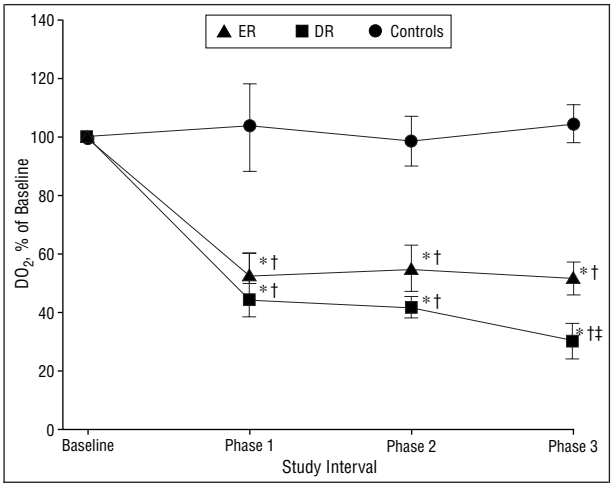

Figure 3. *Changes in systemic cerebral oxygen delivery (DO_2) during study. ER indicates early resuscitation group; DR, delayed resuscitation group; asterisk,* P<*.05 compared with baseline; dagger,* P<*.05 compared with control group; and double dagger,* P<*.05 compared with ER group. Phases are described in the "Study Protocol" subsection of the "Subjects and Methods" section.*

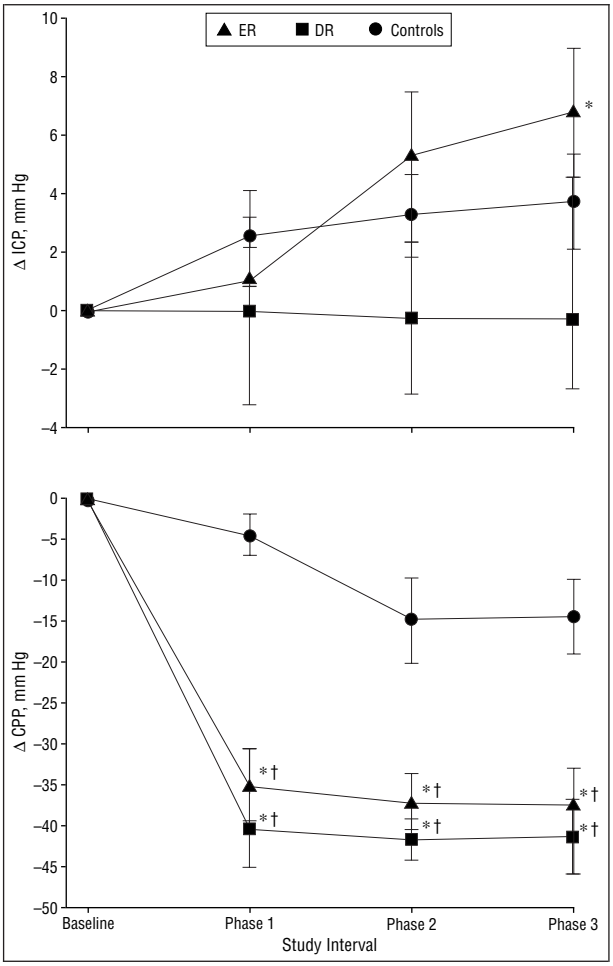

Figure 4. *Changes in intracranial pressure (ICP) (top) and cerebral perfusion pressure (CPP) (bottom) during study. ER indicates early resuscitation group; DR, delayed resuscitation group; asterisk,* P<*.05 compared with baseline; and dagger,* P<*.05 compared with control group. Phases are described in the "Study Protocol" subsection of the "Subjects and Methods" section.*

The ICP in the ER group was significantly greater than baseline and demonstrated a strong trend toward being greater than that of the DR group (P=.07). This was not due to MAP, which was similar between experimental groups. Rather, the elevation in ICP in the ER group was likely due to a reduction in the intracranial compliance brought about by the increase in CVP and intracellular swelling due to RL administration. Harini et al[16] have shown that increasing the CVP following shock and brain injury reduces intracranial compliance. It has been shown that fluid resuscitation with RL increases cerebral water content, which also decreases intracranial compliance.[10] Reduced intracranial compliance results in a more rapid increase in ICP as vasogenic edema develops after the cryogenic injury.[17]

The bilateral decrease in CBF in both experimental groups after lesion and hemorrhage was not as pronounced as the change in CO or DO_2 and was not significantly different from that of the control group. This suggests that cerebral autoregulation remained relatively intact in hemispheres with and without lesions. Interestingly, CBF in the ER group did not improve with resuscitation, although CO in this group improved to nearly 75% of baseline. Cerebral blood flow is dependent on CPP and cerebral vascular resistance (CVR) according to the formula CBF=CPP/CVR. Cerebral autoregulation results in relaxation of vascular smooth muscle to minimize CVR, thereby maximizing CBF during hypotension.[18] Our results indicate that CVR is equal in the experimental groups because CPP and CBF are equal at each time. However, this does not take into account the decrease in blood viscosity, which resulted from hemodilution, in the ER group. As mentioned above, a lower fluid viscosity reduces resistance to flow. Poiseuille's law ($Q=\pi\Delta Pr^4/8\eta L$) states that flow (Q) is proportional to the pressure gradient (ΔP) across a conduit multiplied by the radius of the conduit (r) to the fourth power and is inversely proportional to the length (L) of the conduit multiplied by the fluid viscosity (η). When Poiseuille's law is applied to the cerebral vascular system, Q is

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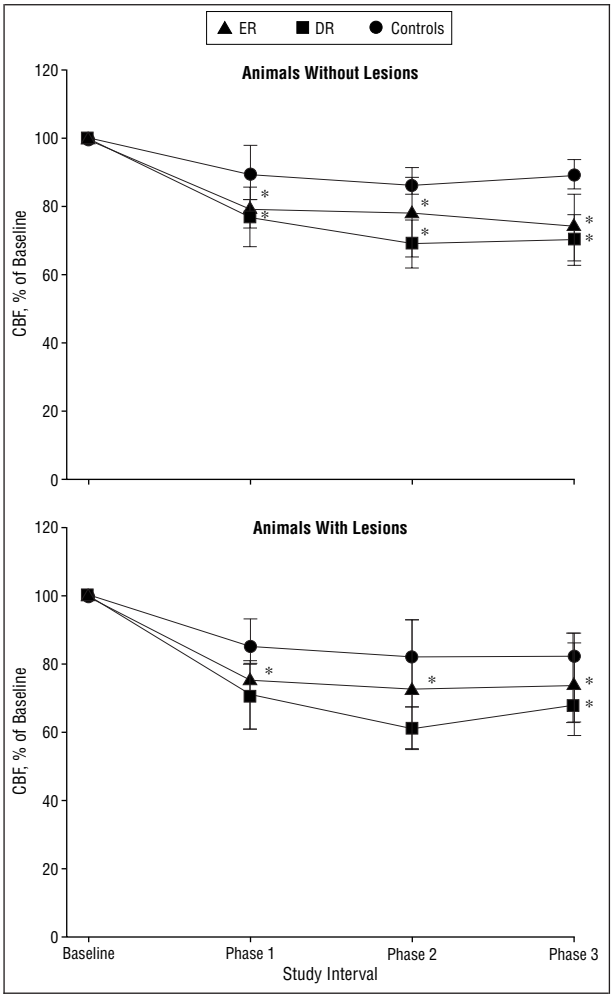

Figure 5. *Changes in cerebral blood flow (CBF) during study. ER indicates early resuscitation group; DR, delayed resuscitation group; and asterisk, P<.05 compared with baseline. Phases are described in the "Study Protocol" subsection of the "Subjects and Methods" section.*

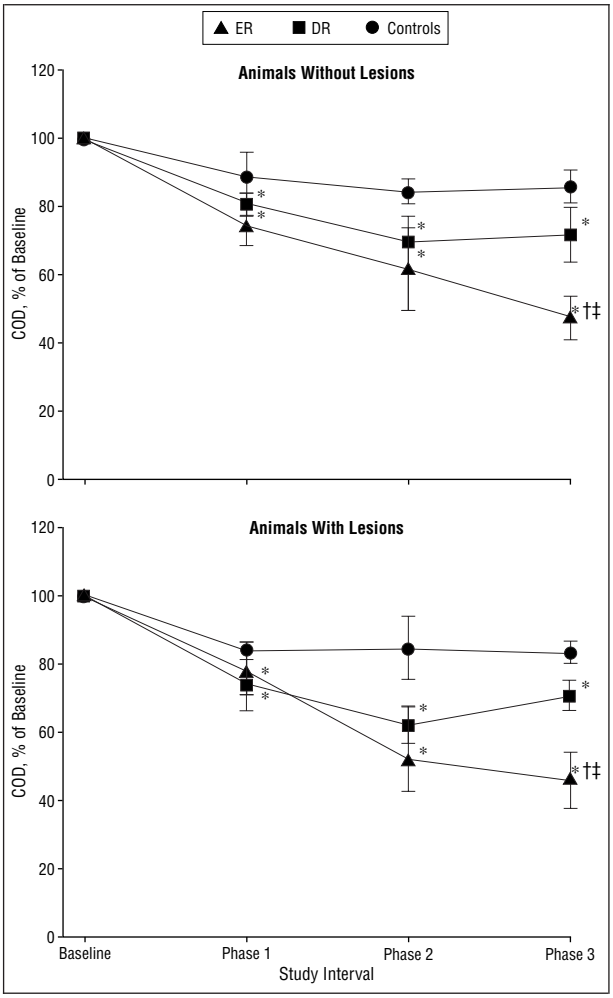

Figure 6. *Changes in regional cerebral oxygen delivery (COD) during study period. ER indicates early resuscitation group; DR, delayed resuscitation group; asterisk, P<.05 compared with baseline; dagger, P<.05 compared with control group; and double dagger, P<.05 compared with ER group. Phases are described in the "Study Protocol" subsection of the "Subjects and Methods" section.*

substituted for CBF; ΔP, for CPP; and $\eta L/r^4$, for CVR. The length of the cerebral vessels (L) is assumed to be constant between groups; the viscosity of blood (η) becomes less in the ER group as serum hemoglobin levels become significantly lower; and r is substituted for the intraluminal diameter of the cerebral vasculature. We propose that for CVR to remain constant despite a decrease in η in the ER group, r must also decrease. Since the term for CVR is inversely proportional to the fourth power of r, only small changes in r are required to cause significant effects. Several processes may have occurred that could account for our results. Shock followed by fluid resuscitation with RL leads to endothelial cell swelling,[19] capillary plugging with polymorphonuclear leukocytes,[19,20] and a decrease in pial arteriolar diameter.[21] Endothelial cell swelling and capillary plugging can occur following shock alone, but our results suggest that resuscitation with RL may exacerbate these processes. Interestingly, Mazzoni et al[19] have shown that luminal narrowing and decreased red blood cell flux, caused by swelling of skeletal muscle endothelial cells during shock, is reversed by resuscitation with hypertonic saline solution but not improved by resuscitation with RL. Another possible explanation for our results is that cerebral autoregulation is attenuated after RL resuscitation. It has been shown that pial arteriolar diameter is decreased, relative to that of controls, 1 hour after resuscitation with RL but not with hypertonic saline solution.[21] Wahl et al[22] observed the effects of osmolarity on pial arteriolar diameter and found that constriction of pial arterioles occurs with osmolarity below 317 mOsm/L, and progressive dilatation occurs at osmolarities above this level. Loss of autoregulatory vasodilation in the ER group may have prevented CVR from decreasing, despite a decrease in blood viscosity.

An important finding in our study is the significantly higher COD in the DR group after resuscitation. The ability to maintain CBF during shock without requiring fluid resuscitation—thus avoiding the inherent hemodiluting effects—allowed the DR group to have a significantly improved COD at phase 3. The improved COD, despite a lower DO_2 at phase 3, substantiates the highly conserved ability to autoregulate CBF in this group.

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The smaller lesions in the DR group may be associated with an earlier improvement in COD. Vulnerable but viable cells in the ischemic penumbra may be salvaged by earlier return of COD.[10] Alternatively, the ER group may have suffered a more severe insult, which resulted in a larger lesion. This is unlikely, however, as consistency in lesion size in "lesion-only" animals has been found using this technique in a 7-year experience.[9]

Several clinical studies show the detrimental effects of hypotension when combined with severe head injury,[4,23] but none has demonstrated that CBF or COD is improved with prehospital fluid resuscitation. Only 1 clinical trial has demonstrated an improved outcome in hypotensive patients with severe head injury after prehospital fluid resuscitation. In a multicenter, double-blinded, randomized trial, post hoc logistic regression showed that improved survival to discharge in hypotensive patients (MAP<90 mm Hg) with Glasgow Coma Scale scores of 8 or greater was significantly correlated with hypertonic saline solution as a treatment compared with RL. That study, however, did not include a DR group.[24] However, based on this study, recent recommendations set forth by a head injury guidelines task force categorically exclude head-injured patients from delayed resuscitation protocols.[6] Laboratory studies that recommend early, aggressive (prehospital) fluid resuscitation after hemorrhagic shock and head trauma make the assumption that COD is improved with asanguineous resuscitation.[21,25-27] These studies were undertaken to evaluate the effects of different resuscitation fluids on cerebral hemodynamics, but none contained a DR group.

This is the first study, to our knowledge, that evaluates cerebral hemodynamics following head injury and unresuscitated hemorrhagic shock. Our results suggest that prehospital resuscitation with RL after uncontrolled hemorrhage and severe head injury worsens cerebral hemodynamics and may contribute to secondary brain injury (ie, increased lesion size). Our results cannot be extrapolated to include other asanguineous fluids such as hypertonic saline solution or diaspirin cross-linked hemoglobin, which are superior to RL in improving CBF while maintaining a low ICP.[7,27] Furthermore, our report, in conjunction with others showing improved survival following delayed fluid resuscitation, suggests that further studies to evaluate the effect of delayed fluid resuscitation after head injury and shock are needed.

Some caution regarding interpretation of our data is warranted. The study was short; we only studied the animals for 70 minutes. It is conceivable that the DR animals would have shown similar changes in ICP, COD, and lesion size with resuscitation. Our model was simulated uncontrolled hemorrhage. Although we believe the model to be a reasonable representation of the clinical scenario, a large animal model of actual organ injury is needed.

Despite these flaws, our results suggest that prehospital fluid administration actually decreases COD while increasing ICP and lesion size.

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DISCUSSION

Erwin F. Hirsch, MD, Boston, Mass: Dr Bourguignon and his coauthors have developed a very interesting experimental model to compare early and delayed resuscitation following major hemorrhage and closed head injury. The rationale for such study is based on the current recommendations by the neurosurgical community, which mandates the maintenance of MAP by means of IV therapy for those patients with closed head injury and additional evidence of hemorrhage. Such therapeutic efforts are primarily directed to the maintenance of cerebral perfusion pressure and as such to hopefully minimize secondary head injury.

While patients whose injuries do not include closed head injury should be transported without delay, probably without administration of IV fluids, I want to remind this audience that the paper that was published from Houston is open to a lot of debate and discussion, and the book has not been closed yet as to the value or nonvalue of resuscitation. Furthermore, it was not Dr Maddox who started with this. Frank Lewis in San Francisco many years ago developed a very interesting mathematical model which said that the IV fluids administered in the prehospital system really do not contribute very much to survival of patients.

The hemodynamic changes that were presented in the model today were the ones that we all probably would have expected. However, there were some interesting findings in cerebral metabolism that were perhaps unexpected. Number one, the cerebral oxygen delivery was higher in the nonresuscitated group than the resuscitated group. Probably this was a mathematical issue, since probably the cardiac output of the resuscitated animals did not elevate sufficiently to counterbalance the decrease in hematocrit. Cerebral blood flow was similar in both groups of animals. The point of the conclusions of the authors is that they believe that the cerebral autoregulation is sufficiently intact in their model to maintain cerebral oxygen delivery. I have several questions.

Why did you interrupt your study at 70 minutes? In real life, these times from EMS arrival to definitive care are significantly longer.

Dr Shackford in several different presentations has demonstrated the positive effects of hypertonic saline in the resuscitation of hypovolemic shock. Why didn't you include a third arm of using hypertonic saline to see the effect of hypertonic saline in this model?

Patients sustaining closed head injuries rarely sustain hemorrhagic injuries that are very easy to control. Would you speculate for us what type of monitoring methodology you would suggest for those patients with closed head injury and complex orthopedic and other injuries, which may take a significant period of time before hemorrhage is controlled?

David W. Butsch, MD, Barre, Vt: Do you have a hypothesis as to why the resuscitation lowers the cerebral oxygen delivery?

Jeremy R. Morton, MD, Portland, Me: There are several parallels that can be drawn between the observations described by the authors and our military experience in recent years. One of the very few redeeming features of war is the experience and knowledge it provides in the care of traumatic injuries. You will recall that World War II brought great advances in volume resuscitation in the field using plasma. This was a critical, life-saving measure, since the logistics at that time required that the wounded soldiers be transferred first to a battalion aid station, then to a clearing company, and finally to an evacuation hospital or field hospital before definitive surgery could be performed.

During our experience in Korea and in Vietnam, there were no real front lines, and the wounded could be transferred directly and quickly from the battle sites to nearby surgical hospitals using helicopters. We discovered that starting IVs on patients in the field was generally not time well spent and that even severely injured soldiers generally fared better if they were transferred directly, without volume resuscitation. The studies described here this morning have added some important science to those observations made in the battlefield and will perhaps stimulate a closer look at the way domestic trauma victims are currently treated at the site of injury.

Kenneth W. Burchard, MD, New Lebanon, NH: Since we all understand that the duration of hypoperfusion exacerbates or increases the amount of ischemia reperfusion injury that follows once the reperfusion is reestablished, would the authors speculate on what happens to the brain once the full resuscitation was actually in place after the delayed resuscitation effort.

Dr Bourguignon: In answering the first question, "Why is the study so short?" initially our question was, "What's happening in the first hour, the golden hour of trauma resuscitation?" So, we wanted to focus our study on this time period. We do have ongoing laboratory efforts to prolong this study. In fact, we are developing a model of true hemorrhagic shock and head injury to improve on this simulated hemorrhagic shock model. Our plans are to expand the study time to evaluate the effects of resuscitation more thoroughly.

Dr Burchard, this will also answer your question. We do need to find out what happens to the delayed resuscitation animals after they receive resuscitation fluids. The difference between the 2 groups will be that when the delayed group is resuscitated, it will be with blood products and crystalloid, so theoretically, the effects of dilution will not occur. The results remain to be seen.

The next question asked about the continuous and similar blood pressure between the 2 groups. Many studies have shown that, following uncontrolled hemorrhage and standard crystalloid resuscitation, MAP remains depressed, except for, possibly, a very transient elevation following resuscitation attempts. Mean arterial pressure in the resuscitated groups does not differ significantly from the nonresuscitated or delayed resuscitation groups. Our model was designed to emulate these findings. We realize the model is not perfect; as I mentioned, we are working on a true uncontrolled hemorrhage model to verify these results. There was a clinical trial from Sacramento and Dr Holcroft's group, which compared hypertonic saline to RL resuscitation in the field. They showed that the hypertonic saline group had a higher MAP in the emergency room. In a subset of those patients with a Glasgow Coma Score of less than 8, survival to discharge was improved. We do plan to look at hypertonic saline using this model in future studies.

Another question asked about orthopedic injuries. I believe part of the question asked about an injured extremity and what to do with combined extremity and head injury. The hemorrhage from extremity injuries is easily controlled. This is, in fact, a "different animal," so to speak, because when hemorrhage can be controlled, the model is no longer that of uncontrolled hemorrhage. The Wiggers model emulates this situation well and shows convincingly that crystalloid resuscitation is beneficial when hemorrhage stops as resuscitation efforts begin. Secondly, what should you do with the orthopedic injury itself? Fracture fixation should be delayed until the head injury is addressed and ICP monitors or neurosurgical intervention is accomplished.

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