Cerebrovascular Resuscitation after Polytrauma and Fluid Restriction

Steven A Earle, MD, Marc A de Moya, MD, Jennifer E Zuccarelli, BA, Michael D Norenberg, MD, Kenneth G Proctor, MD, PhD

BACKGROUND: There are few reproducible models of blast injury, so it is difficult to evaluate new or existing therapies. We developed a clinically relevant polytrauma model to test the hypothesis that cerebrovascular resuscitation is optimized when intravenous fluid is restricted.

STUDY DESIGN: Anesthetized swine (42 ± 5 kg, n = 35) received blasts to the head and bilateral chests with captive bolt guns, followed by hyperventilation (4 breaths/min; FiO₂ = 0.21). After 30 minutes, resuscitation was divided into phases to simulate typical prehospital, emergency room, and ICU care. For 30 to 45 minutes, group 1, the control group (n = 5), received 1L of normal saline (NS). For 45 to 120 minutes, additional NS was titrated to mean arterial pressure (MAP) > 60 mmHg. After 120 minutes, mannitol (1g/kg) and phenylephrine were administered to manage cerebral perfusion pressure (CPP) > 70 mmHg, plus additional NS was given to maintain central venous pressure (CVP) > 12 mmHg. In group 2 (n = 5), MAP and CPP targets were the same, but the CVP target was > 8 mmHg. Group 3 (n = 5) received 1 L of NS followed only by CPP management. Group 4 (n = 5) received Hextend (Abbott Laboratories), instead of NS, to the same MAP and CPP targets as group 2.

RESULTS: Polytrauma caused 13 deaths in the 35 animals. In survivors, at 30 minutes, MAP was 60 to 65 mmHg, heart rate was > 100 beats/min, PaO₂ was < 50 mmHg, and lactate was > 5 mmol/L. In two experiments, no fluid or pressor was administered; the tachycardia and hypotension persisted. The first liter of intravenous fluid partially corrected these variables, and also partially corrected mixed venous O₂, gastric and portal venous O₂, cardiac output, renal blood flow, and urine output. Additional NS (total of 36 ± 1 mL/kg/h and 17 ± 6 mL/kg/h, in groups 1 and 2, respectively) correlated with increased intracranial pressure to 38 ± 4 mmHg (group 1) and 26 ± 4 mmHg (group 2) versus 22 ± 4 mmHg in group 3 (who received 5 ± 1 mL/kg/h). CPP was maintained only after mannitol and phenylephrine. By 5 hours, brain tissue PO₂ was > 20 mmHg in groups 1 and 2, but only 6 ± 1 mmHg in group 3. In contrast, minimal Hextend (6 ± 3 mL/kg/h) was needed; the corrections in MAP and CPP were immediate and sustained, intracranial pressure was lower (14 ± 2 mmHg), and brain tissue PO₂ was > 20 mmHg. Neuropathologic changes were consistent with traumatic brain injury, but there were no statistically significant differences between groups.

CONCLUSIONS: After polytrauma and resuscitation to standard MAP and CPP targets with mannitol and pressor therapy, we concluded that intracranial hypertension was attenuated and brain oxygenation was maintained with intravenous fluid restriction; cerebrovascular resuscitation was optimized with Hextend versus NS; and longer term studies are needed to determine neuropathologic consequences. (J Am Coll Surg 2007;204:261–275. © 2007 by the American College of Surgeons)

Almost every day, for as long as the wars in Iraq and Afghanistan continue, our soldiers and marines will suffer polytrauma, maiming, or death from improvised explosive devices (IED). In fact, the majority of combat

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Received October 13, 2006; Revised November 16, 2006; Accepted November 16, 2006. From the Dewitt-Daughtry Family Department of Surgery, Divisions of Trauma and Surgical Critical Care (Earle, de Moya, Zuccarelli, Proctor) and the Department of Pathology (Norenberg), University of Miami Miller School of Medicine, Miami, FL. Correspondence address: Kenneth G Proctor, PhD, Divisions of Trauma and Surgical Critical Care, Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, Ryder Trauma Center, 1800 NW 10th Ave, Miami, FL 33136.
casualties are now caused by IEDs.\textsuperscript{1} The recent upsurge in urban terrorist bombings\textsuperscript{2-6} suggests that blast injury will become a disturbing reality at both military and civilian trauma centers in the 21\textsuperscript{st} century.\textsuperscript{7}

There are few reproducible animal models of blast injury.\textsuperscript{8} Most existing models for resuscitation research are inadequate because there is minimal (if any) soft tissue injury; trauma is usually equated with hemorrhagic shock, and resuscitation is based on blood volume loss in a controlled laboratory setting. In contrast, blast victims can have multiple soft-tissue injuries, with or without active hemorrhage, and resuscitation is directed at restoring blood pressure rather than blood volume.\textsuperscript{9,10} Associated compartment syndromes can confound compensatory responses. With no valid models, it is difficult to evaluate new or existing therapies, and it is virtually impossible to develop specific evidence-based guidelines for treatment.

Recent data from Walter Reed Army Hospital suggest that occult traumatic brain injury (TBI) is common in many soldiers exposed to blast, even when there are no obvious external signs or loss of consciousness.\textsuperscript{10-12} Blast overpressure might also produce lung injuries that resemble pulmonary contusion.\textsuperscript{9,10} The resultant hypoxemia can potentiate secondary damage after TBI.\textsuperscript{13,14} One goal of this study was to develop a clinically relevant model of blast-induced polytrauma.

The other major goal of this study was to test the hypothesis that resuscitation after polytrauma is optimized with IV fluid (IVF) restriction. Cerebrovascular resuscitation in a combat environment can be complicated by a lack of basic monitoring capability, limited resources, and prolonged evacuation.\textsuperscript{15-17} On one hand, the ability to achieve adequate resuscitation with minimal IVF offers considerable logistic advantages for the military. On the other hand, IVF restric-

### Abbreviations and Acronyms

<table>
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<th>Abbreviation</th>
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<tr>
<td>BIS EEG</td>
<td>bispectral electroencephalogram</td>
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<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
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<tr>
<td>CVP</td>
<td>central venous pressure</td>
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<td>ICP</td>
<td>intracranial pressure</td>
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<td>IED</td>
<td>improvised explosive device</td>
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<tr>
<td>IVF</td>
<td>intravenous fluid</td>
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<td>MAP</td>
<td>mean arterial pressure</td>
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<td>NS</td>
<td>normal saline</td>
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<td>TBI</td>
<td>traumatic brain injury</td>
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### METHODS

Animals were housed in a facility approved by the American Association of Laboratory Animal Care, with veterinarians available at all times. All procedures were performed according to National Institutes of Health Guidelines for Use of Laboratory Animals and were approved by our Institutional Animal Care and Use Committee. Animals were anesthetized in all surgical interventions, and all efforts were made to minimize the number of animals involved and to alleviate their pain and distress.

#### General instrumentation

Farm-raised crossbred fasted swine of both genders (42 ± 2 kg, n = 35) were sedated with an intramuscular injection of 30 mg/kg ketamine and 3.5 mg/kg xylazine. The animals underwent orotracheal intubation and mechanical ventilation (Impact Portable Adult Ventilator Model 754, Impact Systems), with tidal volumes 10 mL/kg and 8 to 16 breaths/min to maintain PaCO\(_2\) = 40 ± 5 mmHg. The FiO\(_2\) was 0.4 except where otherwise noted. Anesthesia was initiated with continuous intravenous infusions of 10 mg/kg/h ketamine, 0.5 mg/kg/h xylazine, and 50 g/kg/h fentanyl. Pulse oximetry (Nellcor Pulse Oximeter) was continuously monitored.

With the animal in the supine position, catheters were placed in the femoral artery for continuous arterial blood pressure monitoring (Zoll Hemodynamic Monitor) and in the external jugular vein for IVF administration. Additional catheters were placed in the urinary bladder to measure urine output, in the pulmonary artery to measure mixed venous pulmonary artery oxygen saturation, pulmonary artery pressures, and cardiac output, and in the portal vein to measure oxygen saturation (Abbott Critical Care Systems, Abbott Laboratories). Gastric tissue oxygen saturation was measured by suturing a surface probe (InSpectra Tissue Spectrometer, Hutchinson Technologies Inc) to the outer surface of the anterior gastric wall. Laser Doppler blood flow probes were sutured to the inferior pole of the kidney and to the outer surface of the anterior wall of the stomach to measure microcirculatory blood flow (BPM 402, Vasamedics).

Abbreviations and Acronyms

BIS EEG = bispectral electroencephalogram
CPP = cerebral perfusion pressure
CVP = central venous pressure
ICP = intracranial pressure
IED = improvised explosive device
IVF = intravenous fluid
MAP = mean arterial pressure
NS = normal saline
TBI = traumatic brain injury
The animal was then rotated into the prone position for the remainder of the experiment. Brain tissue PO\textsubscript{2} and intracranial pressure (ICP) were continuously monitored through an intraparenchymal oxygen electrode and fiber optic pressure transducer (LICOX MCB Oxygen Monitor, Integra Neurosciences) that was placed through a small left frontal craniotomy. In addition, leads were placed so that a bispectral electroencephalogram (BIS EEG) was continuously recorded (Model A-1050 monitor, Aspect Medical Systems). The suppression ratio of the BIS EEG is defined as the percentage of isoelectric EEG activity in the last minute, and is consistent with cerebral ischemia. So, BIS monitoring allows precise evaluation of secondary injury to the brain, as we\textsuperscript{18,19} and others have reported.\textsuperscript{20,21}

During a 60-minute postinstrumentation stabilization period, 1L of normal saline (NS) was administered to all animals. All IVFs were stopped and the FiO\textsubscript{2} was reduced to 0.21 for 15 minutes before injury.

**Improvised explosive device polytrauma simulation**

Anesthetized, fully instrumented, and ventilated swine in the prone position received blunt TBI, bilateral lung contusions, and hyperventilation for 30 minutes.

The blunt TBI was produced with a commercially available power actuated tool or “nail gun” (Remington Power Trigger, Model 479, Desa Specialty Products) that was activated by a 22-caliber #1 cartridge.

Within a minute of blunt TBI, bilateral blunt chest injuries were produced by firing a captive bolt gun (model ME, Karl Schermer & Co), first against the right and then the left chest. The location was the midaxillary line at the level of the fourth intercostal space with a 45-degree cephalad trajectory. The gun was activated with a #21 10-mm cartridge. Landmarks were the posterior axillary line at the angular scapular groove, as described in several previous studies.\textsuperscript{22-24}

Kinetic energy from each of the guns was calculated by determining the mass of the captive bolt and by measuring its velocity with high speed digital photography. These measurements were made at Vision Research Inc in the Allan Carlisle Photography laboratory with a Phantom Digital High Speed Camera, Analysis System, and CineViewer 606 (Photosonics).

For 30 minutes after this insult, animals were mechanically ventilated at 4 breaths/min on FiO\textsubscript{2} = 0.21. This superimposed a hypoxic or hypercapnic stimulus that would mimic the apnea that might accompany TBI in real life.

**Resuscitation and treatment groups**

The remainder of the experiment was divided into phases that were intended to simulate the types of medical care that would occur in the prehospital phase or during emergency medical transport (30 to 45 minutes postinjury; 0 to 15 minutes of first aid), emergency room (ER, 45 to 120 minutes postinjury; 15 to 90 minutes of medical treatment), and intensive care unit (ICU, 120 to 300 minutes postinjury; 90 to 270 minutes of medical treatment). For 300 to 330 minutes after polytrauma, anesthesia and other IVFs were turned off, and the ventilator was switched to the “assist-control” mode so that a minimal inspiratory effort would trigger a full breath. There were four treatment groups, and the protocol is outlined in Figure 1.

In group 1, the standard of care or control group (n = 5), “prehospital” resuscitation consisted of immediate ventilatory support (FiO\textsubscript{2} = 0.4; rate = 12 to 20 breaths/min) and a 1-L bolus of NS. In the “emergency room phase,” PEEP was increased to 5 cm H\textsubscript{2}O, and additional NS was infused to a resuscitation target of mean arterial pressure (MAP) > 60 mmHg. In the “ICU phase,” prophylactic mannitol (1 g/kg) was administered for intracranial hypertension (ICP > 20 mmHg), and phenylephrine was titrated along with additional NS to maintain a cerebral perfusion pressure (CPP) > 70 mmHg at a CVP >12 mmHg.

Mannitol, rather than hypertonic saline, was chosen for ICP control based on current evidence-based guidelines for managing severe brain trauma.\textsuperscript{14} The consensus statement is that “mannitol is effective for the control of raised ICP after severe head injury. Effective doses range from 0.25 to 1 g/kg body weight.” The use of mannitol for ICP control after severe brain injury is supported at the level of a guideline because there are insufficient data to support a treatment standard on this topic.

The remaining three groups were fluid restricted. Group 2 (NS, CVP = 8 mmHg, n = 5) received NS to the same MAP targets, and NS + phenylephrine + mannitol to the same CPP target, but the filling pressure was 8 mmHg.

Group 3 (NS 1 L, n = 5) received a total of only 1 L of NS and then mannitol and phenylephrine to
the CPP targets, without regard for filling pressure or MAP.

Group 4 received Hextend (HEX, 6% hydroxyethyl starch in lactated electrolyte injection; Abbot Laboratories), instead of NS, to the group 2 targets (HEX, CVP = 8 mmHg, n = 5). In two additional experiments, no fluid or pressor was administered after polytrauma.

Test of cerebrovascular reactivity and compliance
Before injury, and at hourly intervals thereafter, cerebrovascular reactivity and compliance were evaluated. This technique has been previously described in detail. \(^{18,19,25}\) Briefly, inhaled CO\(_2\) was maintained at 7.5% for 5 minutes, which produced an average end-tidal CO\(_2\) of 65 to 70 mmHg. The degree of the CO\(_2\)-evoked ICP and brain tissue oxygenation changes depends on cerebral compliance and vascular reactivity in animals and patients.

Physiologic data
The following were monitored continuously for 60 minutes before and 360 minutes after polytrauma: core temperature, end tidal CO\(_2\), heart rate, MAP, CVP, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, mixed venous O\(_2\) saturation, portal venous O\(_2\) saturation, gastric tissue O\(_2\) saturation, gastric laser Doppler blood flow, renal laser Doppler blood flow, brain tissue PO\(_2\), ICP, BIS EEG, and urine output. Blood gases (PaO\(_2\), PaCO\(_2\), pH, base excess, and arterial O\(_2\) saturation), lactate and electrolytes (Na\(^+\), K\(^+\), glucose, and osmolarity) were recorded at 15- to 30-minute intervals on a Nova Stat Profile Ultra. At 360 minutes, an overdose of anesthesia was administered for euthanasia.

Histologic specimens
The brain was weighed. The presence and size of surface lesions (measured and contrecoup contusions, hemorrhages including epidural and subdural hemorrhages) were documented, measured, and photographed. The brain was suspended in 10% buffered formalin for 1 week. The cerebral hemispheres, brainstem, and cerebellum were coronally cut into 5-mm thick sections. Tissue blocks were obtained of all gross lesions and from representative areas of the neocortex, hippocampus, basal ganglia, thalamus, hemispheric white matter, midbrain, and cerebellar hemisphere. Three-millimeter thick sections were processed routinely for histology (dehydration in graded alcohol, clearing in xylene, then...
paraffin embedding). Paraffin sections (8 μm) were stained routinely with hematoxylin and eosin to examine for neuronal shrinkage (early ischemia), neuronal eosinophilia (evidence of neuronal necrosis), neuropil spongiosis (edematous changes), microglial nuclear enlargement and pallor (microglial activation), endothelial nuclear pallor and enlargement (endothelial activation), and presence of neutrophils (evidence of acute inflammation). Darkened neurons reflected early ischemic injury. Alzheimer type II astrocytosis reflected early damage to astrocytes after trauma. Semi-quantitative assessment of histologic changes were performed “blindly” and graded on a crude 0-to-3 scale, where 0 = no changes, 1 = slight changes, 2 = moderate changes, and 3 = marked changes.

Statistics
Treatments were applied in random order in two cohorts (groups 1 versus 3; and groups 2 versus 4). Data are expressed as mean ± SEM. Student t-test and one-way ANOVA for multiple comparisons were calculated with the SPSS for Windows release 14.0 program (SPSS Inc). A two-tailed p < 0.05 was considered significant.

RESULTS

Description of polytrauma model
Blunt TBI was produced by a power actuated piston or captive bolt (mass = 103 g) striking a 4-cm (diameter) aluminum disk at 30 m/s (kinetic energy = 0.5 [0.103 kg] [30 m/s]² = 46.4 joules). The disk was taped to the skin overlying the occipital bone along the midline. This blast produced no skull fracture or obvious damage to the head (other than mild erythema). The gross appearance of a typical injury on autopsy is shown in Figure 2. After craniectomy, a subdural hematoma was obvious (Figs. 2A [before durotomy] and 2B [after durotomy]), and the contusion (Fig. 2C) and contrecoup injury at the base of the brain (Fig. 2D) were grossly evident.

Bilateral blunt chest trauma was produced by a power actuated piston with a mushroom head (mass = 352 g)
striking the right and then the left chest at 26 m/s (kinetic energy = 0.5 [0.352 kg] [26 m/s]^2 = 119.0 joules). The most common chest injury pattern was a bruise on the chest, but there was no other obvious deformity. Tube thoracostomy was usually not required. At autopsy, multiple nondislocated rib fractures were common, but the parietal pleura was not often violated. Lung contusions were obvious on gross examination. Figure 3 shows the typical appearance of the lungs. Gross changes include diffuse contusions with stiffened heavy tissue, pleural rents, pneumothorax, or mediastinal extravasation of air. Despite these sequelae, PaO\(_2\) usually remained > 200 mmHg on FiO\(_2\) 0.4 for at least 5 hours with standard supportive care.

There were 13 (37%) deaths after polytrauma (Fig. 1), which defines the severity of the combined insult. About half of these deaths occurred within 30 minutes, ie, before resuscitation. The other half occurred within 120 minutes; typically, there were two patterns. One was minimal response to the resuscitation fluid, but there were still signs of life; this was judged as intractable hypotension. The other was ICP > 30 mmHg, which was judged as a nonsurvivable surgical lesion.

Animals who survived 30 minutes after polytrauma with ICP < 30 mmHg typically manifested hypotension, hypoxia, hypercapnia, and tachycardia. On initial resuscitation (fluid bolus, ventilatory support, supplemental O\(_2\)) followed later by CPP management (including mannitol and pressor therapy), most physiologic variables corrected in all groups. With no fluid at 30 minutes (n = 2), there was persistent hypotension and tachycardia. The hypoxia and hypercapnia corrected with ventilatory support and supplemental O\(_2\), but cardiac output, mixed venous O\(_2\) saturation, and lactate clearance were all depressed. There was no urine output. One animal survived only 60 minutes, and the other survived 300 minutes in these premorbid conditions. This untreated control arm clearly demonstrated that some fluid resuscitation was necessary for survival. Every animal that survived to resuscitation survived to the end of observation with at least some neurologic function, as judged by spontaneous respiratory efforts during ventilator weaning. This suggests the adequacy of resuscitation with the four fluid combinations in these experimental conditions.

**Physiologic changes with “standard of care” or three different fluid restriction strategies**

Figure 4 shows MAP and CPP as a function of time. The left panel shows that baseline MAP ranged from 85 to 100 mmHg and fell to 60 to 65 mmHg by 30 minutes after polytrauma. The first liter of IVF transiently increased MAP 10 to 19 mmHg in the three NS groups, but the increase was > 35 mmHg (p = 0.059 versus control) and more sustained in the Hextend group. In all groups, MAP increased at 120 minutes, when mannitol was administered and pressor therapy begun. From that point until the end of observation, CPP was maintained at the > 70 mmHg target in all groups (right panel). But in the Hextend group, CPP was > 70 mmHg immediately on resuscitation (p = 0.023 versus control).

Figure 5 shows the IVF required to maintain the MAP and CPP targets. Each animal received a bolus of 1 L of NS (approximately 25 mL/kg) during the instrumentation period and before injury. After polytrauma, each animal received 1 L of either NS or Hextend, plus mannitol (1 g/kg), which partly explains the brisk diuresis. Altogether, group 1 required a total of 161 ± 6 mL/kg NS for resuscitation, administered as a continuous infusion of 36 ± 1 mL/kg/h plus 0.18 ± 0.04 mg/kg phenylephrine. Group 2 required about half as much IVF (75 ± 29 mL/kg; 17 ± 6 mL/kg/h, p = 0.002 versus control) and also less phenylephrine (0.13 ± 0.03 mg/kg; p = 0.34 versus control). Group 3 received a single 1-L bolus of NS at resuscitation (22 ± 1 mL/kg; 4.8 ± 0.2 mL/kg/h; p < 0.001 versus control), then phenylephrine only for the remainder of the experiment (0.25 ± 0.07 mg/kg; p = 0.20 versus control). Group 4...
received 28 ± 13 mL/kg Hextend (6 ± 3 mL/kg/h; p < 0.001 versus control) and the least amount of phenylephrine (0.07 ± 0.02 mg/kg; p = 0.06 versus control). Groups 3 and 4 were in relative fluid balance because the IVF infusion almost exactly matched the urine output. In contrast, urine output was less than half of the IVF rate in groups 1 and 2.

Figure 6 shows other markers of vascular volume. In the control group, CVP was maintained at about 12 mmHg and hematocrit remained near the baseline value of about 25, suggesting euvolemia. With Hextend, CVP was maintained at 8 mmHg (p = 0.003 versus control), but hematocrit was also consistent with euvolemia. In group 2, CVP was 8 mmHg (p = 0.024 versus control), but there was a progressive hemococoncentration to 30 (p = 0.071 versus control), suggesting relative hypovolemia. In group 3, hematocrit was similarly increased (p = 0.027 versus control) and CVP was 4 mmHg (p < 0.001 versus control), also consistent with hypovolemia. In all groups, plasma Na+, K+, and osmolarity changes were variable and not considerably different between groups (data not shown). So, the combined data in Figures 6 and 7 suggest that intravascular volume was similar with 6 mL/kg/h Hextend or 36 mL/kg/h NS, but was slightly reduced with either 5 or 17 mL/kg/h NS.

Figure 7 suggests that at least some IVF was probably third spacing into the brain and lungs. The left panel shows that ICP progressively increased to 35 to 40 mmHg in group 1, and ICP was 25% to 40% lower in groups 2 and 3 (p = 0.019 and 0.007, respectively, versus control). With Hextend, ICP remained near 15 mmHg for the entire posttrauma observation (p < 0.001 versus control), except during the brief tests of cerebrovascular reactivity each hour (data not shown). In all groups, increased FiCO₂ for 5 minutes provoked a 2- to 3-mmHg ICP increase before injury and a 6- to 10-mmHg increase after injury. This is consistent with reduced cerebrovascular compliance, but the changes were similar in all groups, so the data are not shown. Except during the CO₂ challenges, PaCO₂ was tightly regulated at 40 ± 5 mmHg by varying the respiratory rate; there were no differences between groups (data not shown).

The right panel of Figure 7 shows that in the three NS groups, peak inspiratory pressure on constant tidal vol-
Volume (10 mL/kg/breath) increased from about 20 cm H₂O in baseline conditions to about 25 cm H₂O after 5 hours. In the Hextend group, peak inspiratory pressure was about 5 cm H₂O higher throughout the posttrauma resuscitation period (p = 0.01 versus control).

There was a clear trend to diminished EEG activity and also a trend to increases in EEG burst suppression, indicating ischemic EEG changes. But these changes were highly variable and not statistically different between groups, so the data are not shown.
Figure 8 shows that brain tissue PO$_2$ decreased from a baseline value of about 12 mmHg to < 2 mmHg after injury and before resuscitation in all groups (left panel). The first liter of IVF corrected brain tissue PO$_2$ back to baseline in all groups. But in group 3, brain tissue PO$_2$ was not maintained. It slowly decreased to about 6 mmHg and stabilized at that value until the end of the observation period (p = 0.045 versus control). In the other three groups, brain tissue PO$_2$ stabilized at > 20 mmHg. The right panel shows that PaO$_2$ decreased from a baseline value of about 225 mmHg to about 50 mmHg and then corrected to > 200 mmHg with resuscitation. There was no PaO$_2$ difference between treatments.

All other markers of resuscitation and tissue oxygenation were similar between groups. Figure 9 shows that mixed venous O$_2$ saturation fell from a baseline value of about 70% to about 25% before resuscitation, and lactate increased to > 6 mmol/L. Both of these variables corrected with resuscitation and there was no difference between groups.

There were quantitatively similar changes in cardiac output, renal blood flow, and portal venous and gastric oxygenation with injury and with resuscitation, and there were no differences between groups, so those data are not shown.

**Semiquantitative neuropathologic changes**

Figure 10 shows representative histologic specimens stained with hematoxylin and eosin from the cerebral cortex from an uninjured animal (panel A), and corresponding sections after injury and treatment with standard of care (panel B) and with Hextend (panel C). With standard of care (group 1), there was a striking degree of neuronal shrinkage (arrows) and neuropil vacuolization (edema). With Hextend (group 4), there were several dark, slightly shrunken neurons, with prominent perineuronal spaces (arrows). The scale bar = 120 μm.

In an attempt to quantitate the neuropathologic changes within and between groups, sections from the cerebral cortex were evaluated in a blinded fashion. Table 1 shows that every animal had evidence of severe TBI, but there was large variability within and between individuals. Changes included subarachnoid hemorrhage, petechiae, ischemia, neutrophil infiltrates with focal areas of necrosis, shrunken, darkened neurons, Alzheimer type II astrocytosis, or spongiosis (neurophil edema). No apop-
tosis or spheroids and, or retraction balls were noted, but that is not surprising at this early time point. Within each group, the mean (±standard error) was calculated from unweighted averages from each category. According to this system, the overall damage was judged as follows: group 2 > group 3 > group 1 > group 4. One specimen was not analyzed in group 3 because of technical reasons.

Figure 8. Brain tissue PO$_2$ (mmHg), left, and PaO$_2$ (mmHg), right, versus time in four groups. Note that brain tissue PO$_2$ was not maintained in group 3, but was > 20 mmHg in the other three groups. Hex, Hextend; NS, normal saline; PE, phenylephrine.

Figure 9. Systemic markers of resuscitation. Mixed venous O$_2$ saturation (%), left, and arterial lactate (mm), right, corrected in all four groups. Hex, Hextend; NS, normal saline; PE, phenylephrine.
DISCUSSION

Our soldiers suffer blast injuries almost every day in Iraq and Afghanistan.28-32 In the best case, if medical resources are available, blood loss can be approximated, and resuscitation is targeted to end points such as blood pressure, heart rate, or urine output. In the worst case, in field situations, emergency care is delayed, there is no monitoring capability, or resuscitation is limited to the fluids carried by the first responder. In either case, it is difficult to evaluate which therapeutic modality is best because there are no reproducible large animal models to test the ideas. To our knowledge, this is the first controlled laboratory study to compare fluid restriction resuscitation strategies after the type of complicated severe polytrauma that might result from a blast injury on the battlefield.

In this study, the severity of the polytrauma is reflected by the 37% (13 of 35) mortality before randomization (Fig. 1). Animals that survived to the point of emergency medical care lived at least 6 hours with at least some neurologic function, which compares favorably to reports of casualties evacuated alive from the battlefield.7,9-12,15-17,28-32 In all survivors, MAP and CPP were stable (Fig. 4), there was adequate urine output (Fig. 5), and lactate was cleared (Fig. 9), which, at first glance, suggests that all four resuscitation strategies yielded satisfactory results.

The major new findings are that with a reasonable “standard of care” (group 1), which includes an initial NS bolus followed by judicious IVF administration to maintain MAP > 60 mmHg at a moderate filling pressure (CVP > 12 mmHg), brain oxygenation was restored (Fig. 8), but ICP reached dangerous levels >35 mmHg within the 6-hour observation period (Fig. 7), even with mannitol and pressor therapy. Reducing IVF by about half (group 2) reduced ICP by 30% (to 25 mmHg); this ICP value remained dangerously high, according to current evidence-based management guidelines for severe TBI.14 Brain oxygenation was maintained, but there was evidence of hemococoncentration and a volume deficit (Fig. 6). If IVF was additionally restricted to a single 1-L bolus of NS (group 3), brain oxygenation was not maintained. In all three NS groups, CPP was maintained at >70 mmHg only after mannitol and pressor therapy. In striking contrast, an initial 1-L bolus of Hextend immediately corrected CPP >70 mmHg, which is important because CPP maintenance is the cornerstone of TBI management.33,34 In addition, in group 4, brain oxygenation was maintained, and overall IVF requirements were reduced by one-sixth relative to group 1 (Fig. 5). Taken together, these observations are consistent with the conclusion that intracranial hypertension was acutely attenuated, and brain oxygenation was acutely maintained only when IVF was restricted and that resuscitation was optimized when Hextend was used instead of NS. This is consistent with accumulating evidence that Hextend offers unique advantage, relative to crystalloid, for combat
resuscitation and other situations in which resources are limited, such as emergency medical transport or during a mass casualty event.\textsuperscript{16,17} Current military doctrine for treating combat injuries allows permissive hypotensive resuscitation, based on the assumption that aggressive normalization of hemodynamics might exacerbate bleeding.\textsuperscript{17,35} There are ample theoretic data to support this concept.\textsuperscript{36-38} Because bleeding extremity wounds have been the most common combat injury throughout history,\textsuperscript{15} the importance cannot be overstated. On the other hand, permissive hypotensive resuscitation could be catastrophic after concussion from an IED because even brief episodes of hypotension or hypoxia can double morbidity and mortality after TBI.\textsuperscript{13,14,33,34}

In the current war in Iraq, the majority of casualties are caused by IEDs,\textsuperscript{1} and TBI is common.\textsuperscript{11} In theory, the injury caused by an IED can be divided into four components.\textsuperscript{9,10} Primary blast injury is caused by the pressure wave and occurs almost exclusively in gas-containing organs, such as the lung, ear, and gastrointestinal tract. The ear is the most sensitive to this pressure wave, but damage to the lung is responsible for the most morbidity and mortality. Gross lung changes include diffuse contusions with stiffened heavy tissue, pleural rents, pneumothorax, or mediastinal extravasation of air (eg, Fig. 3). Microscopic lung changes include intraalveolar hemorrhage with perivascular or peribronchial disruption and leukocyte infiltration. Secondary blast injury results from blunt or penetrating trauma caused by energized objects. Tertiary blast injury occurs when the whole body collides with fixed objects. Quaternary blast injury results from burns and exposure to toxic inhalants.\textsuperscript{7,9}

The whole body polytrauma caused by an IED depends on several factors, including blast kinetic energy,
fragments and projectiles loaded in the bomb or launched by the explosion, proximity of the patient to the blast, barriers that partially deflect the energy, and of course, biologic variability in the patient. So no two injuries or compensatory responses are exactly alike. Nevertheless, if the injury is survivable, there are common patterns and general principles that can serve as the basis for model development.

Our IED model was based on three assumptions. First, we reasoned that blast overpressure would likely cause some structural lung damage, but have no obvious functional consequence. This reasoning is based on after-action reports that confirm that refractory hypoxemia from the blast is relatively uncommon in a ventilated patient evacuated from the battlefield. 

In any case, the pathophysiology and treatment of blast injury to the lung are almost exactly the same as the pathophysiology and treatment for blunt chest trauma and pulmonary contusion. In our model, and in real life, symptomatic treatment includes judicious IVF administration, supplemental O₂, and appropriate ventilatory support with positive end expiratory pressure. If any one of these conditions is not met, then a progressive respiratory failure develops. Second, we reasoned that in most cases, penetrating TBI after an IED is lethal. It follows that the most common pattern of survivable TBI after IED is blunt trauma caused by either energized objects striking the head or the head striking a fixed object. Of course, survivability depends also on the direction of the blast and anatomic location of the injury. In our model, the blast was applied in the occipital region and in an anterocaudal direction perpendicular to the spinal cord. Third, we reasoned that neurotrauma victims in real life would receive current standards of trauma care, which would include CPP management, if necessary. We have a unique perspective on current problems related to combat casualty care because the US Army has selected the University of Miami as the training site for its forward surgical teams. Whenever our soldiers are in battle, these teams are near the front lines. Since September 11, 2001, most of the army’s teams deployed in Iraq and Afghanistan have trained in our laboratory. Feedback and after-action reports from these teams have grounded our research firmly in reality.

Hextend is an FDA-approved hetastarch solution indicated for hypovolemia during elective surgery, but there have been no randomized clinical trials evaluating the use of Hextend for trauma resuscitation. Relative to hetastarch in saline, Hextend has a beneficial coagulation profile, less antigenicity, and some antioxidant properties. Hextend prevents hyperchloremic metabolic acidosis and improves gastric mucosal perfusion versus saline solutions. The potential value of Hextend has been recognized in a review of special issues faced by battlefield medics. But it should be emphasized that the use of Hextend in trauma patients is off-label, its effects are transient, and there is a potential for coagulopathy. It is regarded as a temporizing measure only and is not recommended for those with TBI. Before our work, there was no evidence that Hextend was safe and effective for resuscitation after trauma with or without TBI. In three different trauma models, we showed that fluid requirements were reduced by at least half, pulmonary and cerebrovascular function were improved, and there was no adverse effect on the coagulation profile with Hextend relative to crystalloid. The results from this study affirm those results.

There are at least four major limitations to this study. First, for ethical reasons, all animals were anesthetized at the time of injury and throughout the experiment. The ketamine or fentanyl anesthesia could impart either a protective or a deleterious effect that may differ from the real-life nonanesthetized trauma patient. Although an anesthesia artifact may have existed, it was imposed equally on all groups. Second, the magnitude of the lung injury in this study was somewhat less than that in our several previous studies, even though the kinetic energy delivered to the chest wall was similar. The exact explanation for this difference was not rigorously pursued, but the animals were about 15% to 20% larger, the injury was delivered in the prone rather than supine position, there was no superimposed hemorrhage, and resuscitation IVF was guided by MAP targets rather than blood volume lost. Third, there was no longterm followup, and it is possible that the short-term physiologic differences between groups have no neurologic or other clinical consequence. There were also no obvious histologic differences after 6 hours (Table 1), so longterm studies are clearly indicated. Fourth, the model did not mimic the shrapnel, heat, or electromagnetic radiation that can be caused by an IED. Also, the captive bolt guns produced injuries to the brain and lungs that varied between individuals. On the other hand, relative to an actual explosion, recreating the polytrauma with captive
bolt guns was relatively inexpensive in terms of equipment and manpower, and the contribution and directionality of the various injury components could be easily manipulated.

In summary, we described a new model of blast injury polytrauma using captive bolt guns in anesthetized pigs. The anatomic injury pattern and functional changes were relatively reproducible and appeared to mimic some key aspects of (survivable) IED-related neurotrauma. The 40% mortality before resuscitation reflected injury severity, but the 0% mortality thereafter reflected the efficacy of current standards of field and hospital care with almost immediate definitive treatment and CPP-directed therapy. In these nearly ideal circumstances, the physiologic sequelae of severe neurotrauma were attenuated for at least 6 hours when IVF was restricted. Additional work is needed to define responses with evacuation delays or less definitive treatment. Also, the data showed that, by many criteria, Hextend was superior to crystalloid, even at the same standard resuscitation end points. More work is needed to determine if these apparent short-term benefits have any longterm neurologic consequences. Optimal fluid management is essential in the treatment of severe TBI to reduce the formation of cerebral edema and avoid secondary injury. Until now, there have been no adequate models to study these effects after blast-induced polytrauma.

Author Contributions
Study conception and design: Earle, de Moya, Proctor
Acquisition of data: Earle, de Moya, Zuccarelli
Analysis and interpretation of data: Earle, Norenberg, Proctor
Drafting of manuscript: Earle, Norenberg, Proctor
Critical revision: Earle, Norenberg, Proctor

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