Effect of initially limited resuscitation in a combined model of fluid-percussion brain injury and severe uncontrolled hemorrhagic shock

SUSAN A. STERN, M.D., BRIAN J. ZINK, M.D., MICHELLE MERTZ, B.S., XU WANG, M.D., AND STEVEN C. DRONEN, M.D.

Department of Emergency Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

Object. Studies of isolated uncontrolled hemorrhage have indicated that initial limited resuscitation improves survival. Limited resuscitation has not been studied in combined traumatic brain injury and uncontrolled hemorrhage. In this study the authors evaluated the effects of limited resuscitation on outcome in combined fluid-percussion injury (FPI) and uncontrolled hemorrhage.

Methods. Twenty-four swine weighing 17 to 24 kg each underwent FPI (3 atm) and hemorrhage to a mean arterial pressure (MAP) of 30 mm Hg in the presence of a 4-mm aortic tear. Group I (nine animals) was initially resuscitated to a goal MAP of 60 mm Hg; Group II (nine animals) was resuscitated to a goal MAP of 80 mm Hg; and Group III (control; six animals) was not resuscitated. After 60 minutes, the aortic hemorrhage was controlled and the animals were resuscitated to baseline physiological parameters and observed for 150 minutes.

Mortality rates were 11%, 50%, and 100% for Groups I, II, and III, respectively (Fisher’s exact test; p = 0.002). The total hemorrhage volume was greater in Group II (69 ± 32 ml/kg), as compared with Group I (41 ± 18 ml/kg) and Group III (37 ± 3 ml/kg) according to analysis of variance (p < 0.05). In surviving animals, cerebral perfusion pressure, cerebral blood flow (CBF), cerebral venous O₂ saturation (ScvO₂), and cerebral metabolic rate of O₂ did not differ among groups. Although CBF was approximately 50% of baseline during the period of limited resuscitation in Group I, ScvO₂ remained greater than 60%, and arteriovenous O₂ differences remained within normal limits.

Conclusions. In this model of FPI and uncontrolled hemorrhage, early aggressive resuscitation, which is currently recommended, resulted in increased hemorrhage and failure to optimize cerebrovascular parameters. In addition, a 60-minute period of moderate hypotension (MAP = 60 mm Hg) was well tolerated and did not compromise cerebrovascular hemodynamics, as evidenced by physiological parameters that remained within the limits of cerebral autoregulation.

KEY WORDS • brain injury • hemorrhage • shock • resuscitation • cerebral blood flow • pig
Fig. 1. Timeline depicting the experimental protocol.

Instrumentation of Monitoring

The abdomen, anterior surface of the neck, and both femoral artery areas were cleaned and prepared with povidone-iodine solution. The right femoral artery was isolated via a cutdown and cannulated with a 1.67-mm-inner-diameter polyethylene catheter for blood withdrawal. The left femoral artery was similarly isolated and cannulated with a No. 5 French pigtail catheter, which was advanced into the left ventricle for BP monitoring and dye-labeled microsphere injection. The right femoral vein was cannulated with a polyethylene catheter (1.67 mm inner diameter) for drug and fluid administration. A No. 5 French flow-directed Swan–Ganz catheter was inserted into the right external jugular vein and advanced into the pulmonary artery for pressure, core temperature, cardiac output monitoring, and blood sampling. The right carotid artery was then isolated and cannulated with polyethylene tubing for continuous BP monitoring.

Uncontrolled hemorrhage was accomplished with the creation of a 4-mm aortic tear. A midline abdominal incision was made, the retroperitoneal fascia incised, and the ventral surface of the infrarenal aorta exposed. A size 4 monofilament stainless-steel surgical wire was placed through the ventral wall of the infrarenal aorta into the aortic lumen, advanced, and exited at a point 4 mm distal to the site of entry. The wire ends were then exteriorized through the abdominal incision and the wound was closed.

The animal was placed prone in a head stabilizer, its head was shaved and prepared with povidone-iodine solution, and the scalp was reflected. A 16-mm-diameter craniotomy was created in the right parietal region adjacent to the sagittal suture and 6 cm anterior to the inion. A T-shaped bolt was screwed into the craniotomy site until it abutted the intact dura. The T-shaped bolt was then connected to a fluid-percussion device as well as to a high-pressure transducer that was used to quantify the brain injury.

A second craniotomy was performed in the left posterior parietal region 3 mm anterior and 5 mm lateral to the bregma, and a neonatal intraventricular catheter was placed in the left lateral ventricle and connected to an ICP monitor. A brain temperature probe was placed adjacent to the ICP catheter. A third craniotomy was made in the midline just anterior to the inion, and a No. 4 French fiberoptic oximetric catheter was placed in the sagittal sinus for cerebral venous blood sampling. All catheters were sealed in place with dental cement.

At the completion of instrumentation, the animals were paralyzed with an intravenous bolus of 1.5 mg/kg succinylcholine followed by a continuous infusion of this agent at 2 to 4 mg/kg/hr. The animals were maintained on the succinylcholine infusion and placed on a volume-cycled ventilator to maintain arterial CO2 pressure between 40 and 45 mm Hg.

Experimental Protocol

Thirty minutes after beginning the succinylcholine infusion, baseline metabolic, hemodynamic, and blood flow measurements were obtained. The combined TBI and hemorrhage protocol consists of the following steps. At the same time the FPI (3 atm) is delivered, hemorrhage is initiated from the left femoral artery catheter at a rate of 35 ml/kg over 30 minutes by using a computer-driven roller pump. To duplicate more closely the physiological and kinetic features of traumatic hemorrhage, the computer was programmed to withdraw blood at a rate that decreased exponentially over time with the fall in BP, as described in previous publications.40,41 Blood shed from the femoral artery catheter was placed in a blood collection bag containing 0.067 ml of citrate per milliliter of blood for an estimated hemorrhage volume of 30 ml/kg of the animal’s body weight. Once the animal’s MAP reached 50 mm Hg, the aortotomy wire was pulled, creating a fixed vascular lesion and allowing free intraperitoneal hemorrhage. When the MAP decreased to 30 mm Hg, the catheter hemorrhage was discontinued and resuscitation was begun. We have used a similar aortic tear hemorrhage model in several previous investigations and it is highly reproducible, has a...
Limited resuscitation after brain injury and severe uncontrolled hemorrhage

Physiological Measurements

The heart rate, systolic and diastolic BP, MAP, central venous, pulmonary artery and left ventricular pressures, and ICP were recorded at baseline and continuously throughout the experimental protocol by using a computerized data acquisition system. The respiratory rate and end-tidal CO₂ were continuously monitored using a capnometer. We measured cardiac output via the thermodilution technique at baseline and every 15 minutes thereafter, for measurement of hemoglobin, hematocrit, and arterial, mixed venous, and cerebral venous blood gas. Arterial and cerebral venous lactate were measured every 30 minutes. Cerebral and renal blood flow measurements were obtained at baseline and at 30 minutes, 60 minutes (just before obtaining control of aortic hemorrhage), and 150 minutes after beginning resuscitation by using dye-labeled microspheres and the reference sample method as described in previous publications. 49, 50

The CaO₂, DO₂, CPP, cerebral DO₂, cO₂ER, AVDO₂, and CMRO₂ were calculated using standard formulas.

Statistical Analysis

Results are reported as the mean ± SD. Hemorrhage volumes and metabolic and hemodynamic data at baseline and time 0 were compared among the three groups by using ANOVA with a post hoc Tukey–Kramer test. Because only one animal from Group III (controls) survived 15 minutes into the resuscitation period, comparisons of physiological parameters beyond this time point were made only between Groups I and II, and the two-sample t-test was used. Repeated-measures ANOVA was used when analyzing longitudinally measured parameters. Mortality differences and survival time among the three groups were compared using Fisher’s exact test and the Kruskal–Wallis test, respectively. A Wilcoxon rank-sum test was used to compare survival times among individual groups. For the latter comparison, a probability value less than 0.025 was considered statistically significant, whereas a probability value less than 0.05 was considered statistically significant for the remainder of the comparisons. Mortality and survival time data for Group II were available for only eight animals because one pig died suddenly at 57 minutes postinjury from an iatrogenic cause. The physiological data collected in the latter animal prior to 57 minutes are included in the data analysis.

Preinjury physiological measurements in 24 swine*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (9 pigs)</th>
<th>Group II (9 pigs)</th>
<th>Group III (controls, 6 pigs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>preinjury weight (kg)</td>
<td>20.6 ± 1.9</td>
<td>20.6 ± 1.9</td>
<td>19 ± 1.0</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>84 ± 19</td>
<td>96 ± 12</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>12 ± 4</td>
<td>10 ± 4</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>CPP (mm Hg)‡</td>
<td>72 ± 19</td>
<td>87 ± 17</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>2.70 ± 0.70</td>
<td>3.09 ± 0.72</td>
<td>3.13 ± 0.60</td>
</tr>
<tr>
<td>brain temp (°C)</td>
<td>36.94 ± 0.72</td>
<td>36.89 ± 0.36</td>
<td>37.45 ± 0.60</td>
</tr>
<tr>
<td>arterial lactate (mEq/L)</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>hemoglobin (g/dl)</td>
<td>11.5 ± 1.1</td>
<td>11.0 ± 1.4</td>
<td>11.7 ± 1.6</td>
</tr>
<tr>
<td>ScvO₂ (%)</td>
<td>0.81 ± 0.06</td>
<td>0.84 ± 0.04</td>
<td>0.74 ± 0.15</td>
</tr>
<tr>
<td>cO₂ER (%)</td>
<td>0.18 ± 0.06</td>
<td>0.15 ± 0.04</td>
<td>0.25 ± 0.15</td>
</tr>
<tr>
<td>cDO₂ (ml/100 g/min)</td>
<td>17.17 ± 5.88</td>
<td>15.67 ± 5.77</td>
<td>10.99 ± 1.63</td>
</tr>
<tr>
<td>cMRQ (ml/100 g/min)</td>
<td>2.85 ± 0.74</td>
<td>2.29 ± 0.81</td>
<td>2.67 ± 1.05</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD. Abbreviations: CO = cardiac output; cDO₂ = cerebral DO₂.
† Goal MAPs were 60 mm Hg and 80 mm Hg in Groups I and II, respectively.
‡ The only parameter for which there were significant differences was CPP (p = 0.018). Significance was calculated for all parameters according to ANOVA with the post hoc Tukey–Kramer test.

Sources of Supplies and Equipment

The cardiac output computer was purchased from American Edwards Laboratories, Irvine, CA. The fluid-perfusion device was manufactured by Stevenson Machine Co., Cincinnati, OH, and the high-pressure transducer was acquired from Sensym, Sunnyvale, CA. The neonatal intraventricular catheters were obtained from Phoenix Biomedical Corp., Valley Forge, PA. Brain temperature probes were purchased from Cole-Parmer, Niles, IL. The fiberoptic oximetric catheters were acquired from Abbott Laboratories, North Chicago, IL, and the citrate (CPD solution) was obtained from Abbott Laboratories, Abbott Park, IL. The data acquisition system was purchased from Biopac, Santa Barbara, CA. The capnometer (Datex Capnomac Ultima) was obtained from Datex Instrumentarium Corp., Helsinki, Finland. The dye-labeled microspheres (Dye-Trac) were manufactured by Triton Technologies, San Diego, CA.

Results

Preinjury physiological measurements are summarized in Table 1. There were no significant differences in baseline or preresoruscitative physiological parameters with the exception of the CPP. However, the differences in CPP were not clinically significant and mean values were within normal physiological limits.

Mortality Rates

Mortality rates were 11%, 50%, and 100% in Groups I, II, and III, respectively (p = 0.002; Fisher’s exact test). Mortality was significantly greater in Group III compared with Group I (p = 0.001; Fisher’s exact test). Although the difference in mortality between Groups I and II did not reach statistical significance (p = 0.131), there was a trend toward greater mortality in the animals that received initial aggressive resuscitation (Group II), as demonstrated by the increase in mortality of 39% (95% confidence interval: −0.79 to 0.01). The median survival times (25th and 75th percentiles) were 150 (150 and 150), 109 (31 and 150), and 7 (6 and 10) minutes in Groups I, II, and III, respectively. The median survival time was significantly
shorter in Group III compared with Group I (p = 0.001) and Group II (p = 0.006). Again, as shown in Fig. 2, although the difference in survival time between Groups I and II did not reach statistical significance, there was a trend toward longer survival times in Group I, which included the less aggressively resuscitated animals, compared with Group II (p = 0.056).

Hemorrhage and Resuscitation Volumes

Catheter hemorrhage volumes were similar among all groups. Intraperitoneal hemorrhage volume and, therefore, total hemorrhage volume were significantly greater in Group II, the aggressively resuscitated animals, compared with animals in Groups I and III (Table 2). Total infusion volumes during the 150-minute resuscitation period did not differ among groups. Group I and II animals received 68 ± 74 ml/kg and 85 ± 29 ml/kg of normal saline (p = 0.534) and 19 ± 10 ml/kg and 20 ± 10 ml/kg of shed blood (p = 0.828), respectively.

Systemic Hemodynamic and Metabolic Responses

Because only one animal in Group III survived longer than 15 minutes into the resuscitation period, the following analyses are for Groups I and II only. Despite aggressive resuscitation, Group II animals were unable to attain the goal MAP of 80 mm Hg prior to control of hemorrhage from the aortic artery injury (Fig. 3 upper). There were no statistically significant differences in cardiac output between surviving Group I and II animals. In both groups cardiac output remained significantly lower than baseline values until after control of aortic hemorrhage was achieved (Table 3). In both groups, the mean hemoglobin levels decreased significantly from baseline with initial crystalloid resuscitation. Aggressive resuscitation resulted in significantly lower hemoglobin levels and, subsequently, lower CaO2 compared with limited resuscitation (Table 3). However, there was no difference in systemic DO2 between the two groups. Similar to cardiac output, DO2 remained significantly below baseline values until after control of aortic hemorrhage was accomplished (Table 3). There were no significant differences in arterial lactate levels between surviving Group I and II animals throughout the experimental protocol (Table 4). Arterial lactate reached maximum levels of 5.6 ± 3.5 mEq/L and 4.5 ± 2.2 mEq/L in Groups I and II, respectively (p = 0.465). Serum bicarbonate levels differed significantly only at 15 minutes.

Cerebrovascular Response

In both groups, ICP fell initially in response to brain
### TABLE 3

*Cardiac output, hemoglobin, \( \text{CaO}_2 \), and \( \text{DO}_2 \) in a swine model of FPI*

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group &amp; Parameter</th>
<th>Baseline</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>105</th>
<th>120</th>
<th>135</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO (L/min)</td>
<td>2.7 ± 0.71</td>
<td>—</td>
<td>2.14 ± 0.88</td>
<td>1.88 ± 0.74</td>
<td>1.69 ± 0.65</td>
<td>1.76 ± 0.72</td>
<td>2.07 ± 0.73</td>
<td>2.34 ± 0.77</td>
<td>2.71 ± 0.88</td>
<td>2.67 ± 0.71</td>
<td>2.80 ± 0.76</td>
<td>2.56 ± 0.78</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin (g/dl)</td>
<td>11.47 ± 1.08</td>
<td>10.4 ± 1.2</td>
<td>8.07 ± 1.95*</td>
<td>8.66 ± 0.97*</td>
<td>8.82 ± 0.86</td>
<td>9.11 ± 1.19</td>
<td>8.99 ± 1.78</td>
<td>8.65 ± 1.93</td>
<td>—</td>
<td>8.95 ± 2.76</td>
<td>—</td>
<td>8.98 ± 3.09</td>
</tr>
<tr>
<td></td>
<td>( \text{CaO}_2 ) (ml/dl)</td>
<td>16.16 ± 1.44</td>
<td>14.79 ± 1.65</td>
<td>11.49 ± 2.60*</td>
<td>12.34 ± 1.34*</td>
<td>12.52 ± 1.11</td>
<td>12.91 ± 1.55</td>
<td>12.64 ± 2.80</td>
<td>12.22 ± 2.74</td>
<td>—</td>
<td>12.53 ± 3.83</td>
<td>—</td>
<td>12.62 ± 4.29</td>
</tr>
<tr>
<td></td>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CO (L/min)</td>
<td>3.09 ± 0.73</td>
<td>—</td>
<td>2.68 ± 1.38</td>
<td>2.60 ± 1.25</td>
<td>2.26 ± 0.53</td>
<td>1.97 ± 1.06</td>
<td>2.50 ± 0.61</td>
<td>2.81 ± 0.66</td>
<td>2.86 ± 0.67</td>
<td>3.30 ± 0.76</td>
<td>3.09 ± 0.59</td>
<td>3.13 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin (g/dl)</td>
<td>11.06 ± 1.40</td>
<td>10.06 ± 1.10</td>
<td>5.67 ± 1.62</td>
<td>6.81 ± 1.51</td>
<td>8.33 ± 1.17</td>
<td>8.5 ± 1.54</td>
<td>8.63 ± 1.49</td>
<td>8.75 ± 0.87</td>
<td>—</td>
<td>9.25 ± 0.50</td>
<td>—</td>
<td>8.75 ± 1.32</td>
</tr>
<tr>
<td></td>
<td>( \text{CaO}_2 ) (ml/dl)</td>
<td>15.61 ± 1.98</td>
<td>14.25 ± 1.57</td>
<td>8.20 ± 2.23</td>
<td>9.69 ± 2.29</td>
<td>11.93 ± 1.64</td>
<td>12.18 ± 2.22</td>
<td>12.40 ± 2.06</td>
<td>12.53 ± 1.24</td>
<td>—</td>
<td>13.21 ± 0.73</td>
<td>—</td>
<td>12.57 ± 1.79</td>
</tr>
<tr>
<td></td>
<td>( \text{DO}_2 ) (ml/kg/min)</td>
<td>23.19 ± 4.94</td>
<td>—</td>
<td>12.05 ± 7.08</td>
<td>13.08 ± 6.17</td>
<td>12.65 ± 2.71</td>
<td>12.09 ± 7.36</td>
<td>14.27 ± 2.29</td>
<td>16.08 ± 4.49</td>
<td>—</td>
<td>20.69 ± 5.75</td>
<td>—</td>
<td>18.57 ± 4.73</td>
</tr>
</tbody>
</table>

* \( p < 0.05 \), Group I compared with Group II. — = not done.

### TABLE 4

*Arterial and CV lactate and arterial bicarbonate values in swine with FPI*

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Group &amp; Parameter</th>
<th>Baseline</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>75</th>
<th>90</th>
<th>120</th>
<th>150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Art lactate (mEq/L)</td>
<td>1.63 ± 0.33</td>
<td>2.31 ± 1.02</td>
<td>—</td>
<td>3.34 ± 1.10</td>
<td>—</td>
<td>4.66 ± 2.11</td>
<td>—</td>
<td>4.91 ± 2.28</td>
<td>5.08 ± 2.51</td>
<td>5.59 ± 3.52</td>
</tr>
<tr>
<td></td>
<td>CV lactate (mEq/L)</td>
<td>1.70 ± 0.36</td>
<td>2.14 ± 0.72</td>
<td>—</td>
<td>3.6 ± 1.25</td>
<td>—</td>
<td>4.59 ± 1.88</td>
<td>—</td>
<td>5.21 ± 2.48</td>
<td>5.44 ± 2.70</td>
<td>5.69 ± 3.80</td>
</tr>
<tr>
<td></td>
<td>Art bicarb (nmol/L)</td>
<td>29.16 ± 2.48</td>
<td>25.03 ± 2.94</td>
<td>22.24 ± 3.70†</td>
<td>21.71 ± 2.71</td>
<td>20.01 ± 4.12</td>
<td>19.83 ± 4.42</td>
<td>19.37 ± 4.71</td>
<td>18.19 ± 5.09</td>
<td>19.14 ± 5.16</td>
<td>19.50 ± 5.97</td>
</tr>
<tr>
<td></td>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Art lactate (mEq/L)</td>
<td>1.62 ± 0.29</td>
<td>2.71 ± 0.85</td>
<td>—</td>
<td>4.48 ± 2.23</td>
<td>—</td>
<td>4.06 ± 1.79</td>
<td>—</td>
<td>3.85 ± 1.80</td>
<td>4.3 ± 1.51</td>
<td>4.25 ± 1.57</td>
</tr>
<tr>
<td></td>
<td>CV lactate (mEq/L)</td>
<td>1.78 ± 0.27</td>
<td>2.63 ± 0.72</td>
<td>—</td>
<td>4.60 ± 2.10</td>
<td>—</td>
<td>4.54 ± 2.28</td>
<td>—</td>
<td>4.00 ± 1.50</td>
<td>4.42 ± 1.53</td>
<td>4.45 ± 1.53</td>
</tr>
<tr>
<td></td>
<td>Art bicarb (nmol/L)</td>
<td>30.31 ± 3.65</td>
<td>24.60 ± 2.88</td>
<td>18.22 ± 4.15</td>
<td>17.00 ± 6.80</td>
<td>19.43 ± 3.13</td>
<td>18.24 ± 5.98</td>
<td>18.20 ± 2.45</td>
<td>16.90 ± 2.34</td>
<td>18.75 ± 4.91</td>
<td>19.23 ± 4.40</td>
</tr>
</tbody>
</table>

* Art = arterial; bicarb = bicarbonate; CV = cerebral venous; — = not done.

† \( p < 0.05 \), Group I compared with Group II.
Injury and hemorrhage, but increased with the initiation of resuscitation. Maximum ICP levels were 16.4 ± 5.3 mm Hg and 17.5 ± 8.2 mm Hg in Groups I and II, respectively (p = 0.752; two-sample t-test). Although ICP values in Group II were significantly greater than those in Group I at 45 and 50 minutes, over time ICP did not differ significantly between groups (p = 0.142; repeated-measures ANOVA). In both Groups I and II, mean CPP values fell significantly following TBI and hemorrhage and remained significantly lower than baseline levels throughout the initial 60-minute resuscitation period (Fig. 3 lower). Aggressive compared with limited resuscitation prior to control of aortic hemorrhage did not improve CPP. Despite limiting resuscitation during the initial 60 minutes in the Group I animals, CPP remained higher than 50 mm Hg during the majority of this time period. In both groups, mean CPP improved to baseline levels shortly after control of aortic hemorrhage and further resuscitation. Although CPP levels in Group II were significantly greater compared with Group I at 80, 115, and 120 minutes, over time CPP did not differ between the two groups (p = 0.602; repeated-measures ANOVA).

In both groups, CBF values were significantly lower than baseline values during the initial 60-minute resuscitation period (Fig. 4). Aggressive resuscitation resulted in the return of CBF to baseline values only after control of hemorrhage from the aortic tear. The Group II animals did not demonstrate improved CBF compared with Group I animals, despite initial aggressive resuscitation. Minimum CBF values occurred at 60 minutes in both groups, and were 58 ± 20 ml/100 g/min and 51 ± 27 ml/100 g/min in Groups I and II, respectively (p = 0.556). The ScvO₂ decreased sharply (Fig. 5), whereas the cO₂ER increased (not shown) following TBI and hemorrhage. Both of these parameters improved with resuscitation; ScvO₂ remained greater than the theoretic ischemic threshold of 60%, and cO₂ER was less than the threshold of 40% throughout the initial 60-minute resuscitation period in the Group I animals.20,21 As with CBF values, initial aggressive resuscitation prior to control of aortic hemorrhage did not yield an improvement in these physiological parameters compared with initial limited resuscitation. The AVDO₂ also did not differ between groups; AVDO₂ reached maximum values of 7.2 ± 2.2 and 9.1 ± 2.2 ml/dl at time 0 (just before resuscitation) in Groups I and II, respectively, but decreased rapidly during resuscitation and remained less than 5 ml/dl throughout the resuscitation period. The CMRO₂ did not change from baseline values throughout the experimental protocol and did not differ between groups (Fig. 6). Cerebral venous lactate measurements increased in parallel with arterial lactate values, and did not differ between groups (Table 4).

**Discussion**

In this model of combined FPI and uncontrolled hemorrhage, aggressive resuscitation compared with limited resuscitation prior to achieving control of hemorrhage resulted in an increase in hemorrhage volume, failure to improve cerebrovascular physiological parameters, and a trend toward increased mortality rates. These data indicate that in the setting of combined TBI and uncontrolled hemorrhage, aggressive resuscitation may not minimize the potential for secondary brain injury as is currently believed. In addition, our data provide a fairly complete profile of the cerebral metabolic state and indicate that even during the 60-minute period of limited resuscitation in the Group I animals, the metabolic needs of the brain were being met. Sagittal sinus oxyhemoglobin saturation remained greater than the theoretic ischemic threshold of 60% throughout resuscitation, including the 60-minute period in which resuscitation was limited.12,22 In addition, although CBF levels decreased and remained at approximately 50% of baseline during the initial 60 minutes before control of aortic hemorrhage, AVDO₂ remained within normal limits and was no greater than in animals that were aggressively resuscitated from the start. Furthermore, AVDO₂ is a better indicator of global ischemia than either sagittal sinus oxyhemoglobin saturation or CBF alone. Finally, the cMRO₂ did not differ among groups and did not change from baseline throughout the resuscitation period. These results do not support and indeed directly conflict with the widely held concept that aggressive resuscitation of patients with TBI and hemorrhagic shock is beneficial from a physiological and metabolic standpoint.
Limited resuscitation after brain injury and severe uncontrolled hemorrhage

Currently all patients with TBI and accompanying hemorrhage, regardless of the setting, are treated the same. That is, they are aggressively resuscitated with the goal of restoring the intravascular volume and BP toward normal to avoid or minimize the potential for a secondary ischemic brain insult caused by hypotension. These standards are based on studies in which it has been demonstrated that outcome from TBI is significantly worsened when accompanied by a secondary insult such as hypotension. The deleterious effects of hypotension on the outcome of severe brain injury were demonstrated in the recent data analysis by Chesnut, et al., of 717 patients from the TCDB. In this study, a single episode of hypotension, as defined by a systolic BP less than 90 mm Hg, was found to double the incidence of mortality and significantly increase morbidity compared with patients who suffered similarly severe TBI but no documented hypotension. In addition, these investigators noted that prehospital hypotension was among the five most powerful predictors of outcome. In several other studies investigators have similarly demonstrated the devastating effects that secondary insults such as hypotension can have on outcome in brain-injured patients.8,39,45

The mechanism for the poor outcome in patients with both brain injury and hypotension is believed to be alteration of cerebrovascular resistance and impairment of cerebral autoregulation. Laboratory and clinical data indicate that the entire cerebral autoregulatory curve is shifted to the right, resulting in a higher limit for the lower autoregulatory CPP threshold. Hence, CPPs that would be well tolerated in the normal brain result in reduced CBF and ischemia in the injured brain.8,17,20,22

Consistent with these findings, Rosner, et al.,33 report data from a clinical series in which 158 patients with severe TBI were aggressively managed to maintain a minimum CPP of 70 mm Hg. The overall mortality rate of patients in this study was 29%, and ranged from 52% in those with an admission GCS score of 3 to 12% in those with an admission GCS score of 7. The proportion of survivors with favorable outcomes, as defined by a Glasgow Outcome Scale score of 4 or 5 or a return to previous activity, was 59%, and ranged from 35% in patients with an admission GCS score of 3 to 75% in those with an admission GCS score of 7. The authors note that this represents a substantial reduction in mortality rates and improvement in outcome compared with the data from the TCDB analysis. In two smaller series, Chan and colleagues present similar data, which may mean that maintenance of CPP is associated with improved outcome in brain-injured patients, although the threshold level for CPP varies among these studies.11,19,20,27

Based on these data and the concept that injured brain regions with impaired autoregulation are more susceptible to a secondary ischemic injury from low perfusion pressure, initial treatment for all patients with multiple traumas and brain injury has been directed at rapid volume expansion to maintain or enhance CPP. Because CPP cannot be measured during the early phases of resuscitation, that is, in the prehospital setting or in the emergency department, treatment recommendations for these settings center around arterial BP. The Brain Trauma Foundation Guidelines recommend maintenance of a mean arterial BP of 90 mm Hg or higher to attempt to maintain a CPP greater than 70 mm Hg. However, it is also noted in these guidelines that there have been no studies performed to test the efficacy of these recommendations, and for ethical reasons a prospectively controlled study of the effects of hypotension on the outcome of severe head injury cannot be conducted.18 We would argue that there are insufficient data to support this approach, at least in the prehospital and emergency department settings, and further study is thus indicated for several reasons.

First, although the TCDB analysis and related studies have clearly demonstrated that secondary insults such as hypotension are detrimental to outcome in brain-injured patients, these were uncontrolled observational descriptive reports of large databases. These studies did not assess resuscitation strategy, and no inferences can be made or conclusions drawn from these data with respect to the appropriate treatment for these patients.7,19,20,39,45 Similarly although Rosner, et al.,33 presented impressive outcome statistics, and Chan and colleagues presented substantive blood flow and metabolic data to support a CPP threshold of 70 mm Hg in brain-injured patients, these studies cannot be considered definitive. The data from Chan and colleagues represent a small series of patients without controls, and these authors provided no outcome data. Similarly, the study by Rosner, et al., was uncontrolled; their conclusion that the therapeutic strategy of maintaining CPP at or above 70 mm Hg resulted in improved outcome is based on data from unmatched historical controls, specifically the TCDB analysis. This is problematic and one must be very cautious in drawing conclusions based on such comparisons for several reasons. First, because patients were not entered under the same protocol one cannot assume that they represent equivalent study populations. Moreover, the apparent improvement in outcome in the study by Rosner, et al., may
be related more to the avoidance of hypotension and hypoxia, or to other improvements in the standard of care of patients with TBI, which were made after the publication of the TCDB analysis but before the Rosner study, than to the maintenance of the CPP. In addition, the study by Rosner, et al., did not provide corresponding blood flow or cerebral metabolic data, and, hence, the mechanism for the apparently improved outcome is unknown. To date there have been no prospective randomized controlled trials in which the effect of resuscitation to various CPP thresholds has been evaluated.

Just as important, the foregoing data are not generalizable to the prehospital or emergency department setting. First, the therapeutic methods used to maintain CPP in these studies included the infusion of systemic vasopressors, the drainage of cerebrospinal fluid through a ventricular catheter, and the infusion of mannitol. Obviously the first two treatment options would not be available to, or appropriate for, emergency department patients with brain injury and hemorrhagic shock. Second and more important, the data were collected from the relatively controlled environment of the neurosurgical intensive care unit several hours and even days after the initial injury. The pathophysiological processes that predominate several hours or days postinjury may not be the same as those that are characteristic of the period immediately following injury, that is, in the prehospital and emergency department settings.

For example, one can assume that in the study patients, hemorrhage from other injuries had already been controlled; this would not be the case in the prehospital and emergency department settings. As demonstrated by our data and other recently published laboratory studies, the effect of and outcome from fluid resuscitation will vary depending on whether hemorrhage is controlled.2,10,40,41 Two other important pathophysiological differences between the early and late phases post-TBI are the timing and degree of cerebral edema and postrauamatic cerebral vasospasm. In general, cerebral edema is not maximal until at least 24 to 48 hours after TBI, and similarly, posttraumatic cerebral vasospasm generally does not develop until approximately 48 hours postinjury.4,6,10,26,31,47 Both of these phenomena place the brain at greater risk for secondary ischemic injury and, hence, higher perfusion pressures may be required during the later phases after TBI compared with the early acute stage.

In addition to the limitations of the published data on which current protocols are based, and the complete lack of prospective randomized controlled clinical trials, there are laboratory data that indicate that the current standard for early aggressive resuscitation with isotonic crystalloid in the setting of TBI may not be ideal. In several studies in which a cryogenic model of brain injury was used to compare various resuscitation regimens, increased cortical water content and elevation of ICP levels was demonstrated following resuscitation with either normal saline or lactated Ringer’s solution.37,42,48,51 Similarly, studies in which various combined brain injury and hemorrhagic shock models were used to compare the efficacy of either hypertonic or colloid solutions with standard normal saline or lactated Ringer’s solution consistently demonstrate exacerbation of or greater increases in ICP when animals are resuscitated with either normal saline or lactated Ringer’s solution.1,15,30,46

A final limitation of the published data on which current protocols are based involves the laboratory models used to date. So far, in all laboratory studies of combined TBI and hemorrhagic shock controlled hemorrhages have been used, and in most a cryogenic model of brain injury has been chosen. A controlled hemorrhage or a cryogenic brain injury model cannot adequately replicate many of the pathophysiological processes known to occur in patients with multiple traumas including brain injury and acute hemorrhage. In a controlled hemorrhage model, bleeding occurs solely from a surgically implanted catheter and the vascular circuit remains intact; hemorrhage volume and duration are determined by the investigator, rather than the animal’s response to injury. Thus, the investigator is unable to assess the effect an intervention may have on a site of vessel injury. This is significant because, if a given resuscitation regimen yields an increase or decrease in hemorrhage volume, it will potentially alter hemodynamic parameters as well as cerebrovascular dynamics, as was demonstrated in our study. With regard to brain injury models, a cryogenic injury results in a relatively focal lesion. However, a clinically relevant TBI model will deliver significant energy to produce rapid compression and deformation of cerebral tissue, leading to more diffuse neuroaxonal injury. The FPI model has been recommended by many investigators because it yields such a diffuse injury pattern and consistently induces neurological, physiological, and histological changes comparable to those observed in human TBI.9 We believe that the current model is a more representative one of patients with multiple traumas, in that the animals experience a large life-threatening vascular injury with significant intraperitoneal hemorrhage, and that it is a clinically relevant model of TBI.

**Limitations of the Study**

This study has several limitations, and certainly it would be premature to recommend that we limit resuscitation in brain-injured patients with multiple traumas based solely on the present data. First, although there was no metabolic evidence of global ischemia in animals that initially received limited resuscitation, one cannot completely rule out the possibility that they suffered focal or regional areas of cerebral ischemia. Second, we evaluated only short-term mortality and have no measure of neurological outcome. Third, we recognize the limitations of the current model. It represents a very specific injury pattern that may not be generalizable to all patients who suffer multiple traumas with TBI. However, no single animal model will allow us to address all of the complex pathophysiological processes that occur in the setting of combined TBI and hemorrhagic shock, and we believe that the current model offers significant advantages over those used previously. Finally, we used isoflurane anesthesia, which has been demonstrated to increase CBF and ICP in the setting of experimental brain injury.14,29,34 Certainly an unanesthetized model would be more ideal and representative of the acutely injured patient; however, this would not be humane or ethically responsible. Isoflurane is commonly used clinically and, therefore, we believe it is an appropriate choice for the current experimental protocol.
Limited resuscitation after brain injury and severe uncontrolled hemorrhage

Conclusions

Our data indicate that in the setting of ongoing, uncontrolled hemorrhage and TBI, early aggressive resuscitation, which is currently recommended, may not be the most appropriate therapeutic strategy, because it may result in exacerbation of ongoing hemorrhage and failure to optimize cerebrovascular physiological parameters. Additionally, in this model a 60-minute period of moderate hypotension (MAP 60 mm Hg) was well tolerated and did not compromise cerebrovascular hemodynamics, as evidenced by physiological parameters that remained within the limits of cerebral autoregulation. Previous laboratory and clinical data clearly demonstrate that in the setting of TBI, secondary ischemic insults, which may occur with hemorrhagic hypotension, are not well tolerated and have devastating effects on outcome. Hence, the greatest potential for reducing the high morbidity and mortality rates associated with this disease process rests with the development of better methods of prevention, early detection, and treatment of these secondary insults. Although this goal may be common to both the early and late phases of treatment, the collective data indicate that the most effective method of accomplishing this goal may vary, depending on the setting. Continuing simply to apply data from the neurointensive care unit to the emergency department and prehospital settings will not result in the development and delivery of optimal treatment strategies for patients with TBI.

References

18. Joint Section on Trauma and Critical Care of the American Association of Neurological Surgeons and the Brain Trauma Foundation: Guidelines for the Management of Severe Head Injury. Park Ridge, Ill: American Association of Neurological Surgeons, 1995
27. McGraw CP: A cerebral perfusion pressure greater than 80 mm Hg is more beneficial, in Hoff JT, Betz AL (eds): Intracranial Pressure VII. Berlin: Springer-Verlag, 1989, pp 839–841

---

Manuscript received September 3, 1999.
Accepted in final form April 28, 2000.
This research was sponsored in part by Office of Naval Research Grant No. N00014-99-1-0907 to Dr. Stern.
*Address reprint requests to:* Susan A. Stern, M.D., Department of Emergency Medicine, University of Michigan Medical Center, TC-B1354-0303, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109–0303. email: sue stern@umich.edu.