Acute ethanol intoxication in a model of traumatic brain injury with hemorrhagic shock: effects on early physiological response

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Object. Traumatic brain injury (TBI) is exacerbated by hypotension and hypoventilation. Because previous studies have shown a potentiating effect of ethanol (EtOH) on TBI and hemorrhagic shock (HS), the authors investigated the effects of EtOH on the early physiological response to TBI with and without HS.

Methods. Anesthetized swine, weighing approximately 20 kg each, underwent fluid-percussion TBI of 3 atm with or without 30 ml/kg hemorrhage for a period of 30 minutes. The mean arterial blood pressure, intracranial pressure, cerebral perfusion pressure (CPP), cardiac output, cerebral venous oxygen saturation, and metabolic parameters were monitored for 3 hours postinjury. Ventilation and the response to hypercapnia were also measured. Regional cerebral blood flow and renal blood flow were measured using dye-labeled microspheres. Five groups were studied: control, TBI, TBI/EtOH, TBI/HS, and TBI/HS/EtOH. The EtOH (3.5 g) was given intragastrically 100 minutes preinjury.

The TBI/HS/EtOH group demonstrated a 3-hour mortality rate of 56% and postinjury apnea requiring ventilation in 44% of animals compared with 0% in all other groups. Minute ventilation and the hypercapnic ventilatory response were significantly reduced in the postinjury period in the TBI/HS/EtOH group. The animals in this group had significantly lower CPP and cardiac output in the first 60 minutes postinjury, as well as lower renal and cerebral blood flow. Postinjury cerebral venous lactate levels were higher, and cerebral venous pH was lower in the TBI/HS/EtOH group.

Conclusions. In this model of TBI, acute EtOH intoxication in the presence of HS potentiates the physiological and metabolic alterations that may contribute to secondary brain injury.

Key Words • ethanol • traumatic brain injury • hemorrhagic shock • cerebral blood flow • ventilation • pig

TRAUMATIC brain injury (TBI) is frequently complicated by other injuries that may result in systemic arterial hypotension and hypoxemia. In clinical and laboratory investigations it has been found that neurological outcome is worsened and mortality is increased when TBI is accompanied by hypotension and hypoxemia. Ethanol (EtOH) intoxication may also have a potentiating effect on traumatic injury. Our previous work in experimental models of hemorrhagic shock (HS) without brain injury showed exaggerated early hypotension, but no difference in survival time in EtOH-treated animals. In TBI models, EtOH intoxication reduced cerebral perfusion pressure (CPP) and cerebral blood flow (CBF), and impaired ventilation. In a model of combined TBI and HS, EtOH-treated animals showed decreased survival time and CPP and increased cerebral oxygen extraction ratios postinjury when compared with controls. This experiment was designed to assess the effects of EtOH in isolated TBI compared with TBI/HS. The primary hypothesis was that EtOH intoxication would worsen cerebral and systemic physiological parameters to a greater extent in animals subjected to TBI/HS compared with TBI alone.

Materials and Methods

This investigation was approved by the University of Michigan Committee on Use and Care of Animals. Animal care standards were in compliance with the “Guide for the Care and Use of Laboratory Animals.”

Animal Preparation and Instrumentation

Forty immature Yorkshire swine, weighing approximately 20 kg each, were sedated with 20 mg/kg of intramuscularly administered ketamine, given isoflurane (2%) through nosecones, and endotracheally intubated. Thereafter animals were maintained on 1.15% isoflurane at a fraction of inspired oxygen rate of 28 to 31%. An
Physiological Measurements

A computerized physiological data acquisition system was used for continuous monitoring of systolic and diastolic arterial blood pressure, mean arterial blood pressure (MABP), ICP, pulmonary arterial pressures, end-tidal carbon dioxide (ETCO₂) concentration, and brain injury. The CPP, which was derived from MABP minus ICP, was recorded continuously, and cardiac output was measured using a thermistor technique. Systemic vascular resistance (SVR) was calculated using the formula: SVR = (MABP - central venous pressure) / cardiac output × 80.

Ventilatory parameters, including minute ventilation (Vi), tidal volume, ventilatory frequency (VF), and ETCO₂, were measured continuously. The hypercapnic ventilatory response was determined by infusing 6% CO₂ into the ventilatory circuit while maintaining all other gas concentrations at the standard levels. Ventilatory and physiological responses to hypercapnia were recorded before and after 5 minutes of 6% CO₂ exposure. The hypercapnic response is the slope of the line created by calculating the change in Vi divided by the change in ETCO₂ concentration (ΔVi / ΔETCO₂).

Arterial and venous blood samples were obtained every 15 minutes for the 1st hour postinjury and every 30 to 60 minutes thereafter. Analysis included measurements of systemic arterial and cerebral venous blood gas levels, hematocrit, hemoglobin, and serum sodium, potassium, calcium, glucose, and lactate. Serum EtOH levels, which were obtained preinjury and 2 hours postinjury (or at death if animals died prior to 2 hours postinjury) were measured using a nicotinamide adenine dinucleotide/alcohol dehydrogenase colorimetric assay and read on an ultraviolet spectrophotometer.

The CBF and renal blood flow determinations were made immediately before injury and at 30 and 180 minutes postinjury by using dye-labeled microspheres with a reference sample method. Blue, yellow, or red 15-μm microspheres were injected via the left ventricular catheter while reference blood was withdrawn from the femoral artery at 6 ml/minute for 2 minutes. After the animals were killed, 3-g tissue samples were taken from the right and left anterior and posterior cerebral cortex, cerebellum, and medulla, and two cortical samples were taken from each kidney. Tissue and blood samples were digested with 4 M potassium hydroxide and the spheres were recovered by vacuum filtration through a polyester membrane with a 10-μm pore size. Dye was extracted with dimethyl formamide, and absorbance was measured using the spectrophotometer. The final rCBFs were calculated using matrix inversion software to compare tissue absorbances with reference blood sample absorbances.1

Study Groups

Five groups were studied: 1) control, sham for injury and hemorrhage; 2) TBI only; 3) TBI/EtOH, TBI with EtOH administration; 4) TBI/HS, TBI, and hemorrhage; and 5) TBI/HS/EtOH, TBI, hemorrhage, and EtOH administration. Animals in the TBI groups received a 15-msec fluid-percussion brain injury at a target peak pressure of 3 atm. Animals in the HS groups were subjected to a 30-ml/kg hemorrhage over 30 minutes, which was started simultaneously with TBI. Blood was withdrawn using a computer-driven roller pump. To simulate the dynamics of acute bleeding, the hemorrhage rate was decreased exponentially during the 30-minute span. Animals in the EtOH-treated groups received 3.5 g/kg of 95% EtOH diluted 1:1 with tap water as an intragastric bolus 100 minutes before injury. Non-EtOH-treated animals received an equal amount of tap water.

Animals that became apneic in the postinjury period received ventilation with a volume-cycled ventilator to maintain PaO₂ at 90 to 120 mm Hg and PaCO₂ at 40 to 50 mm Hg. Animals surviving at 3 hours postinjury were killed with 30-mg/kg injections of pentobarbital. At death, the brain and kidneys were removed and sectioned for organ blood flow analysis.

Data Analysis

Values are presented as the means ± standard deviations. Comparisons between groups were made using two-way analysis of variance (ANOVA) and repeated-measures ANOVA. Post-hoc evaluations were performed using the Tukey test to identify significant differences between groups. For independent assessment of the effects of TBI, HS, and EtOH on study outcome parameters, indicator variables were used to code for these interventions. A regression technique that estimated the effect of group assignment while adjusting for the other interventions was used to derive coefficients for the indicator variables. Pearson correlation coefficients were calculated to determine the variance in EtOH levels correlated with changes in some parameters. Because of early deaths in the TBI/HS/EtOH group, fewer animals were available for comparison beyond the 60-minute datapoint. A probability value of 0.05 or less was considered statistically significant for all comparisons.

Sources of Supplies and Equipment

The fluid-percussion device was purchased from Stevenson Machine Co., Cincinnati, OH. The brain temperature probe and the Masterflex roller pump were acquired from Cole-Parmer Instrument Co., Chicago, IL and the No. 4 French fiberoptic oximetric catheter from Abbott, North Chicago, IL. The computerized data acquisition system was obtained from Biopac, Santa Barbara, CA, and the cardiac output computer was purchased from American Edwards, Irvine, CA. Ventilatory parameters were monitored using the Datex Capnomac Ultima, which was purchased from Datex Instrumentarium Corp., Helsinki, Finland. The blood gas and chemistry analyzer (Gem Premier model) was obtained from Malinekrodt Sensor Systems, Ann Arbor, MI, and the Ektachem DT 60II and DTSC II multichemistry analyzer from Kodak Co., Rochester, NY. The colorimetric assay was purchased from Sigma Diagnostics, St. Louis, MO, and the spectrophotometer (model 8452A Diode-Array) from Hewlett-Packard, Waldbronn, Germany. The dye-labeled microspheres (Dye-Trak) and the dimethyl formamide were purchased from Triton Technologies, San Diego, CA, and Fischer Scientific, Fair Lawn, NJ, respectively.

Results

Physiological Findings

Baseline parameters were well matched between groups (Table 1). The mean EtOH levels, although not significantly different between the TBI/EtOH and TBI/HS/EtOH groups, were variable. Three animals in the TBI/HS/EtOH group, despite receiving an identical dose, demonstrated preinjury EtOH levels in the range of 250 to 330 mg/dl, compared with a range of 100 to 160 mg/dl in other EtOH-treated animals.

Five (56%) of nine animals in the TBI/HS/EtOH group died in the 180-minute postinjury monitoring period, compared with none of the animals in other groups. Two of
these five animals showed high preinjury EtOH levels, and the mean time to death for the five animals that died prematurely was 93 minutes. The overall mean survival time was significantly reduced in the TBI/HS/EtOH group (Table 2).

The primary ventilatory response to TBI alone or TBI with EtOH was a small decrease from baseline values in $V_t$ and $V_e$ in the first 30 minutes postinjury. In the TBI/HS group $V_e$ increased in the 1st hour postinjury, presumably in response to the metabolic acidosis induced by hemorrhage. In the TBI/HS/EtOH group, ventilation was significantly impaired in the early postinjury period. Four of nine animals in the TBI/HS/EtOH group developed postinjury apnea requiring assisted ventilation, compared with none in the other groups. The mean postinjury $V_e$ was consistently reduced and the hypercapnic response was significantly reduced in the TBI/HS/EtOH group in the postinjury period ($p = 0.011$, repeated-measures ANOVA). The main effect was a reduction in $V_e$. In the regression analysis for $V_e$ and the hypercapnic response at

### TABLE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Postinjury Time (min)</th>
<th>Control</th>
<th>TBI</th>
<th>TBI/EtOH</th>
<th>TBI/HS</th>
<th>TBI/HS/EtOH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>survival (min)</td>
<td></td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>132 ± 62</td>
<td>0.001</td>
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<tr>
<td>$V_e$ (resp/min)</td>
<td>15</td>
<td>41 ± 11</td>
<td>26 ± 8</td>
<td>30 ± 9</td>
<td>39 ± 15</td>
<td>25 ± 11</td>
<td>0.013/0.081</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>40 ± 12</td>
<td>29 ± 10</td>
<td>35 ± 12</td>
<td>40 ± 14</td>
<td>22 ± 9</td>
<td>0.013/0.018</td>
</tr>
<tr>
<td>$V_e$ (L/min)</td>
<td>30</td>
<td>6.4 ± 1.3</td>
<td>4.7 ± 1.3</td>
<td>4.8 ± 1.2</td>
<td>5.9 ± 2</td>
<td>3.8 ± 0.7</td>
<td>0.006/0.028</td>
</tr>
<tr>
<td>cardiac output (L/min)</td>
<td>30</td>
<td>3.07 ± 0.2</td>
<td>2.82 ± 0.1</td>
<td>3.06 ± 0.2</td>
<td>1.92 ± 0.2</td>
<td>1.21 ± 0.1</td>
<td>&lt;0.001/0.034</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>6.94 ± 0.1</td>
<td>5.45 ± 0.1</td>
<td>5.80 ± 0.1</td>
<td>2.83 ± 0.6</td>
<td>1.42 ± 0.2</td>
<td>&lt;0.001/0.017</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>30</td>
<td>95 ± 10</td>
<td>96 ± 11</td>
<td>104 ± 24</td>
<td>59 ± 15</td>
<td>42 ± 10</td>
<td>&lt;0.001/0.099</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>94 ± 11</td>
<td>82 ± 30</td>
<td>107 ± 21</td>
<td>71 ± 9</td>
<td>51 ± 18</td>
<td>&lt;0.001/0.298</td>
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<tr>
<td>ICP (mm Hg)</td>
<td>30</td>
<td>39 ± 4</td>
<td>46 ± 25</td>
<td>27 ± 10</td>
<td>8 ± 4</td>
<td>11 ± 6</td>
<td>&lt;0.001/0.97</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>10 ± 5</td>
<td>31 ± 11</td>
<td>26 ± 11</td>
<td>9 ± 3</td>
<td>11 ± 7</td>
<td>&lt;0.001/0.98</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>30</td>
<td>88 ± 11</td>
<td>52 ± 19</td>
<td>60 ± 12</td>
<td>52 ± 14</td>
<td>31 ± 11</td>
<td>&lt;0.001/0.016</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>84 ± 14</td>
<td>62 ± 15</td>
<td>64 ± 16</td>
<td>62 ± 8</td>
<td>40 ± 14</td>
<td>&lt;0.001/0.029</td>
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<tr>
<td>cerebral SVO2 (%)</td>
<td>30</td>
<td>72 ± 8</td>
<td>67 ± 19</td>
<td>67 ± 8</td>
<td>53 ± 12</td>
<td>43 ± 14</td>
<td>0.002/0.59</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>72 ± 7</td>
<td>68 ± 10</td>
<td>68 ± 10</td>
<td>62 ± 6</td>
<td>48 ± 12</td>
<td>&lt;0.001/0.04</td>
</tr>
<tr>
<td>pH</td>
<td>30</td>
<td>7.3 ± 0.04</td>
<td>7.30 ± 0.03</td>
<td>7.28 ± 0.06</td>
<td>7.28 ± 0.03</td>
<td>7.17 ± 0.08</td>
<td>&lt;0.001/0.01</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>7.36 ± 0.05</td>
<td>7.27 ± 0.05</td>
<td>7.26 ± 0.05</td>
<td>7.29 ± 0.03</td>
<td>7.14 ± 0.12</td>
<td>&lt;0.001/0.01</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± standard deviation. Statistical tests used are as follows: survival time was calculated according to Kruskal–Wallis; for all other parameters the first probability value listed is the ANOVA for all groups and the second is the Tukey post-hoc test comparing TBI/HS/EtOH with TBI/HS. The TBI/HS/EtOH group had only seven animals at the 60-minute datapoints because of the death of two animals prior to this. Abbreviation: resp = respiration.
30 minutes postinjury, the effect coefficients for EtOH intoxication reached significance \((p = 0.029\) for \(V_E\), and \(p = 0.020\) for \(R/Q\)) but those for TBI and HS did not (Fig. 1, Table 2). Postinjury \(P_aCO_2\) tended to be higher in the TBI and TBI/EtOH groups, but no significant intergroup differences were noted. The mean \(P_aO_2\) remained in the range of 120 to 140 mm Hg in all groups throughout the postinjury period.

The ICP increased significantly after fluid-percussion injury in the TBI and TBI/EtOH groups (Table 2). In the groups with concurrent hemorrhage, ICP increased in the first few minutes following fluid-percussion injury, but returned to preinjury levels by the 30-minute timepoint. The addition of hemorrhage to TBI caused cardiovascular impairment, with reduced cardiac output, MABP, and CPP. However, significantly greater reductions in cardiac output and CPP were observed in the TBI/HS/EtOH group than in the TBI/HS group at 30 and 60 minutes postinjury. The main factor contributing to lower CPP was a fall in \(P_aO_2\), rather than increased ICP. The mean systemic vascular resistance was variable, with no significant intergroup differences, but tended to be higher in the EtOH groups at 60 minutes postinjury (3000 ± 700 dyne/sec cm⁻² in EtOH groups compared with 2500 ± 500 dyne/sec cm⁻² in other groups).

The CBF was not significantly reduced at 30 or 180 minutes postinjury with TBI alone, but was significantly reduced with TBI and HS in all tested regions. The six brain regions had a comparable reduction in CBF. The TBI/HS/EtOH group had the biggest reduction in \(rCBF\) (Fig. 2). No correlation was found between \(EtOH\) levels and CBF (Pearson correlation coefficient \(< -0.15\) for all regions).

Renal blood flow was compromised to a greater degree by HS and EtOH than was CBF. At 30 minutes postinjury, renal blood flow was significantly lower in the TBI/HS/EtOH group in both kidneys when compared with all other groups. With the regression analysis, the effect coefficients for both HS and EtOH were significant for renal blood flow at 30 minutes postinjury, but the magnitude of the effect was greater for HS than for EtOH (for example, right kidney, \(p < 0.001\) for HS, \(p = 0.032\) for EtOH; Fig. 3).

**Metabolic Findings**

Cerebral venous oxygen saturation (SVO₂) levels were decreased at the 15-minute postinjury mark in all groups with TBI. By 30 minutes the mean cerebral SVO₂ had normalized in the TBI and TBI/EtOH groups, but remained low in the TBI/HS and TBI/HS/EtOH groups. Subsequently, the effects of hemorrhage predominated. At 60 minutes postinjury the cerebral SVO₂ levels were lowest in the TBI/HS/EtOH group (Table 2). By regression analysis, HS, but not TBI or EtOH, was associated with a significant effect on cerebral SVO₂ in the postinjury period. The hematocrit levels fell in the HS groups, from a baseline of 30 ± 3% to a mean of 25 ± 5% at 60 minutes, but no significant difference was found between the TBI/HS and TBI/HS/EtOH groups.

Cerebral venous and arterial lactate concentrations did not increase significantly with TBI alone, but did increase with EtOH and HS. Significantly higher lactate concentrations were found in the TBI/HS/EtOH group compared with all other groups (Fig. 4). The increase in lactate concentration was seen preinjury in EtOH-treated animals. However, only a weak correlation was noted between preinjury EtOH levels and cerebral venous lactate levels at 60 minutes postinjury (Pearson correlation coefficient = 0.332). Cerebral venous lactate levels were not signifi-
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Significantly higher than arterial levels, and a strong correlation was found between cerebral venous and arterial levels (Pearson correlation coefficient = 0.991 at 60 minutes postinjury). With regression analysis, both EtOH and HS, but not TBI, were associated with a significant effect coefficient for cerebral venous lactate concentrations at 30 and 60 minutes postinjury ($p < 0.005$ for HS, $p = 0.001$ for EtOH).

Cerebral venous pH was significantly lower in the EtOH- than non-EtOH–treated groups after EtOH loading and before injury. However, the effects became more pronounced in the postinjury period in the TBI/HS/EtOH group (Table 2). By regression analysis EtOH was found to be a more important factor in the reduction in cerebral venous pH than HS (at 60 minutes postinjury $p = 0.118$ for HS, and $p = 0.005$ for EtOH). Cerebral venous bicarbonate concentrations were also decreased in the TBI/HS/EtOH group, with the effect becoming significant at 60 minutes postinjury. Glucose levels remained in the normal range with no significant differences between groups. Blood levels of sodium, potassium, and calcium did not change significantly in response to TBI, HS, or EtOH.

**Discussion**

**Secondary Brain Injury and EtOH**

Intoxication with EtOH is a major predisposing factor in TBI. Numerous clinical studies document that 30 to 50% of adult patients with serious TBI are intoxicated with EtOH at the time of injury.$^{14,28,53,72}$ Much less is known about the specific effects of EtOH in TBI. Secondary brain injury results from physiological insults such as hypoxemia, hypotension, and uncontrolled intracranial hypertension that occur after the primary injury.

Secondary brain injury produces further damage to nerve tissue and may increase neurological deficits.$^{12}$ In clinical studies, morbidity and mortality rates from TBI increase if secondary brain injury occurs.$^{5,29,42,43,48,63}$ In the present study, animals subjected to TBI and HS in the presence of acute EtOH intoxication demonstrated decreased survival time, early ventilatory impairment, increased metabolic acidosis, and decreased CPP, cardiac output, and renal blood flow. These findings indicate that EtOH may play an important role in secondary brain injury.

Clinical studies lend some indirect support to the idea that EtOH may worsen secondary brain injury after TBI. In one study it was found that EtOH-intoxicated patients hospitalized with TBI were more likely to require endotracheal intubation and ventilatory support in the prehospital setting or emergency department.$^{22}$ In other studies increased brain hemorrhage volumes, worse neurological outcome, and increased permanent occupational disability have been found in patients with severe TBI who had high levels of EtOH in their blood or who were known to be alcoholic.$^{32,54}$ In a large clinical study in which data from the Traumatic Coma Data Bank were used, a history of chronic excessive EtOH use was associated with worse outcome after severe TBI, but acute EtOH intoxication was not.$^{55}$ Prehospital deaths were excluded in this study, and the injury mechanism and severity were not taken into account. Large-scale studies on motor vehicle crash victims in which injury forces have been controlled for have found a potentiating effect of EtOH intoxication on morbidity and mortality rates.$^{16,66}$ In studies on patients with non-TBI trauma, EtOH intoxication has been associated with lower blood pressure at admission and a greater need for blood transfusion.$^{15,51}$

**Comparison With Other Laboratory Investigations**

The effects of EtOH in TBI have been examined in other laboratory studies. Previously we reported that EtOH intoxication resulted in decreased survival time,
impaired hemodynamic response, and worsened measures of cerebral perfusion in an experiment in which only TBI/HS and TBI/HS/EtOH groups were compared. In that study ventilation was controlled and animals were splenectomized and subjected to less severe hemorrhage. In the present study, the effects of EtOH on isolated TBI were quite modest, but when TBI was combined with HS, EtOH had a significant potentiating effect.

In earlier studies in which a porcine fluid-percussion TBI model without HS was used, we found that EtOH intoxication, at levels similar to those seen in the current study, impaired ventilation and the hypercapnic response and led to decreased CPP and rCBF. The effects were more pronounced than those seen in the TBI/EtOH group in the present study. This was likely caused by the use of a different anesthetic regimen, which in the previous studies included ketamine, acepromazine, and thiamylal for induction and halothane as the maintenance anesthetic.

Investigators using TBI models in other species have found that EtOH increases mortality rates, worsens neurological outcome, and increases brain lesion volumes. Investigators using TBI models in other species have found that EtOH increases mortality rates, worsens neurological outcome, and increases brain lesion volumes.18,19,30,31,62 Albin and Bunegin provided neuropathological evidence for EtOH-induced secondary brain injury after TBI. Using a direct pressure/focal ischemia brain injury model in dogs, in which hypotension was induced with trimetaphan, they found that EtOH-treated hypotensive animals had significantly greater brain lesion volumes at 5 days postinjury than control hypotensive animals.

Possible Mechanisms for EtOH Potentiation of Secondary Brain Injury

In our porcine model, EtOH intoxication and HS appear to act synergistically in worsening the physiological response to TBI. At least two explanations can be offered for the observed effects. The first is that EtOH acts in a synergistic manner with hemorrhage to produce circulatory shock. In this paradigm, alterations in cerebral physiology are secondary to systemic cardiocirculatory depression. Previous studies conducted in HS models without TBI indicate that EtOH intoxication may lead to exaggerated early hypotension, impaired myocardial contractility, and an impaired ventilatory response to the metabolic acidosis induced by hemorrhage. In our study, the fact that cardiac output was reduced in the TBI/HS/EtOH group, but postinjury SVR was not, supports the idea that hemodynamic changes were caused by reduced myocardial contractility and not EtOH-induced peripheral vasodilation.

A second explanation of the observed effects invokes the wide-ranging neurochemical actions of EtOH intoxication. Biomolecular effects that have been reported with TBI and with EtOH intoxication include: 1) changes in γ-aminobutyric acid, N-methyl-D-aspartate, opiate, and adenosine receptor activity; 2) nitric oxide formation; 3) oxygen radical reactions; and 4) impaired intracellular signaling processes. However, almost no information is available on the neurochemical effects of EtOH in TBI models. It is possible that biomolecular actions of EtOH in the setting of TBI alter the function of neurons in the medulla or other regions of the brain that control respiratory function and cardiovascular tone. This could worsen ventilatory impairment and circulatory shock when hemorrhage is combined with TBI in the presence of EtOH.

These two explanations are not mutually exclusive, and it is possible that EtOH has direct cardiovascular along with indirect neurochemical effects in this model. Ethanol also has effects on cerebral vasculature, and at high levels has been reported to cause cerebral arteriolar vasoconstriction. Although we observed a trend toward lower rCBF in the TBI/HS/EtOH group in this study, we cannot determine if it was the result of cerebral arteriolar vasoconstriction. Systemic metabolic effects of EtOH such as increased blood lactate levels and metabolic acidosis may also contribute to neurochemical changes. One theory that combines the two previous explanations is that hemorrhage, with concurrent TBI, has a permissive or enabling effect on the neurochemical actions of EtOH. Hemorrhagic shock may lead to hypoperfusion of brain tissue, with brain cells becoming ischemic or dysfunctional. The effects of EtOH on membranes, receptors, and oxygen radical reactions may be activated or accentuated in this altered cellular environment, which could lead to further neuronal dysfunction or damage. If neurons that control cardiorespiratory function are affected, this could further impair the systemic cardiorespiratory response to TBI and HS. The specific mechanisms that mediate the effects of EtOH in TBI and HS remain to be determined.

Conclusions

In this porcine model of TBI with HS, acute EtOH intoxication has an early potentiating effect on the physiological and metabolic changes that may contribute to secondary brain injury. Animals treated with EtOH that subsequently underwent TBI and HS had impaired ventilation and decreased CPP, CBF, cardiac output, and renal blood flow in the 1st hour postinjury, along with higher blood lactate levels and lower cerebral venous pH. If similar changes occur in humans, this could partly explain the increased morbidity and mortality rates seen in EtOH-intoxicated patients who suffer traumatic injury.

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References

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