Effects of Ethanol in an Experimental Model of Combined Traumatic Brain Injury and Hemorrhagic Shock

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ABSTRACT

Objectives: Given that clinical and laboratory studies suggest that ethanol and hemorrhagic shock (HS) potentiate traumatic brain injury (TBI), the authors studied the effects of ethanol in a model of combined TBI and HS.

Methods: A controlled porcine model of combined TBI and HS was evaluated for the effect of ethanol on survival time, hemodynamic function, and cerebral tissue perfusion. Anesthetized swine (17–24 kg) were instrumented, splenectomized, and subjected to fluid percussion TBI with concurrent 25-mL/kg graded hemorrhage over 30 minutes. Two groups were studied: control (n = 11) and ethanol (n = 11). Ethanol, 3.5 g/kg intragastric, was given 100 minutes prior to TBI/HS. Systemic and cerebral physiologic and metabolic parameters were monitored for 2 hours without resuscitation. Regional cerebral blood flow (rCBF) and renal blood flow were measured with dye-labeled microspheres. Data were analyzed with 2-sample t-test and repeated-measures ANOVA.

Results: Ethanol levels at the time of injury were 162 ± 68 mg/dL. Average TBI was 2.65 ± 0.35 atm. Survival time was significantly shorter in the ethanol group (60 ± 27 min vs 94 ± 28 min, p = 0.011). The ethanol group had significantly lower mean arterial pressure, cerebral perfusion pressure, and cerebral venous O_2 saturation in the postinjury period. Cerebral O_2 extraction ratios and cerebral venous lactate levels were significantly higher in the ethanol group. A trend toward lower postinjury rCBF in all brain regions was observed in the ethanol group.

Conclusion: In this TBI/HS model, ethanol administration decreased survival time, impaired the hemodynamic response, and worsened measures of cerebral tissue perfusion.

Key words: alcohol; ethanol; injury; shock; hemorrhage; brain; trauma.

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Ethanol intoxication is present in approximately one third of adults who suffer multiple trauma or traumatic brain injury (TBI).[1–4] A number of clinical and laboratory studies have demonstrated a potentiating effect of ethanol on traumatic injury, including brain injury, but have not provided insight into possible mechanisms.[5–14] Many trauma victims have concurrent TBI and hemorrhagic shock (HS). Clinical investigations indicate that systemic arterial hypotension, reduced cerebral perfusion pressure (CPP), and reduced cerebral blood flow (CBF) are associated with increased morbidity and mortality following TBI.[15–23] Previously, we have studied the effects of ethanol in porcine models of isolated HS or TBI. Ethanol-treated animals subjected to HS alone demonstrated increased systemic hypotension.[24,25] In a porcine model of isolated TBI, we found that ethanol impaired ventilation and reduced mean arterial pressure (MAP), CPP, and CBF in the early postinjury period.[26,27] Previous studies have not assessed the effects of ethanol in the presence of concurrent TBI and HS. Therefore, the current study evaluated the effects of ethanol in a new model of combined TBI and HS. The hypothesis of this study was that ethanol-treated animals would have decreased survival time and worsened cardiovascular and cerebral physiologic parameters when compared with animals that did not receive ethanol.

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METHODS

Study Design: A porcine model of combined TBI and HS was evaluated for the effect of ethanol on survival

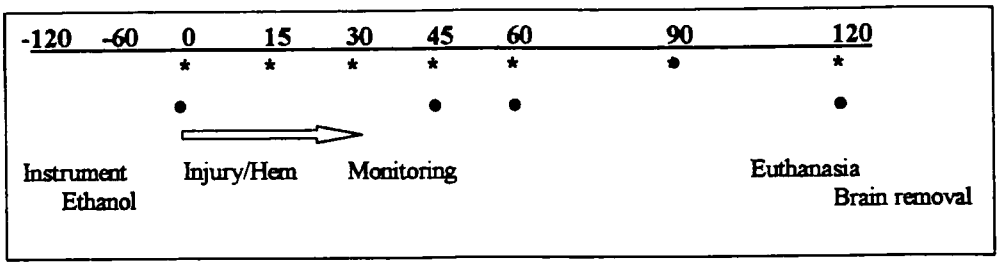

FIGURE 1. Timeline for the experimental protocol. Numbers are in minutes. * = Physiologic and metabolic measurements obtained. ● = Microspheres injected for reduced cerebral blood flow and renal blood flow measurement. Ethanol = ethanol administered for ethanol group. Injury/Hem = traumatic brain injury induced and hemorrhage performed (open arrow).

time, hemodynamic function, and cerebral tissue perfusion. The study was controlled and nonblinded. 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.

Subjects and Instrumentation: Immature swine (17–24 kg) of either sex were given a veterinary health screening examination. Animals determined to be healthy were sedated with IM ketamine 20 mg/kg, given nosecone isoflurane 2%, and endotracheally intubated. Thereafter, the animals were maintained on isoflurane 1.15% (1 MAC [minimal alveolar concentration]) with an FI_{O_2} of 28–31%. An orogastric tube was inserted for ethanol or placebo administration. Bilateral femoral artery and vein and right carotid artery catheters were placed for drug administration, blood sampling, hemorrhage, and arterial pressure monitoring. A pulmonary artery thermodilution catheter was placed for pressure, core temperature, and cardiac output (CO) monitoring. A left ventricular catheter was inserted via the femoral artery for injection of microspheres to determine regional blood flow measurements. Splenectomy was performed using standard surgical techniques. The animal was then placed prone in a head stabilizer and the scalp was reflected. A 16-mm craniotomy was created with a hand drill 1.5 cm to the right of the sagittal suture, and 6 cm anterior to the inion. A T-shaped bolt that connects to the fluid percussion device was screwed into the craniotomy site until it abutted the intact dura. The fluid percussion device (Stevenson Machine Co., Cincinnati, OH) consists of a saline-filled plexiglass cylinder (length 60.5 cm, ID 7 cm) that is connected to a 0.8-cm ID plastic tube, both of which are saline-filled. The end of the smaller plastic tube has a threaded metal fitting that screws into the craniotomy bolt. On the opposite end of the device is a pendulum arm with a 4.8-kg weight at its distal end. This arm is drawn back to a predetermined setting and released. The weight strikes a plexiglass piston, which in turn strikes a rubber seal at this end of the cylinder. The resulting saline fluid wave that is generated in the closed system transmits a 15-msec pressure pulse to the intact dura. A high-pressure transducer (Sensym, Sunnyvale, CA) screwed into one side-port of the craniotomy bolt permits quantification of delivered pressure.

A second craniotomy was performed in the left posterior parietal region, 3 mm anterior and 5 mm lateral to the bregma. A neonatal intraventricular catheter (Phoenix Biomedical, Valley Forge, PA) was placed in the left lateral ventricle and connected to an intracranial pressure transducer. A brain temperature probe (Cole-Parmer, Niles, IL) was placed in the ventricle adjacent to the catheter and the site was sealed with dental cement. A third, T-shaped craniotomy was made just anterior to the inion over the midline, and the sagittal sinus was identified and accessed with a 14-ga IV catheter. A 4-Fr fiberoptic oximetric catheter (Abbott, North Chicago, IL) was placed through the 14-ga catheter into the sinus for cerebral O_2 saturation monitoring and blood sampling. The catheters were then sealed in place with dental cement.

Measurements: Following instrumentation, the animals were paralyzed with succinylcholine 1.5 mg/kg as an IV bolus, followed by an infusion of 2–4 mg/kg/hr. A volume-cycled ventilator was used to maintain PaO_2 at 90–120 torr, and $PaCO_2$ at 40–50 torr. A computerized physiologic data acquisition system (Biopac, Santa Barbara, CA) was used for monitoring of systolic and diastolic arterial blood pressures (BPs), MAP, intracranial pressure (ICP), pulmonary artery pressures, and end-tidal CO_2 concentration. Brain injury was measured with the Sensym transducer and recorded on the Biopac system with a sampling frequency of 700/sec. CO was measured by thermodilution technique (American Edwards Cardiac Output Computer, Irvin, CA). Arterial and venous blood was sampled every 15 minutes for the first hour after injury, and every 30 minutes thereafter. Measurements performed every 15 minutes included systemic arterial and cerebral venous blood gases, hematocrit, hemoglobin, and blood sodium, potassium, and calcium (Gem Premier Blood Gas and Chemistry Analyzer, Mallinckrodt Sensor Systems, Ann Arbor, MI). Lactate and glucose were measured at preinjury, and 30, 60, and 120 minutes after (Kodak Ektachem DT 60II and DTSC II Multichemistry Analyzer, Rochester, NY). Ethanol levels, obtained preinjury and 2 hours postinjury, or upon death of the animal, were mea-

sured by gas chromatography (Hewlett Packard model 5890, Palo Alto, CA).

Cerebral and renal blood flow determinations were made immediately before injury, and at 45, 60, and 120 minutes postinjury using dye-labeled microspheres (Dye-Trak, Triton Technologies, San Diego, CA) with a reference sample methodology. Blue, yellow, white, or red 15-μ microspheres were injected via a pigtail catheter into the left ventricle while reference blood was withdrawn from the femoral artery at 6 mL/min for 2 min. Following euthanasia, 3-g tissue samples were taken from the right and left anterior and posterior cerebral cortex, cerebellum, and medulla. Two cortical tissue samples (1.5 g each) were taken from the right and left kidneys. The tissue and blood samples were digested with 4 mol potassium hydroxide and the spheres were recovered by vacuum filtration through a polyester membrane with a 10-μm pore size. Dye was extracted from the spheres using dimethyl formamide (Fisher Scientific, Fair Lawn, NJ). Absorbance was measured on a spectrophotometer (Hewlett Packard 8452A, Diode-Array, Walbron, Germany). Final regional blood flows were calculated by comparing tissue absorbances with reference blood sample absorbances using matrix inversion software. The combined weights of the 6 regions represented approximately one-third of total brain weight.

Interventions: Two experimental groups were studied. The animals in the ethanol group received 3.5 g/kg of 95% ethanol as a 1:1 dilution with tap water by orogastric tube 100 minutes prior to brain injury. The control animals received an equivalent volume of tap water by the same route. The animals from both groups were subjected to fluid-percussion TBI, and this point was designated as time 0. At the same time hemorrhage was initiated from the femoral artery catheter. The animals were bled 25 mL/kg over 30 minutes via a computer-driven roller pump (Masterflex, Cole-Parmer Instrument Co., Chicago, IL). To simulate the physiology and kinetics of acute hemorrhage, the hemorrhage rate was decreased exponentially over the 30-minute span. Blood and brain temperatures were maintained in the range of 36–38°C throughout the experimental period with a warming blanket. The physiologic and metabolic variables described above were monitored for 2 hours following TBI/HS or until death of the animal. From these measurements the following parameters were calculated:

$$CPP = MAP - ICP$$

$$DcO_2 = CBF \times CaO_2, \text{ where } CaO_2 = Hb(1.34)(\% \text{ saturation}/100) + (PaO_2)(0.0031)$$

$$O_2ERc = (SaO_2 - ScvO_2)/SaO_2$$

$$CMRO_2 = CBF(1.34)(Hb)(SaO_2 - ScvO_2)$$

TABLE 1 Preinjury Characteristics*

Parameters	Control		Ethanol		p-value†
MAP (mm Hg)	99	(11)	81	(13)	0.003
ICP (mm Hg)	16	(5)	18	(5)	NS
CPP (mm Hg)	82	(11)	63	(12)	0.001
CO (L/min)	2.6	(0.8)	2.8	(0.5)	NS
Hb (g/dL)	10.8	(1.3)	11.9	(0.9)	0.040
$ScvO_2$ (%)	79	(5)	76	(8)	NS
DcO_2 (mL/100g/min)	14.6	(6)	12.9	(5)	NS
O_2 ERc	0.20	(.05)	0.23	(0.08)	NS
$CMRO_2$ (mL/100g/min)	2.83	(1.2)	2.84	(1.2)	NS
Brain temperature (°C)	35.8	(0.6)	36.2	(0.6)	NS
Lactate, cerebral venous (mmol/L)	2.0	(1.0)	3.0	(1.2)	0.065
Ethanol (mmol/L; mg/dL)			35 162	(15); (68)	

*Values are mean (SD). For MAP, ICP, CPP, CO, and brain temp, n = 11 in both groups. For other parameters, n = 11 in the control and 10 in the ethanol group.
†Two-sample t-test. NS = not significantly different.

where DcO_2 = cerebral O_2 delivery; CaO_2 = arterial O_2 content; Hb = hemoglobin concentration; O_2ERc = cerebral O_2 extraction ratio; SaO_2 = arterial O_2 saturation; $ScvO_2$ = cerebral venous O_2 saturation; and $CMRO_2$ = cerebral metabolic rate for O_2.

Animals surviving to 2 hours postinjury were euthanized with 30 mg/kg pentobarbital and the brain and kidneys were removed and sectioned for CBF analysis. An experimental timeline is shown in Figure 1.

Data Analysis: Values are expressed as mean ± SD. Comparisons between the 2 study groups were made with a 2-sample t-test. Repeated-measures analysis of variance (ANOVA) was used to compare parameters that had >2 sampling points. A p-value of 0.05 was considered significant. Since so few animals in the ethanol group survived beyond 45 minutes, meaningful statistical comparisons were not possible beyond this sampling point. A prestudy power analysis revealed that 11 animals would be needed per group to be able to detect a difference in survival time of 30 minutes, assuming a standard deviation of 25 minutes with a power of 0.80.

RESULTS

Preinjury Characteristics: Eleven animals were studied in each group. Preinjury characteristics are summarized in Table 1. The ethanol effects were evident in many of the preinjury measurements. The ethanol-treated animals had significantly lower preinjury MAP and CPP and higher preinjury Hb concentrations. However, preinjury CO, ICP, $ScvO_2$, DcO_2, O_2ERc, regional CBF (rCBF), and $CMRO_2$ values and brain temperatures were not significantly different between groups. A malfunction in processing of microspheres prevented measurement of renal

and cerebral blood flows in 1 ethanol group animal; therefore data for DcO_2, O_2ERc, and $CMRO_2$ were available for 10 animals in this group.

Survival Time: Ethanol levels at the time of injury were 162 ± 68 mg/dL. Average TBI was 2.64 ± 0.39 atm in the ethanol group and 2.66 ± 0.31 atm in the control group. Survival time was significantly shorter in the ethanol group than the control group (60 ± 27 min vs 94 ± 28 min, p = 0.011, 2-sample t-test). Seven animals in the ethanol group died at or before 60 minutes postinjury, compared with 2 in the control group. Two-hour mortality was 91% in the ethanol group and 65% in the controls.

Physiologic Response: MAP and CPP fell in both groups in the postinjury period, but the ethanol-treated animals had significantly lower MAP and CPP through 45 minutes when compared with the control animals. No significant time–group interaction was found for MAP, or CPP, indicating that the magnitudes of ethanol effects on MAP and CPP were similar in the preinjury and postinjury periods (Table 2, Fig. 2). CO dropped in both groups following TBI/HS, and mean CO was lower at each time point in the ethanol group, but the between-group means were not significantly different. However, a significant time–group effect for CO was observed (Fig. 3). Elevated ICP did not occur in response to fluid percussion injury with concurrent hemorrhage (Fig. 2). Brain temperatures remained relatively constant in the postinjury period and were not significantly different between groups (Table 2).

Cerebral blood flow was reduced in both groups following TBI/HS. As in previous studies, we found no significant regional differences in the CBF responses. Mean rCBF values at 45 minutes postinjury were lower in the ethanol-treated animals than in the controls for all 6 brain regions, with the difference being statistically significant in the left anterior cerebral cortex, but not in the other 5 regions (Fig. 4). Renal blood flow also was reduced following TBI/HS to a similar degree as was rCBF. The ethanol group had significantly lower blood flow in 3 of the 4 renal tissue samples at 45 minutes postinjury (Table 2).

The DcO_2 and $ScvO_2$ decreased in both groups following TBI/HS, with a concurrent increase in O_2ERc. The changes in $ScvO_2$ and O_2ERc were significantly greater in the ethanol group (Fig. 5, Table 2). $CMRO_2$ values did not change significantly following TBI/HS, and were not different between groups at 45 minutes postinjury (Table 2).

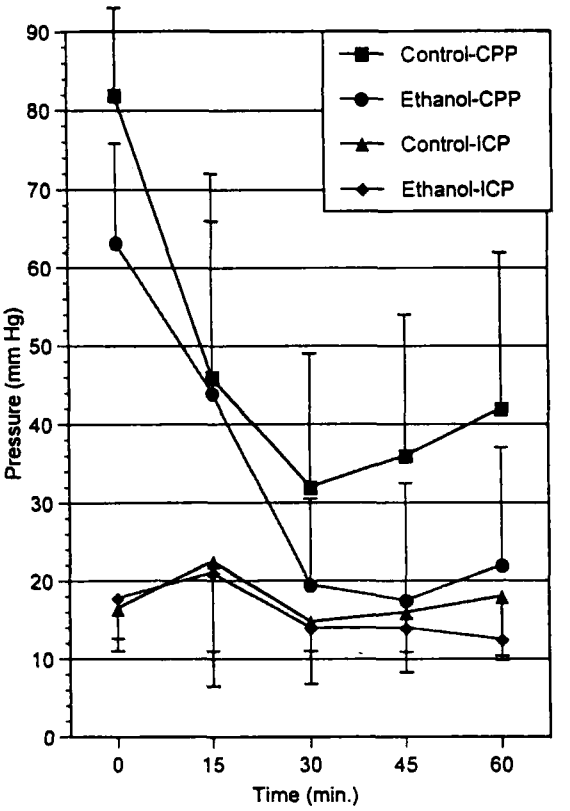

FIGURE 2. Cerebral perfusion pressure (CPP) and intracranial pressure (ICP) in the ethanol and control groups. For CPP, p = 0.010, repeated-measures ANOVA for preinjury, 30-minute, and 45-minute time points. ICP values were not significantly different between groups at any point.

TABLE 2 Selected Postinjury Data*

Parameter	Time	Control		Ethanol		p-value
Number surviving	45 min	10		8		
	60 min	9		4		
	120 min	4		1		0.311†
Ethanol (mmol/L; mg/dL)	Death			40 184	(21); (97)	
Brain temperature (°C)	45 min	36.7	(0.6)	36.6	(0.8)	NS
MAP (mm Hg)	45 min	52	(17)	31	(17)	0.002‡
Renal blood flow (mL/100g/min)	45 min	80	(49)	33	(36)	0.021§
$ScvO_2$ (%)	45 min	55	(22)	21	(15)	0.005‡
DcO_2 (mL/100g/min)	45 min	6.15	(3.3)	4.00	(2.3)	0.104¶
$CMRO_2$ (mL/100g/min)	45 min	2.54	(0.8)	2.85	(2.3)	0.697¶
Lactate, cerebral venous (mmol/L)	30 min	3.2	(2.4)	5.7	(2.0)	0.021¶
HCO_3 (mmol/L)	45 min	28	(2.7)	24	(3.4)	0.016‡
pH, cerebral venous	45 min	7.24	(0.08)	7.13	(0.11)	0.016‡
Hemoglobin (g/dL)	30 min	10.1	(1.2)	11.1	(0.9)	0.078‡
	45 min	9.7	(1.0)	9.8	(1.1)	

*Numbers are means with standard deviations in parentheses. Time = elapsed time postinjury.
†Fisher's exact test (2-tailed).
‡Repeated-measures ANOVA for time points preinjury, 30 minutes, and 45 minutes.
§Two-sample t-test for left kidney superior cortex specimen.
¶Two-sample t-test.

Hematologic and Metabolic Response: Lactate concentrations in arterial and cerebral venous blood rose significantly in both groups following TBI/HS, but mean values were not different for arterial and cerebral venous blood. The increase in cerebral venous lactate at 30 minutes postinjury was significantly greater in the ethanol group (Table 2). Cerebral venous bicarbonate concentrations, which were not different between groups at the preinjury time point, fell in both groups, and were significantly lower in the ethanol group in the postinjury period (Table 2). Cerebral venous pH was significantly lower in the ethanol group both preinjury and postinjury, but the magnitude of the difference was greater in the postinjury period (Table 2). Hb concentrations did not fall until 45 minutes postinjury. At 30 minutes postinjury, mean Hb concentrations remained higher in the ethanol group ($p = 0.037$, 2-sample t-test). Analysis by repeated-measures ANOVA for the entire study period showed a nonsignificant trend toward higher Hb concentrations in the ethanol group (Table 2). Other measured metabolic parameters, including sodium, potassium, calcium, and glucose, did not change significantly with TBI/HS, and were never significantly different between groups.

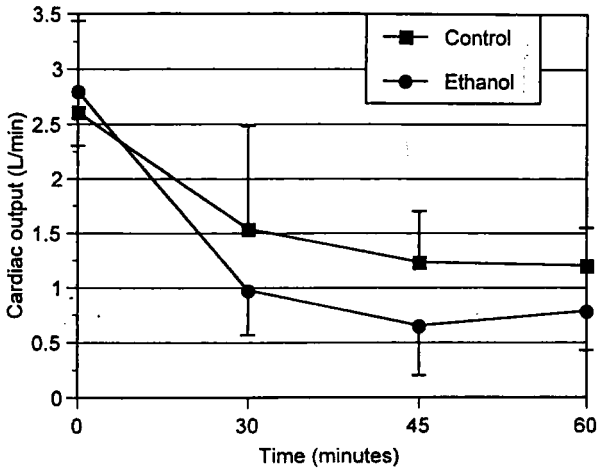

FIGURE 3. Cardiac output in the ethanol and control groups. Overall means: $p = 0.32$, repeated-measures ANOVA. Time–group effect: $p = 0.007$, repeated-measures ANOVA for preinjury, 30-minute, and 45-minute time points.

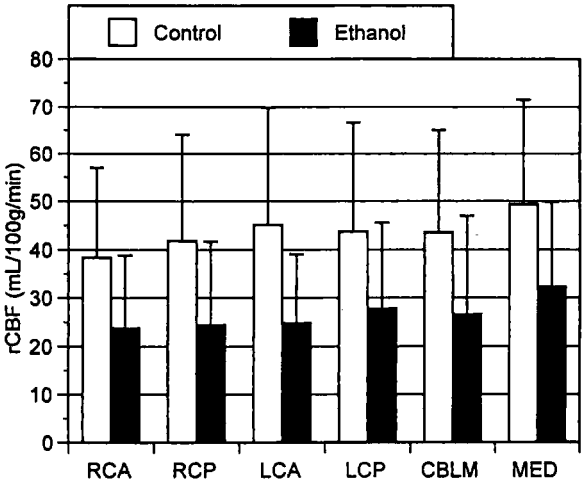

FIGURE 4. Regional cerebral blood flow (rCBF) at 45 minutes postinjury. Key to brain region abbreviations with p-values for 2-sample t-test: RCA, right cerebral cortex anterior, $p = 0.066$; RCP, right cortex posterior, $p = 0.059$; LCA, left cortex anterior, $p = 0.033$; LCP, left cortex posterior, $p = 0.090$; CBLM, cerebellum, $p = 0.078$; and MED, medulla, $p = 0.065$.

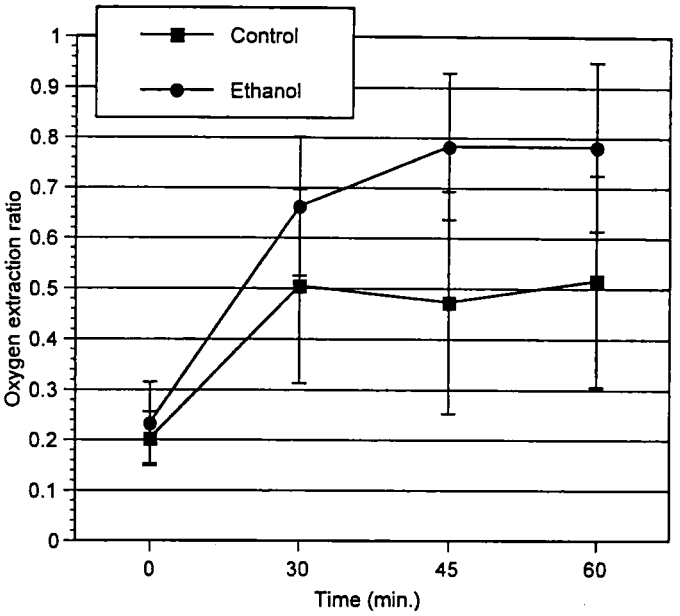

FIGURE 5. Cerebral oxygen extraction ratio (O_2ERc) in the ethanol and control groups. Overall means: $p = 0.005$, repeated-measures ANOVA. Time–group effect: $p = 0.002$, repeated-measures ANOVA for preinjury, 30-minute, and 45-minute time points.

DISCUSSION

In this porcine model of TBI with concurrent HS, ethanol administration significantly reduced survival time, and worsened systemic and cerebral physiologic parameters. In noninjured humans, ethanol intoxication in this range (33–43 mmol/L [150–200 mg/dL]) does not lead to significant effects on hemodynamic parameters.[28] Some ethanol effects were present prior to initiation of TBI and HS (MAP, CPP, Hb), but other measures of cerebral physiology such as $ScvO_2$, O_2Erc, and cerebral venous lactate were altered in the ethanol group only after injury. Effects on rCBF showed a strong trend toward lower mean values in the ethanol group.

Since neuropathologic changes were not assessed, we cannot definitively conclude that cerebral ischemia occurred in the ethanol group. The degree of CBF lowering observed in the ethanol-treated animals was above the threshold that is usually used to define cerebral ischemia in humans (around 20 mL/100g/min), but the threshold

for cerebral ischemia in immature pigs is not known. Baseline brain blood flow values in our model were higher than those reported in adult humans, and are more consistent with what has been described in 2- to 4-year-old children.[29] Even if absolute cerebral ischemia did not occur in the ethanol-treated animals, the overall pattern of physiologic and metabolic changes suggests that ethanol, at relatively low levels, causes adverse effects in the brain when TBI is combined with HS.

The finding that CBF was not maintained in a normal range in the face of reduced CPP demonstrates that cerebral autoregulation of blood flow was impaired in both groups. However, the magnitude of reduction in blood flow was greater in the kidneys than in the brain in the ethanol group. This suggests that some degree of autoregulation of CBF remained intact following TBI/HS. The $CMRO_2$ data also indicate that compensatory mechanisms were active in the ethanol-treated animals. $CMRO_2$ remained fairly constant in the postinjury period despite the reduction in CPP and CBF in the ethanol-treated animals. This was due to increased extraction of O_2 in the ethanol group.

Our previous studies using a similar porcine fluid percussion TBI model without hemorrhage have also found that ethanol reduced CPP and rCBF.[26,27] The current study demonstrates that systemic and cerebral hypoperfusion is greater when hemorrhagic hypotension is superimposed on TBI. For example, mean CPP values in the first hour postinjury with TBI and ethanol without hemorrhage were approximately 40 mm Hg, compared with slightly less than 20 mm Hg in the current experiment. In the previous experiments with isolated fluid percussion injury in the range of 2.5–2.75 atm, ICP increases in the range of 25–40 mm Hg were usually seen during the first 30 minutes postinjury. In the current study, ICP increased in the first 10 minutes following TBI, but hemorrhage ablated this increase by about 15 minutes postinjury.

The concept of secondary brain injury is important when considering ethanol effects in TBI. Secondary brain injury can be defined as brain dysfunction or cellular damage that occurs after the primary brain injury, and is due to factors unrelated to the primary injury forces.[30] In the clinical setting, hypoxia and systemic arterial hypotension are the two most important secondary insults in the early postinjury period.[15,18,20,23] Laboratory investigations have also found that systemic arterial hypotension is associated with worse neurologic outcome and increased mortality following TBI.[31–39] These studies have not examined the biomolecular basis for secondary brain injury. However, other work has shown that ischemic brain cells release or enhance the formation a number of biomolecular mediators of injury, including O_2 radical molecules, excitatory amino acids, and endogenous opioids.[40] These mediators may promote further damage to already compromised neurons and endothelial cells.

A previous study has examined ethanol effects in a TBI model with induced hypotension.[12] Albin and Bunegin induced a focal brain injury by direct pressure on the cerebral cortex in dogs. Ethanol levels of 43 mmol/L [200 mg/dL] were produced by IV infusion, and MAP was lowered to 50 mm Hg for 1 hour with trimetaphan. The ethanol-treated animals with induced hypotension had significantly greater brain lesion volumes 5 days postinjury than did the control hypotensive animals.[12] These findings provide neuropathologic evidence for ethanol potentiation of secondary brain injury.

Ethanol may contribute to secondary brain injury via its effects on the early physiologic response to TBI, and/or by influencing the neurochemical response. As we begin to search for specific mechanisms, a starting point is to ask whether ethanol effects on cerebral function in TBI and HS may simply be the result of systemic cardiovascular effects. Numerous laboratory investigations in models of HS without TBI have found that ethanol worsens hemodynamics and increases mortality.[24,25,41–44] The primary mechanism proposed for these effects is direct suppression of myocardial contractility.[42,44] We cannot determine whether the effects observed in the current study were due to direct suppression of myocardial function, or due to central neurochemical effects of ethanol on cardiovascular tone and myocardial contractility. Two previous studies in human volunteers found that ethanol ingestion led to significant increases in plasma norepinephrine concentrations, but also reduced α-adrenoceptor-mediated vasoconstriction, resulting in lower-than-expected BP.[45,46]

In addition to direct cardiac effects, ethanol may alter cerebrovascular tone. A number of laboratory studies suggest that ethanol induces constriction of cerebral arteries and pial arterioles, but the results have been variable, depending on the species, model, and dose of ethanol used.[47–50] In general, it appears that higher concentrations of ethanol (>65 mmol/L [>300 mg/dL]) cause cerebral vasoconstriction. Some authors have theorized that ethanol effects on the cerebral vasculature may be mediated by nitric oxide release.[50] We cannot determine from our data whether ethanol-induced cerebral vasoconstriction contributed to decreased survival time or impaired physiologic responses.

A consistent finding in this study and our previous studies is higher Hb concentrations in the ethanol-treated animals. This is presumably due to suppression of antidiuretic hormone (ADH) by ethanol, with a resultant osmotic diuresis and contracted plasma volume.[51] A higher Hb concentration in the ethanol group led to higher cerebral O_2 delivery in the preinjury period, but these positive effects were apparently offset by lower CBF in the postinjury period. Recent studies linking the nitrosylation of Hb with nitric oxide-mediated control of vasoreactivity underscore the potential importance of ethanol effects on Hb in HS.[52]

The neurochemical effects of ethanol are extremely wide-ranging, and may be dose-dependent. As noted above, a number of neurochemical systems that are affected by ethanol are also thought to contribute to the pathophysiology of TBI. These include brain lactate formation, excitatory amino acids and the N-methyl-D-aspartate (NMDA) receptor, gamma-aminobutyric acid (GABA)-receptor systems, O_2 radical-mediated cell damage, and endogenous opioid production.[53-66] Neurochemical analysis in our study was limited to cerebral venous blood lactate concentrations.

The metabolism of ethanol stimulates the conversion of pyruvate to lactate.[67] In the current study this produced a 1–2-mmol/L elevation in serum lactate in the preinjury period in the ethanol group compared with the controls. Following TBI and hemorrhage, the magnitude of the increase in lactate concentrations was greater in the ethanol-treated animals, but the effect was no more substantial in cerebral venous blood than in systemic arterial blood. Cerebral venous bicarbonate levels and pH were lower in the ethanol group, presumably in compensation for the increase in lactate. Both clinical and animal studies of TBI have found elevated cerebrospinal fluid or brain lactate levels within hours after TBI.[68,69] Whether this elevation in brain lactate levels represents a primary part of the pathophysiology of TBI or is an aftereffect of cellular damage and ischemia remains to be determined.

LIMITATIONS AND FUTURE QUESTIONS

The extrapolation or generalizability of the results of this study must be tempered by some limitations in the methodology. Study numbers were relatively small. Although sample sizes provided adequate power to detect a difference in survival time, which was the primary outcome measure, the number of animals per group may have been too small to detect significant differences in other parameters such as rCBF. Other limiting factors are the use of immature animals and the anesthetic agent. Although the cardiovascular system of immature pigs is thought to be quite similar to that of humans, and our baseline values would corroborate this, less is known about the pig cerebrovascular system. The effects of isoflurane on cardiovascular function are reported to be less than other inhalation agents, but little is known about the specific cerebrovascular and neurochemical effects.[70] We elected to use these agents because other anesthetic agents such as the barbiturates and benzodiazepines are known to produce GABA effects similar to ethanol. The possibility exists that the observed effects are due to synergy between ethanol and isoflurane, rather than solely from ethanol.

In this study, ethanol was given prior to full instrumentation of the animals to allow adequate time for gastrointestinal absorption. This made it impossible to record true baseline measurements. Ethanol effects on MAP, CPP, and blood lactate concentration were evident even prior to the initiation of TBI and hemorrhage. However, based on CO, CPP, cerebral O_2 saturation, O_2 delivery, and extraction values that were in normal or low-normal ranges, ethanol did not adversely affect cerebral function in the preinjury period. Measurement of urine output and serum osmolality would be useful in our model to assess the magnitude of ethanol-induced osmotic diuresis.

Some interesting questions can be posed based on our findings and previous work with ethanol and TBI. The first relates to the cerebrovascular response to ethanol. While our data showed global reductions in CBF following TBI and HS, we did not look directly at arteriolar diameter. Techniques that would allow real-time monitoring of cerebral arteriolar diameter would be useful in determining the cerebrovascular response in the early postinjury period.

Major questions remain as to which of the neurochemical mediators of injury are most important in ethanol effects on TBI. Direct measurement of glutamate and GABA, and indirect measurement of O_2 radicals are possible in brain tissue and cerebral venous blood. Opioid and NMDA-receptor agonist and antagonist agents may also be useful in defining ethanol effects in TBI. Some of our future experiments will focus on these mediators.

A final question relates to dosage and chronicity of use. Ethanol may have varying effects with dose. Few studies account for this, and some do not use levels that are clinically relevant. Ideally, future TBI studies will test various doses of ethanol to determine whether effects vary with blood concentration. In the clinical setting many subjects with TBI have both acute ethanol intoxication and chronic ethanol abuse. Animal studies such as ours address only acute intoxication. The effects of ethanol on the brain response may be far different when the brain has developed tolerance to ethanol. Future studies will need to explore ethanol effects in animal models that incorporate chronic alcohol consumption.

CONCLUSION

In this animal model of TBI and HS, acute ethanol administration reduced survival time and had detrimental effects on systemic and cerebral physiology. These effects occurred early in the postinjury period. The primary reason for worsened cerebral perfusion in the ethanol-treated animals appeared to be impaired cardiovascular function. The exact physiologic and neurochemical mechanisms responsible for these effects remain to be determined.

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