Effects of ethanol on respiratory function in traumatic brain injury

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It has been observed that traumatic brain injury (TBI) increases the susceptibility of the brain to subsequent hypoxia, and prolonged apnea occurs in ethanol (EtOH)-treated animals following brain injury. This investigation tests the hypothesis that EtOH suppresses ventilation and hypercapnic respiratory drive following TBI. Immature pigs were anesthetized with halothane and received a 2 to 3 atm fluid-percussion brain injury. Respiratory parameters, including tidal volume, frequency, ventilation (V̇), and arterial blood gases were measured on 100% O₂ and on 5% to 6% inspired CO₂ in O₂ prior to and at 10, 60, 120, and 180 minutes after TBI. Hypercapnic response sensitivity (S) was measured as the change in V̇ per mm Hg increase in PaCO₂. Intracranial pressure, mean arterial blood pressure, heart rate, brain temperature, glucose, and EtOH levels were also monitored. Three groups were studied: the first group of six received EtOH (3.5 gm/kg, intragastrically) without brain injury; the second group of six received TBI without EtOH; the third group of eight received EtOH and TBI. Ethanol levels were 121 ± 13 (standard error of the mean) mg/dl in the EtOH/TBI group (136 ± 25 in the EtOH group) at the time of injury, and 175 ± 12 mg/dl in the EtOH/TBI group (200 ± 20 mg/dl in the EtOH group) at 120 minutes after injury. The EtOH/TBI animals had significantly lower V̇ and S, and higher PaCO₂ following brain injury (p < 0.05, repeated-measures analysis of variance). No significant differences were identified between groups for pH, PaCO₂, intracranial pressure, heart rate, brain temperature, or glucose levels. Ethanol intoxication leads to significant impairment of respiratory control following traumatic brain injury and may contribute to brain injury in intoxicated trauma victims.

KEY WORDS • traumatic brain injury • respiratory function • ventilation • ethanol • pig

ETHANOL (EtOH) consumption leads to an increased risk of accidents and trauma;13,25 studies in emergency department patients have shown that up to 50% of brain-injured adults have consumed EtOH prior to suffering traumatic brain injury (TBI).4,8,17,31 A number of animal studies, each using a different model and species, has found that EtOH worsens brain injury and neurological outcome and increases mortality following brain injury.1,11,12,22 These investigations have focused primarily on neuropathological lesions and mortality and have not examined the acute physiological changes that occur following TBI.

In our previous study of EtOH’s effect on cerebral blood flow (CBF), it was found that EtOH-treated animals had significantly longer periods of post-injury apnea when compared to injured control animals.30 After the initial apnea period, EtOH-treated animals appeared to have reduced respiratory effort compared to animals receiving injury alone. These findings were unexpected, given that average EtOH levels at the time of injury were less than 200 mg/dl and only mild respiratory depression occurs with this degree of EtOH intoxication in humans.33

To more fully examine the effects of EtOH on respiratory control after TBI, a controlled study was undertaken, using the porcine fluid-percussion brain-injury model. The hypothesis of this study is that EtOH intoxication leads to significant depression of ventilation (V̇) and to a decreased respiratory drive in response to PaCO₂ increases following this injury.

Materials and Methods

Operative Technique

After their food and water had been withheld overnight, immature pigs weighing between 16 and 23 kg were sedated by intramuscular injection of ketamine (350 mg) and acepromazine (1.1 mg/kg). Thiopentone, 5 to 10 mg/kg, was administered intravenously to provide a brief period of deeper sedation during which a tracheostomy was performed. A No. 6 tracheostomy tube was placed and the animal was anesthetized with 1% halothane in oxygen; this concentration was maintained at 1% for the remainder of the experiment. The right femoral artery and vein were isolated and cannulated for arterial blood pressure monitoring and blood sampling. The animal was then placed prone in a head stabilizer and the scalp was reflected. A 1.5-cm diameter craniotomy was performed in the
Ethanol, brain injury, and respiration

**PROTOCOL**

Fig. 1. Chart summarizing the experimental protocol in studying the effects of ethanol on traumatic brain injury. Traumatic brain injury (TBI) was at time 0. Hal. = halothane; ABG = arterial blood gas determination; $V_E$ = steady-state ventilation.

right parietal region, 2 cm from the midline and 6 cm anterior to the external occipital protuberance. The terminal bolt of the fluid-percussion device was screwed into the craniotomy site until it abutted the intact dura. The fluid percussion device was similar to that described by Sullivan, et al., but modified for use in swine. It was equipped with a piezo-electric pressure transducer with a frequency response sufficient to accurately measure the brain injury delivered. The terminal bolt and intraventricular catheter sites were sealed with dental cement. A second craniotomy was performed in the left posterior parietal region and an intraventricular catheter was placed and connected to an intracranial pressure (ICP) monitor. A temperature probe was placed in the ventricle adjacent to the catheter to monitor brain temperature, and a rectal temperature probe monitored core body temperature.

The experimental protocol is summarized in Fig. 1. There were three experimental groups: the first group of six received EtOH without brain injury; the second group of six received TBI without EtOH; the third group of eight received EtOH and TBI. The EtOH and EtOH/TBI animals received 100% EtOH, 3.5 gm/kg, as a 1:2 dilution with water via orogastric tube 80 to 90 minutes prior to injury. Control animals received an equivalent volume of normal saline. Time 0 was designated as the time of TBI.

**Hemodynamic and Respiratory Measurements**

A polygraph was used to continuously record blood pressure, ICP, heart rate, respiratory flow, respiratory frequency, tidal volume ($V_T$), and airway CO$_2$ concentrations. A pneumotachygraph was placed in line with the tracheostomy tube and anesthesia machine for continuous measurement of respiratory flow; this flow was electronically gated and integrated to yield $V_E$. Inspired and expired CO$_2$ concentrations were also measured continuously with a mass spectrometer. Flow and CO$_2$ signals were digitized at 50 Hz for subsequent computer determination of $V_E$, $V_T$, and frequency. A personal computer with an analog-to-digital converter programmed in ASYST was used. Measurements of $V_E$ were made by integrating expired respiratory flow over at least a 2-minute stable period and dividing by the time of the integration period.

Respiratory measurements were obtained 30 minutes prior to time 0 (baseline) and at times 10, 60, 120, and 180 minutes. A respiratory measurement consisted of calculation of steady-state $V_E$ and respiratory frequency over a 2-minute period with the animal breathing oxygen. (The $V_T$ and $V_E$ are expressed per kilogram of body weight.) Inspired CO$_2$ was then increased to between 5% and 6% to generate an approximately 10-mm Hg increase in PaCO$_2$. After 10 minutes, the respiratory measurement was repeated and the frequency of inspired CO$_2$ (FICO$_2$) returned to zero. Arterial blood gases were obtained at the end of both the normocapnic and hypercapnic periods. The hypercapnic response is quantified as the slope of the line generated by plotting the change in steady-state $V_E$ per mm Hg increase in PaCO$_2$ ($\Delta V_E/\Delta PaCO_2$). If apnea occurred after TBI, the animal was observed for 60 sec-onds and then given bag-valve ventilation for up to 10 minutes with P$_{E}CO_2$ maintained at 40 to 45 mm Hg. If spontaneous respiration did not resume, the PaCO$_2$ was allowed to increase approximately 60 mm Hg to ensure that respiration was not inhibited by inadvertent hyperventilation. If apnea persisted, the animal was placed on a ventilator with rate and $V_T$ adjusted to maintain PaCO$_2$ at 40 to 50 mm Hg. At each respiratory measurement, apneic animals were given 5% inspired CO$_2$ and observed for signs of spontaneous respiration. If spontaneous respiration did not occur, the $V_E$ and hypercapnic response were recorded as zero.

Hemodynamic measurements (mean arterial blood pressure (MABP), ICP, and heart rate) were obtained with each respiratory measurement. Blood–EtOH levels, obtained at times 0 and 120, were measured by gas chromatography. Blood glucose was measured by means of a glucose analyzer. Data were analyzed between groups using repeated-measures analysis of variance (ANOVA), with significance accepted at the $p = 0.05$ level. Postinjury ventilatory and pressure data collected each hour were analyzed for effects related to group, time, and interaction between group and time. Apnea times and brain-injury levels were compared between groups using the Wilcoxon ranked-sum test.

**Results**

The experimental groups were well matched in terms of baseline hemodynamic and respiratory measurements (Table 1). The mean brain injury was 2.6 ± 0.5 atm (mean ± standard deviation) and was not different between the TBI only and the EtOH/TBI groups. The mean EtOH levels for the EtOH/TBI and EtOH groups were 121 ± 13 standard error of the mean (SEM) mg/dl and 136 ± 25 mg/dl, respectively, at the time of injury and had risen to 175 ± 12 mg/dl and 200 ± 20 mg/dl, respectively, at 120 minutes after TBI.

Mean arterial blood pressures (Table 1) and cerebral perfusion pressures (CPPs) (Fig. 2 left) were consistently
lower in the EtOH/TBI group, although this difference did not achieve statistical significance (at 3 hours, $p = 0.16$ for MABP; $p = 0.14$ for CPP; ANOVA). When intergroup comparisons were done, MABP and CPP at 3 hours were significantly lower in the EtOH/TBI group than in the EtOH group ($p < 0.05$; ANOVA with Bonferroni multiple comparison test). The ICP was not significantly different among the groups (Table 1), with the typical ICP response being an immediate transient increase with TBI lasting less than several seconds, followed by a mild increase in ICP to 15 to 20 mm Hg. No other significant differences were detected between the experimental groups in heart rate, brain or rectal temperature, glucose, hematocrit, hemoglobin, or arterial pH.

The EtOH/TBI animals had higher PaCO$_2$ (Fig. 2 center) and lower V$_e$ (Fig. 2 right) throughout the 180-minute period following brain injury compared to the EtOH and TBI groups ($p < 0.05$, repeated-measures ANOVA). Postinjury apnea was 1.9 ± 0.07 minutes (mean ± SEM) in the TBI group, compared with 6.9 ± 2.6 minutes in the EtOH/TBI group ($p = 0.2$; Wilcoxon ranked-sum test). Two animals in the EtOH/TBI group had persistent apnea throughout the experimental period. None of the animals in the TBI group had greater than 5 minutes of apnea and none of the animals in the EtOH group experienced any apnea. The EtOH animals had mild decreases in ventilation and intact hypercapnic responses. The TBI animals did not exhibit respiratory depression at the 10-minute postinjury point and demonstrated a tendency toward increased ventilation compared with preinjury (Fig. 2 right). Decreasing ventilation in the EtOH/TBI animals was attributable primarily to depression in the respiratory rate (Fig. 3 left), not a decrease in $V_e$ (Fig. 3 right).

The respiratory response to increased PaCO$_2$ was also impaired in the ethanol-treated, brain-injured animals (Fig. 4). Five of eight EtOH/TBI animals had a decrease in ventilation compared to preinjury, whereas only one of eight TBI animals had a decrease.
in $V_e$ at 60 minutes postinjury in response to 5% to 6% inspired CO$_2$, while all six TBI animals had an increase in $V_e$. The EtOH animals maintained a normal hypercapnic response throughout the experimental period. The $\Delta V_e/\Delta$PaCO$_2$ was significantly lower in the EtOH/TBI group (2.3 ± 1.3 ml/min/kg/mm Hg) than in the TBI group (14 ± 3.6 ml/min/kg/mm Hg) or EtOH group (11.1 ± 3.5 ml/min/kg/mm Hg) ($p < 0.05$, repeated-measures analysis of variance).

**Discussion**

This study demonstrated that the combination of EtOH intoxication and fluid-percussion brain injury led to significant respiratory depression and an impaired ventilatory response to increased PaCO$_2$ in halothane-anesthetized pigs. The experiment was designed to simulate the clinical situation of TBI following alcohol ingestion; orogastric EtOH was delivered approximately 1.5 hours prior to brain injury, and the EtOH level at the time of injury was in a range that produces mild-to-moderate intoxication in humans.

**Comparison of Responses**

By comparing the responses of the three experimental groups in our study, the researchers found that the marked respiratory depression seen in the EtOH/TBI group cannot be attributed solely to EtOH intoxication. In this model, the combination of EtOH intoxication and brain injury led to much greater respiratory depression than either EtOH intoxication or brain injury alone. The EtOH group data were consistent with human studies which showed that EtOH intoxication without brain injury (serum levels approximately 100 mg/dl) in healthy volunteers led to only a mild depression of hypoxic and hypercapnic respiratory drives.

Previous animal investigations of the effects of EtOH in brain injury have focused on neuropathological changes, neurological outcome, and mortality. Flamm, *et al.*, using a weight-drop method to induce spinal cord and cerebral cortex lesions in cats found that administration of intravenous EtOH (serum levels 448 mg/dl) led to significantly larger lesions and worse neurological outcome in both spinal cord and brain injury groups. Albin and Bunegin* had similar findings when using a pressure-induced focal ischemia model in dogs. Lesion volumes were significantly larger at 5 days postinjury in EtOH-treated animals (serum levels approximately 200 mg/dl). Their study also examined the effects of hypotension combined with EtOH intoxication and the effect of dimethyl sulfoxide (DMSO), a free-radical scavenger. Induced hypotension significantly increased lesion volumes in EtOH-treated animals, and DMSO appeared to attenuate this effect. Franco, *et al.*, found significantly increased 8-day mortality in EtOH-treated mice that received a weight-drop closed-head injury. Although each of these studies found that EtOH has deleterious effects when combined with brain injury, changes in physiological parameters, including respiratory function, were not reported.

Kim, *et al.*, considered the effects of EtOH on apnea times in a rat model of TBI. In those animals that resumed spontaneous respiration for either an extended or transient period following TBI, the initial apnea periods were 16 seconds in the EtOH group (320 mg/dl) compared with 11.7 seconds in animals not receiving EtOH. The authors did not report postinjury blood gases or ventilatory responses. In comparing these results with our study, we found that mortality in the rat model was approximately 50% and was slightly increased by EtOH to 58% (no statistical difference). Traumatic brain injury was apparently less severe in our porcine fluid-percussion model, since it is likely that only two of eight animals would have died if ventilatory support had not been provided. Apnea periods were longer in both treated and untreated groups in this study, and the effect of EtOH was greater, perhaps reflecting a species difference.

In a similar model used in a previous study, with more animals per experimental group and therefore greater statistical power, we found significantly prolonged postinjury apnea in EtOH/TBI animals. If apnea of similar duration occurs in alcohol-intoxicated humans who suffer from TBI, anoxic brain damage may be superimposed on traumatic injury. In addition, many animal studies have shown that the posttraumatic brain is especially sensitive to hypoventilation. Andersen, *et al.*, found marked alterations in cerebral energy metabolism, including marked decreases in the phosphocreatine/inorganic phosphate ratio and the brain tissue pH, which were not present with either the injury or the hypoventilation alone. In humans, Chestnut, *et al.*, analyzed data from 717 cases in the Traumatic Coma Data Bank and found that in severe head injury (Glasgow Coma Scale ≤ 8), evidence of hypoventi-
lation or hypoxia (apnea or cyanosis or PaO₂ ≤ 60 mm Hg) was independently associated with significant increases in morbidity and mortality.

**Role of Adequate CPP**

In terms of physiological responses, maintenance of adequate CPP is an important factor in clinical outcome. In cases from the Traumatic Coma Data Bank, Chestnut and colleagues found hypotension (systolic blood pressure < 95 mm Hg) to be profoundly detrimental and associated with a 150% increase in mortality. Ethanol reduced CPP in TBI animals in both this study and our previous study. The effect of EtOH on CPP is primarily because of MABP rather than increased ICP. In animal studies of hemorrhagic shock, EtOH leads to exaggerated hypotension due to direct myocardial depression. In our model, mean CPP in the EtOH/TBI animals fell below 50 mm Hg (Fig. 2 left) by 10 minutes postinjury. If EtOH causes similar hypotension in humans, then brain injury due to decreased CPP may be superimposed on TBI.

**Effects of EtOH**

The wide-ranging biochemical and physiological effects of EtOH make it difficult to pinpoint a single mechanism that might explain impaired respiratory function following brain injury. Lowering of CPP to this level may lead to ischemia in some regions of the injured brain. In our previous study, CBF was significantly lower in EtOH/TBI animals than in TBI animals. The cerebellum and brainstem, as well as other brain regions, had markedly lower blood flow at 3 hours postinjury. It is possible that respiratory control centers in the brainstem may be subjected to ischemia in this model, leading to impaired ventilation.

Ethanol also causes platelet dysfunction, and this may lead to impaired clotting. Brainstem hemorrhage in EtOH-treated animals could cause pronounced effects on ventilation. However, in our previous study, despite the finding that hemorrhage often occurred in the brainstem and cerebellum, no differences were detected in gross or microscopic pathology of the brainstem in TBI versus EtOH/TBI animals. In contrast, Kim, et al., found that subarachnoid hemorrhage was greatest in animals treated with EtOH and that indomethacin decreased such hemorrhage.

A number of neurochemical mechanisms can be proposed for EtOH-induced ventilatory impairment following TBI. One possibility involves endogenous opioid peptides, such as enkephalins and beta endorphins, which affect respiratory control. Elevations in brain endogenous opioids depress respiratory effort; the effects of these opioids in normal respiratory control are probably minimal, but in states of increased stress, including trauma, endogenous opioids may play a larger role in regulation of respiration. Hayes, et al., found that naloxone, a non-specific opioid antagonist, significantly reversed the systemic hypotension and reduction in CPP in cats subjected to high-grade fluid-percussion brain injury. This observation provides indirect evidence that endogenous opioids may be involved in alteration of brainstem cardiovascular control. Ventilation was controlled in these experiments. McIntosh and colleagues, using a similar model, examined regional changes in brain opioid immunoreactivity following fluid-percussion brain injury and found that dynorphin A immunoreactivity was increased at sites of injury as determined by pathology correlated with blood-flow reductions. One of the regions of increased dynorphin A immunoreactivity was the medulla, in which respiratory centers are located. Treatment with an opioid antagonist prevented the CBF decreases. These studies suggest that fluid-percussion brain injury causes an increase in the release of activity of some brain endogenous opioids.

Evidence also exists that EtOH increases brain endogenous opioid activity. Bar-Or and colleagues reported that plasma beta-endorphins were significantly elevated in human volunteers with acute EtOH intoxication. Although stimulation of endogenous opioid activity is not the predominant mechanism for EtOH's depressant effects on the central nervous system, it may be responsible for EtOH-induced ventilatory depression. Michiels, et al., found that EtOH intoxication in normal humans (serum levels approximately 130 mg/dl) did not significantly affect resting ventilation but decreased the hypercapnic ventilatory response. Administration of naloxone reversed the decrease in hypercapnic response. Clinical reports have suggested that naloxone reverses EtOH-induced coma in approximately 15% of cases, therefore it is possible that EtOH enhances the TBI-induced release of endogenous opioids that may result in the respiratory depression and reduced response to inhaled CO₂ seen in this study.

Oxygen radicals and lipid peroxidation may contribute to cell dysfunction or death following brain injury and stroke. Ethanol has been found to promote free-radical lipid reactions and lipid peroxidation in hepatocytes. In spinal cord trauma, EtOH produced biochemical evidence of increased lipid free-radical damage. Increased free-radical formation was also found in EtOH-treated dogs subjected to pressure-induced focal ischemia brain injury. In their study of TBI in rats, Kim, et al., found that indomethacin, which inhibits cyclooxygenase and thereby decreases oxygen radical production, decreased the times and mortality. No studies have looked specifically at the role of oxidant damage in EtOH-induced ventilatory depression following TBI.

Ethanol affects a number of other neurochemical systems; glutamate-induced excitotoxicity may be a factor in TBI-induced neuronal damage; EtOH inhibits glutamate action at the N-methyl-D-aspartate receptor; and acute exposure to EtOH protects cells from glutamate excitotoxicity by limiting Ca²⁺ influx. Many of the central nervous system effects of EtOH are attributed to potentiation of the inhibitory actions of gamma-aminobutyric acid (GABA). This data would suggest that EtOH protects the brain from TBI, although no experimental data exist on the effects of EtOH on these systems in the setting of TBI. Glutamate and GABA are also implicated as neurotransmitters in the central control of breathing, where enhanced GABA-related activity or depressed glutamate-related activity depresses ventilation. The GABA antagonists reverse the respiratory depression seen in carbon monoxide–induced respiratory depression. Ethanol-induced alterations in these neurotransmitter systems may thus contribute to the respiratory depression observed following TBI.
Halothane anesthesia is a potential confounding variable in this experiment. Like most other inhalation anesthetics, halothane produces respiratory depression, probably by direct action on brainstem respiratory centers. It was chosen as the anesthetic agent in this experiment because, unlike anesthetics administered intravenously, anesthetic depth is easily held constant. Respiratory depression is less when halothane is used than with many of the other inhalation anesthetics. Each of the three experimental groups had 1% halothane administered throughout the experimental period, and no significant effect was seen on ventilation in the EtOH-treated animals or control animals prior to brain injury. The group of animals receiving halothane anesthesia and EtOH without brain injury did not develop apnea or marked respiratory depression during the 3-hour monitoring period and maintained a normal hypercapnic response. Although we cannot exclude the possibility that halothane anesthesia had a synergistic effect when present in combination with both brain injury and EtOH, it does not seem likely that this was a factor in this experiment.

It is not known if early ventilatory depression occurs in EtOH-intoxicated humans who suffer brain injury. Large scale studies of individuals injured in motor vehicle accidents have found that even when factors such as crash characteristics, seat belt use, and vehicle deformation are accounted for, mortality is increased twofold in EtOH-intoxicated drivers compared with sober drivers. Two studies have investigated the time of death in sober compared with EtOH-intoxicated motor vehicle accident victims and found that EtOH-intoxicated traumatized patients were significantly more likely to die in the 1st hour following the accident. Unfortunately, these studies have not looked separately at brain-injured patients and do not provide postmortem data on the cause of death. One possible explanation for early death following TBI in EtOH-intoxicated patients is prolonged apnea or hyperventilation in the period immediately following injury. One study found that EtOH intoxication was associated with a 30% greater likelihood of endotracheal intubation either in the field or the emergency department.

Clinical studies have shown that brain-injured humans who suffer hypoxemia or systemic hypotension after brain injury have a worse neurological outcome and significantly higher mortality than patients who do not have these added physiological insults. In the porcine fluid-perfusion brain injury model, EtOH depresses ventilation as well as the response to increased PaCO₂. If the same responses are seen in the subset of patients with EtOH intoxication and brain injury, these individuals may be at greater risk for poor neurological outcome or death.

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