Regional Cerebral Blood Flow Changes Associated With 
Ethanol Intoxication

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SUMMARY Regional cerebral blood flow (CBF) was measured via the $^{133}$Xenon inhalation technique in 26 healthy volunteers before and 60 minutes after the oral administration of ethyl alcohol or placebo on a double-blind basis. The cerebral blood flow values, corrected for test-retest differences in carbon dioxide showed a significant bilateral increase after ethanol administration. Blood levels of ethanol, estimated with a breath analyser, did not correlate with the CBF changes.

Method

Subjects for the study were recruited through local advertising. The participants were carefully screened for physical and psychiatric disorders and they were required to be free of all medications for a minimum of two weeks before study. They avoided coffee, tea and tobacco for two hours preceding the experiment. Special care was taken to exclude subjects with history of heavy drinking. None of the participants were found to consume more than 1 mixed drink or two beers per week on the average during the previous year and they were instructed to avoid all ethano-containing beverages for 24 hours before the study. The demographic characteristics of the group are given in table 1.

Cerebral blood flow was measured before and after the administration of ethanol or placebo. The $^{133}$Xenon inhalation technique was utilized for CBF measurements. A mixture of the isotope and air was administered through a close-fitting face mask for 1 minute. The rate of removal of $^{133}$Xenon from different parts of the brain during the next 10 minutes was followed by a system of 32 collimated scintillation detectors mounted on a helmet and applied to the scalp. The position of the detectors to the head was standardized by alligning beams of light fixed on the helmet with the external auditory meatus and the outer canthi of the eyes. Cerebral blood flow was computed from these clearance measurements.

SEVERAL INVESTIGATORS have reported an association between alcohol abuse and cerebrovascular disease. Neuropsychiatric complications of chronic, excessive consumption of ethyl alcohol are often associated with significant reductions in cerebral blood flow (CBF). Reduction in cerebral blood flow is seen following acute ethanol withdrawal with normalization in a few days.

Studies on the acute effect of ethanol on CBF have produced conflicting results. Most animal studies indicate a vasoconstrictive effect. Sutherland and associates measured CBF and cerebral metabolism via the nitrous oxide technique, before and twenty minutes after the oral administration of 1 g of alcohol per kg body weight in eleven males with a history of problem drinking. Alcohol ingestion was not associated with any changes in CBF or the metabolic rates of oxygen consumption or carbon dioxide production. Hine and associates studied ten males who had been drinking periodically or chronically for 10–25 years. CBF was measured with the nitrous oxide technique before and twenty minutes after the oral administration of .5 ml of 90 proof whiskey per kg body weight. Post ethanol CBF values showed statistically significant decrease. However, the authors stated that the CBF decrease was very modest and inconsistent in spite of the statistical significance. There were no changes in cerebral metabolic rates for oxygen. Battey and associates examined the effect of intravenous infusions of 5–10 percent solutions of ethyl alcohol (average quantity – 22 cc) in 15 patients convalescing from a variety of medical illnesses. CBF measurements were performed with the nitrous oxide inhalation technique before and during the infusions. CBF was also measured in a second group of subjects who were brought to the hospital emergency room with severe alcoholic intoxication, 1–2 hours after admission and 15–62 hours later, when they were sober. Low concentrations of blood alcohol (.068 mg/percent) did not produce significant changes in either cerebral blood flow or oxygen consumption. However, during severe alcohol intoxication with high blood levels (.32 mg/percent) there was a pronounced increase in cerebral blood flow and reduction in cerebral vascular resistance and oxygen uptake. More recently, Newlin and associates studied the effects of ethanol on CBF with the $^{133}$Xenon inhalation technique in 10 social drinkers. CBF was measured one hour after the oral administration of .75 g per kg body weight of alcohol. The control measurements were performed under resting conditions the same day or on a different day. Alcohol intoxication was associated with a global increase in grey matter flow. The flow increases were bilaterally symmetrical in the posterior regions but the right anterior region showed more pronounced CBF increase than the corresponding area on the opposite hemisphere. We studied the effects of acute ethanol intoxication on CBF with the $^{133}$Xenon inhalation technique in 26 normal volunteers. Unlike the previous investigations, the study was placebo controlled and conducted under double-blind conditions with an improved study design.
The measurements were made in a quiet, semi-dark room with eyes open. End-tidal levels of carbon dioxide (\(\text{P}_{\text{CO}_2}\)), pulse rate, respiratory rate, and blood pressure were monitored during the measurements. A one channel EEG was utilized to detect and prevent the onset of sleep.

After the first CBF measurement, fourteen subjects received 0.5 g per kg body weight of ethyl alcohol (100 proof Vodka) mixed with tonic water. The others were given tonic water without any alcohol. The subjects were assigned to the ethanol and placebo groups on a random basis and the experiment was conducted under double-blind conditions. However, most subjects were able to differentiate between alcohol and placebo. The second cerebral blood flow measurements were carried out 60 minutes after the first one. Scalp radioactivity left over from the first measurement was recorded for 5 minutes before the second measurement and used for the residual activity correction. At the end of the experiment, blood ethanol levels were estimated with a breath analyser. Changes in CBF and other physiological indices after the administration of ethanol and placebo were compared with repeated measures analysis of variance and post hoc Newman Keuls. Pearson correlations were computed between blood alcohol levels and the change in CBF.

**Results**

The ethanol and placebo groups did not show significant differences in age or sex. The two groups were compared on blood pressure, pulse and respiratory rates, with repeated measure analysis of variance (group \(\times\) period). They did not differ on these physiological indices during either run. A second analysis of variance with repeated measures (group \(\times\) period \(\times\) hemisphere \(\times\) region) was performed using the CBF data after correction for test-retest differences in end-tidal carbon dioxide levels with a 3% correction per millimeter of mercury \(\text{P}_{\text{CO}_2}\) partial pressure.\(^{22, 23}\) A significant group by period interaction was noted (\(F = 5.35, p < .02\)). There was no hemispheric main effect. Post hoc Newman Keuls demonstrated no differences between the two groups on the resting flow values and between the two sets of CBF values in the placebo group. However, the post ethanol CBF was found to be significantly higher than the pre-ethanol levels in both hemispheres (\(p < .05\)) (fig. 1). CBF values uncorrected for \(\text{P}_{\text{CO}_2}\) differences showed non-significant changes in the same direction. \(\text{P}_{\text{CO}_2}\) levels during the first and second measurements are given in figure 1. A third set of analysis of variance with repeated measures was carried out using each of the 32 regional CBF values separately. Several brain regions showed significant post-ethanol increases (fig. 2). Post hoc Scheffe's were computed to compare the regional changes in cerebral blood flow induced by ethanol in the two hemispheres. There were no significant differences. Next, the difference in CBF before and after ethanol were correlated with the blood levels of the drug (mean .07 mgs. percent, \(SD .02\)). None of the correlations reached statistical significance (right hemisphere: \(r = -.12\); left hemisphere: \(r = -.27\)).

**Discussion**

Previous research on the effect of ethanol on CBF produced ambiguous results. However, most of these studies suffered from several serious methodological shortcomings. The earlier studies were conducted with the invasive nitrous oxide inhalation technique\(^{24}\) which does not provide regional data. None of the studies were placebo controlled and the participants in two were alcoholic and another one patients recovering from medical illnesses. Alcoholics are known to have abnormalities in regional cerebral blood flow\(^{9, 10}\) and they might differ from normals in the CBF responses to ethanol. The dose of ethanol administered, the duration between ethanol ingestion and CBF and that between the post-ethanol CBF and control runs (in studies where the subjects were used as their own controls) were not standardized in most experiments. Influences of other relevant non-specific factors such as caffeine...
were not adequately controlled. The present study design took into account most of these shortcomings. The participants were carefully screened for significant physical and mental disorders, including alcoholism and substance abuse. The experiment was placebo controlled and conducted under double-blind conditions. Special effort was made to control for various non-specific factors and the amount of alcohol used and the interval between the two runs were standardized. All CBF measurements were performed in the same laboratory under identical conditions.

In the present study, ethanol in moderate quantities was found to increase CBF. The CBF values were corrected for test-retest differences in PECO2 and there were no changes in pulse rate and blood pressure following ethanol administration. Thus, the increase in cerebral circulation was most probably unrelated to the peripheral circulatory and respiratory effects of the drug. The blood flow values obtained via the 133Xenon inhalation technique have been shown to be highly reproducible21, 25, 26 and the placebo group did not show significant changes during the second measurement. The post-ethanol CBF increase was global even though the change did not reach statistical significance in some regions. The changes were most obvious in the frontal areas. Newlin and associates20 also reported more marked post-ethanol CBF increase in the frontal regions. However, unlike their findings, in the present study there were no significant interhemispheric differences in the flow change.

In the normal brain, blood flow and function27 are tightly coupled. Sedatives such as benzodiazepines and barbiturates reduce cerebral brain capillary perfusion.28-30 Ethyl alcohol is a well established CNS depressant and would, therefore, be expected to reduce CBF. However, ethanol has a direct dilatory effect on the capillaries elsewhere in the body.31 Ethanol administration has been associated with reduction in peripheral vascular resistance, dilation of skin capillaries31 and increase in coronary blood flow.32-34 The CBF increase induced by the drug may be partly related to a similar, direct effect on the brain capillaries. It should be noted that a similar increase in cerebral perfusion has been reported following the administration of several volatile anesthetic agents.35 Ethyl alcohol is metabolized to acetaldehyde36 which is known to dilate blood vessels of the brain.18, 37 Thus, ethyl alcohol seems to influence CBF in opposite directions through at least two different mechanisms namely, sedation and vasodilation. This might account for the absence of a significant correlation between blood ethanol levels and CBF. Reports of CBF reduction during alcohol withdrawal12 lend support to the present finding of cerebral vasodilation associated with intoxication. It is also possible that the CBF increase following ethanol intoxication is related to the associated euphoria and disinhibition.

Most animal studies indicated an ethanol induced cerebral vasodilatation. The discrepancy between the results of those studies and the present one might be explained by variations in the dose of alcohol administered and species specific differences. It is questionable whether the findings of the present study, namely, alcohol induced cerebral vasodilatation can be extrapolated to severe intoxication induced with larger doses.

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