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U. S. Naval School of Aviation Medicine



U. S. NAVAL AIR STATION
PENSACOLA, FLORIDA

RESEARCH REPORT



THE EFFECTS OF ETHYL ALCOHOL ON THE BRAIN
EMORY UNIVERSITY SCHOOL OF MEDICINE
AND
U. S. NAVAL SCHOOL OF AVIATION MEDICINE

JOINT RESEARCH REPORT

NO. NM 001 050.01.08

U. S. NAVAL SCHOOL OF AVIATION MEDICINE
NAVAL AIR STATION
PENSACOLA, FLORIDA

JOINT PROJECT REPORT

Emory University under Contract N 9onr-92500
Office of Naval Research, Project Designation No. NR 112-607
U. S. Naval School of Aviation Medicine

and

The Bureau of Medicine and Surgery

NM 001 050.01.08

THE EFFECTS OF ETHYL ALCOHOL ON THE BRAIN

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SUMMARY

1. The cerebral blood flow (CBF), cerebral metabolism (CMRO_2), and vascular resistance (CVR) were measured in 15 subjects before and during intravenous administration of ethyl alcohol and in 12 patients during severe self-induced alcoholic intoxication and following recovery.
2. The administration of ethyl alcohol in doses sufficient to produce facial vasodilatation and the mental changes of mild inebriation did not produce any changes in either cerebral blood flow, cerebral metabolism or vascular resistance.
3. During acute severe alcoholic intoxication there was a marked increase in mean cerebral blood flow, an equally significant reduction in cerebral oxygen uptake and a reduction in cerebral vascular resistance, as compared with the values obtained following recovery.
4. Low concentrations of alcohol in the blood (averaging 68 mgm.%) had little or no measurable effect on cerebral circulation while high levels (averaging 320 mgm.%) produced a marked depression in cerebral oxygen consumption despite an increase in blood flow. There appears to be no rational basis for the use of ethyl alcohol as a vasodilator in patients with cerebral vascular disease.

INTRODUCTION

The ingestion of ethyl alcohol is known to produce dilatation of the blood vessels in the skin and, to a lesser extent, those in other tissues. For this reason it has been advocated for the treatment of peripheral vascular disease and angina pectoris.^{1,2} Its use as a cerebral vasodilator has also been recommended³ because of the dilatation of pial vessels observed in animals given large amounts of ethyl alcohol intravenously.

The symptoms of acute alcoholic intoxication are generally believed to be caused by depression of the central nervous system. In vitro studies, however, have shown that alcohol in concentrations up to 2% produces an increase in oxygen consumption, while concentrations greater than this produce a decrease.⁴ A decrease in cerebral arteriovenous oxygen difference has been found during alcoholic intoxication but this has been attributed to a reduction in cerebral oxygen utilization rather than to an increase in cerebral blood flow.⁵

This paper presents our observations on the cerebral blood flow and oxygen consumption in patients with various stages of alcoholic intoxication resulting from either intravenous administration of ethyl alcohol or the ingestion of large amounts of whiskey.

METHOD

Fifteen patients convalescing from a variety of medical illnesses (pneumonia, arthritis, etc.) were given varying amounts of ethyl alcohol intravenously in a 5-10% solution. The age of the patients ranged from 18 to 65 years with an average of 40 years. Two of them had evidence of cerebral disease, one of whom had malignant hypertension and encephalopathy and the other, severe mental deficiency. The total dosage of alcohol ranged from 4 to 54 cc. of absolute alcohol and averaged 22 cc. The solution was given within 15 to 45 minutes and produced visible evidence of peripheral vasodilatation in most patients and a subjective feeling of warmth. Most of the patients showed symptoms of mild intoxication, such as drowsiness, euphoria, increased volubility, and inappropriate weeping or laughter. The alcohol levels in the blood ranged from 15 to 137 mgm.% with a mean of 68 mgm.%. There was a very good linear correlation between the dosage of alcohol administered intravenously and the blood alcohol level ($r = .93$). The slope of the line of regression represented a blood alcohol level of 22.5 mgm.% for each 0.1 Gm. alcohol administered per kilogram of body weight. Blood alcohol levels on arterial blood were done by the colorimetric method of Gibson.⁶

The cerebral blood flow (CBF) in these patients was measured by the nitrous oxide technique of Kety and Schmidt⁷, with slight modifications.⁸ Fifteen to 30 minutes after completion of the control blood flow procedure, the infusion of alcohol was begun, and was continued through most or all of the second CBF determination. The cerebral oxygen consumption ($CMRO_2$) was obtained by multiplying the CBF by the arterial-internal jugular venous oxygen difference. The cerebral vascular resistance (CVR) was obtained by dividing the mean arterial pressure by the CBF. The mean arterial pressure was measured between the blood samplings with a damped mercury manometer connected to the arterial needle.

Arterial and venous blood samples were drawn over a 20-30 second period just before and after the CBF procedure. Gas analysis of the blood samples for oxygen and carbon dioxide was done by the combined procedure described by Peters and Van Slyke⁹ and analysis for nitrous oxide by the method of Orcutt and Waters¹⁰, using the modifications of both techniques as described by Kety and Schmidt.⁷ The addition of ethyl alcohol to blood samples in concentrations as high as 400 mgm.% was found to have no effect on the accuracy of the nitrous oxide determinations. Hemoglobin concentration was calculated from the oxygen capacity. Arterial pH was determined with the glass electrode of the Cambridge Model R pH meter and corrected to body temperature (37° C.). Arterial pCO_2 was calculated from the pH, CO_2 content and hematocrit with the nomogram of Slinger and Hastings.¹¹ Venous oxygen tension (pO_2) was obtained from the pH, and percent oxygen saturation, using the dissociation curves of Dill.¹²

Similar studies were performed on a second group of 12 patients who had been brought to the hospital emergency clinic with signs of severe alcoholic intoxication. Most of these patients had been found lying in the streets of Atlanta in drunken stupor and all of them were comatose on admission to the hospital. Cerebral blood flow studies were done one to two hours later,

at which time 3 of the group (W.B., H.S., J.W.) were still completely unresponsive, while the others had aroused to a stuporous state. None of the patients was given any medication or stimulant prior to the initial cerebral function studies. All of the patients had a strong odor of alcohol on the breath. Several patients had vomited, and some had urinary and fecal incontinence. Speech was incoherent and rambling. Blood alcohol levels were obtained in 6 subjects and ranged from 234 to 413 mgm.% with a mean of 320 mgm.%. The other 6 patients had essentially the same degree of intoxication and would have been expected to show similar blood alcohol levels. The exact amount and type of alcoholic mixture consumed by the patients could not be determined with accuracy, since most of them either had amnesia for the events preceding their stupor or were loath to admit the extent of their drinking.

The ages of these patients varied from 30 to 62 and averaged 42 years. Cerebral blood flow determinations were repeated 15 to 62 hours after the initial procedure, at which time all of the subjects were sober and reasonably alert. There were surprisingly few "hangover" symptoms present. None of the patients had headache, evidence of dehydration or delirium tremens at the time of the second blood flow determination. Despite a history of chronic alcoholism the patients appeared to be in fairly good physical condition with one exception. This was a 62 year old patient (H.S.) who had severe hypertension and generalized arteriosclerosis.

RESULTS

The intravenous administration of small amounts of ethyl alcohol in the 15 subjects produced little change in the mean values for either cerebral blood flow, oxygen consumption or vascular resistance (Table I). Several of these individuals, however, showed a slight increase of 9 to 12 cc./100 Gm. brain/min. in CBF, while one patient had a decrease of 13 cc./100 Gm./min. There was only a slight fall in the mean cerebral arteriovenous oxygen difference and a small decrease in arterial blood pressure. Mean cerebral respiratory quotients before and during alcohol infusion were 0.90 and 0.88, respectively. There was no correlation between either the CBF or $CMRO_2$ and the individual blood alcohol levels.

In contrast, there were marked alterations observed in the cerebral functions of the patients admitted to the hospital with severe alcoholic intoxication (Table II). During the acute stage of intoxication there was a significant increase in cerebral blood flow ($p < .01$), the mean CBF at this time being 67 cc./100 Gm./min. A considerable increase in cerebral blood flow occurred in all but 3 individuals (H.S., J.W., and W.J.B.), as shown in Figure 1. Following recovery, the mean CBF fell to 47 cc. - a decrease of 30%. These 3 patients had no essential changes in CBF but, as pointed out below, showed the greatest reductions in $CMRO_2$ during alcoholic stupor, with values approximately one half those observed following recovery. During intoxication the mean arterial blood pressure was decreased in almost every patient and a significant reduction in mean CVR was also observed ($p < .01$). Following recovery, the mean CVR rose from 1.5 to 2.4 mm. Hg/cc./100 Gm./min.

With few exceptions the cerebral oxygen consumption during the acute stage of alcoholic intoxication was reduced and, following recovery, rose to approximately normal levels (Figure 2). The mean value for CMRO_2 , when the patients were intoxicated, was 2.2 cc. compared with 3.2 cc./100 Gm./min. when they were sober ($p < .001$). The mean cerebral arterio-venous oxygen difference during intoxication was one half that found after recovery. During alcoholic intoxication there appeared to be an inverse relationship between the degree of increase in CBF in the individual patient and the degree of decrease in CMRO_2 (Figure 3). The patients with the least rise in CBF had the greatest reduction in oxygen utilization, while those with the greatest increase in CBF had little alteration in CMRO_2 . The patient (H.S.) with the lowest CMRO_2 value had no change in CBF.

Acidosis was found in 5 of the 6 patients in whom pH determinations were obtained. The mean arterial pH value in these individuals during intoxication was 7.31 in contrast to a value of 7.40 while sober. The arterial CO_2 tension was elevated in 3 of 5 patients during intoxication. The mean pCO_2 in the 5 patients was 47 mm. Hg during intoxication and 39 mm. Hg following recovery. The majority of patients showed a reduction in cerebral respiratory quotient during intoxication as compared with the value following recovery.

COMMENT

This study demonstrates that low concentrations of alcohol in the blood, 15-137 mgm.%, do not produce significant changes in either cerebral blood flow or oxygen consumption as measured by the nitrous oxide method.

The possibility of excessive contamination of internal jugular blood with venous blood from extracerebral sources must be considered, since this would affect the validity of our determinations. At the level of the jugular bulb this contamination ordinarily is slight. Space does not permit a complete analysis of this problem in relation to the accuracy of the nitrous oxide method during alcoholic intoxication. Under ordinary conditions a considerable contamination will result in a falsely low value for cerebral blood flow. If the extracranial vessels are markedly dilated the cerebral blood flow may be falsely high.

We do not believe that any important error was introduced in these measurements by increased addition of extracerebral venous blood to internal jugular blood. Studies of the nitrous oxide concentrations in external and internal jugular blood in two patients given intravenous alcohol suggested that there was only mild dilatation of extracerebral vessels. Furthermore, the shape of the arterial and internal jugular venous nitrous oxide concentration curves in both groups of patients did not suggest excessive contamination.

Alteration in cerebral blood flow might have been expected in view of the fact that such levels are usually associated with evidence of extracranial and facial vasodilatation. The lack of any alteration in cerebral metabolism in the presence of mental changes of mild intoxication might appear surprising. It is possible, however, that the mental changes observed in these patients are due to depression of specialized areas or synaptic systems of the brain which do not participate greatly in the over-all oxygen consumption of this organ, but are nevertheless important in emotional control and personality integration. Some similar circumstances apparently obtain in patients given semi-narcotic amounts of barbiturates which, although producing definite mental changes, are not associated with alterations in either cerebral blood flow or metabolism.¹³ The absence of significant changes in the arterial-internal jugular venous oxygen difference in patients receiving as much as 80 cc. of alcohol intravenously has also been noted by others.¹⁴

These studies indicate that alcohol in the intravenous doses employed has little effect on cerebral blood flow and, from the standpoint of modifying this function, would not be expected to be of value in the treatment of patients with "strokes" or cerebral vascular disease. Although higher levels of alcohol in the blood were found to produce an increase in cerebral blood flow, such levels are associated with depression of cerebral oxygen uptake, and would require approximately 100 cc. of alcohol or 200 cc. of whiskey orally.

The depressant effect of large doses of alcohol on the brain in the patients with severe alcoholic intoxication has been found in a variety of psychologic and psychomotor studies.¹⁵ Electroencephalographic studies during alcoholic intoxication have shown changes similar to those observed during hypoxic states.¹⁶

The poor correlation found in the present studies between the blood alcohol level and the degree of reduction in cerebral oxygen uptake might have been due to the fact that the level of alcohol in the blood was not always the same as that in the nerve cell itself. However, this seems doubtful in view of the rapid distribution of alcohol throughout the body water.¹⁵ It seems more likely that the failure of correlation was due to individual differences in tolerance, possibly as a result of chronic addiction to alcohol.

As mentioned above, the patients with the greatest increase in CBF during intoxication tended to have the least degree of reduction in cerebral metabolism. Since blood flow is normally adjusted to tissue needs, a depression of cerebral metabolism by alcohol would be expected to be followed by a reduction in blood flow if other factors were not operative. It appears possible that an increase in blood flow during intoxication, by raising oxygen tension in the capillaries and in the extravascular fluid of the brain, counteracted to some extent the depressant effects of alcohol on cerebral metabolism. During alcoholic intoxication the mean venous pO_2 was actually 15 mm. greater than that found following recovery. There was some tendency for the patients with the greatest increase in jugular venous pO_2 during intoxication to have the least reduction in cerebral oxygen uptake. This might provide a rational basis for the use of 100% oxygen in the treatment of acute alcoholic intoxication, as suggested by other workers.¹⁷ This

concentration of oxygen, however, acts as a cerebral vasoconstrictor and this would to some extent offset the advantage of an increase in oxygen content of the arterial blood.

The increased CBF found in association with high levels of alcohol is consistent with the observations of Thomas¹⁸ who observed dilatation of the pial vessels in experimental animals given intravenous or intracarotid injections of ethyl alcohol. However, the increase in blood flow in these animals was transient and had completely subsided in 15 to 30 minutes, despite the continued presence of elevated blood alcohol levels.

Other factors which might well be important in producing the increased CBF were the increase in CO₂ tension and pH changes which existed in several of these patients. A decrease in pH was found in 5 of the 6 patients in whom this determination was made. Acidosis has also been reported by others and is thought to be caused by accumulation of lactic acid and retention of carbon dioxide.¹⁹ Reduction in pH is commonly believed to cause an increase in cerebral blood flow, but recent studies in our laboratory²⁰ and by Schieve and Wilson²¹ have shown that cerebral vessels dilate more consistently with elevations of CO₂ tension than with depression of pH. The mean increase of 8 mm. Hg in carbon dioxide tension observed in our patients is ordinarily sufficient to produce considerable dilatation of cerebral vessels. A reduction in pulmonary ventilation was found in 2 of the 3 patients in which this function was measured and this factor might have produced the observed elevation in pCO₂.

It would appear from these data, that the profound narcosis produced by high concentrations of alcohol in the blood can be accounted for by depression of cerebral metabolism. It is of course possible that a number of other factors such as an acidosis, dehydration, and hypoglycemia may also be operative in some of these patients. Our studies do not provide any information as to the exact mechanism of the depression of the brain in alcoholic intoxication except to indicate that impairment of the cerebral circulation is not a major factor. Despite the fact that the cerebral metabolism of these patients readily returned to normal after they became sober, it is possible that repeated depression of the brain by alcohol may result in permanent cerebral injury and degeneration.

The technical assistance of the following is acknowledged with appreciation:

Mrs. Louise Thompson, and the Misses Mary Bell, Mary Ruth Fordham, Elizabeth Kelley and Mary Upshaw.

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TABLE I

MEAN VALUES AND STANDARD DEVIATIONS FOR CEREBRAL FUNCTIONS IN PATIENTS
BEFORE AND DURING INTRAVENOUS INFUSION OF ALCOHOL

	CBF cc./100 Gm./min.		CMRO ₂ cc./100 Gm./min.		CVR mm. Hg/cc./ 100 Gm./min.		(A-V)O ₂ vol. %		Mean Art. Pressure mm. Hg
	Mean*	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	
Control Determination	47	± 12	2.8	± .3	2.1	± .6	6.2	± .9	94
During Alcohol Infusion	50	± 10	2.8	± .6	1.9	± .4	5.8	± 1.4	89

* All mean values have been calculated from the data on individual patients

TABLE II

PHYSIOLOGIC DATA IN PATIENTS WITH ACUTE ALCOHOL INTOXICATION

	CBF		CMRO ₂		CVR		(A-V)O ₂		Mean Art. Pressure		Hemo-globin Gm./100 cc.	Hemato-crit	Art. Alcohol gm./100 cc.
	I	R	I	R	I	R	I	R	I	R			
H.S.	32	32	0.8	2.6	2.7	3.8	2.7	8.2	85	123	11.7	38	413
J.C.	37	32	1.8	2.7	2.0	3.1	4.7	8.5	75	98	12.8	44	-
G.K.	54	41	2.4	3.0	1.9	2.6	3.9	7.3	101	107	14.1	47	-
J.W.	54	53	2.1	4.0	1.3	1.9	3.9	7.4	70	100	13.1	44	-
R.H.	63	53	2.8	3.6	1.5	2.0	4.5	6.9	95	105	15.2	47	-
L.T.	64	35	2.5	3.0	1.5	3.8	4.0	8.5	97	132	11.3	37	-
W.J.B.	70	67	1.8	3.5	1.3	1.3	2.5	5.2	90	90	14.7	48	-
R.L.W.	73	43	2.5	3.4	1.6	2.6	3.4	7.9	115	111	12.5	37	295
J.B.	78	52	-	2.8	1.4	1.8	-	5.4	109	95	12.9	41	314
B.B.	89	66	2.2	3.9	1.0	1.7	2.4	6.0	86	108	13.7	46	234
C.E.	92	37	2.4	2.2	1.0	3.1	2.6	6.1	93	112	11.9	38	333
S.B.	99	55	3.7	3.9	.8	1.5	3.7	7.1	82	82	12.8	43	328
Mean	67*	47	2.2*	3.2	1.5*	2.4	3.5*	7.0	92	105	12.9	42	320

I = During Intoxication

R = Following Recovery

* Statistically significant difference ($p < .01$) from mean value following recovery.

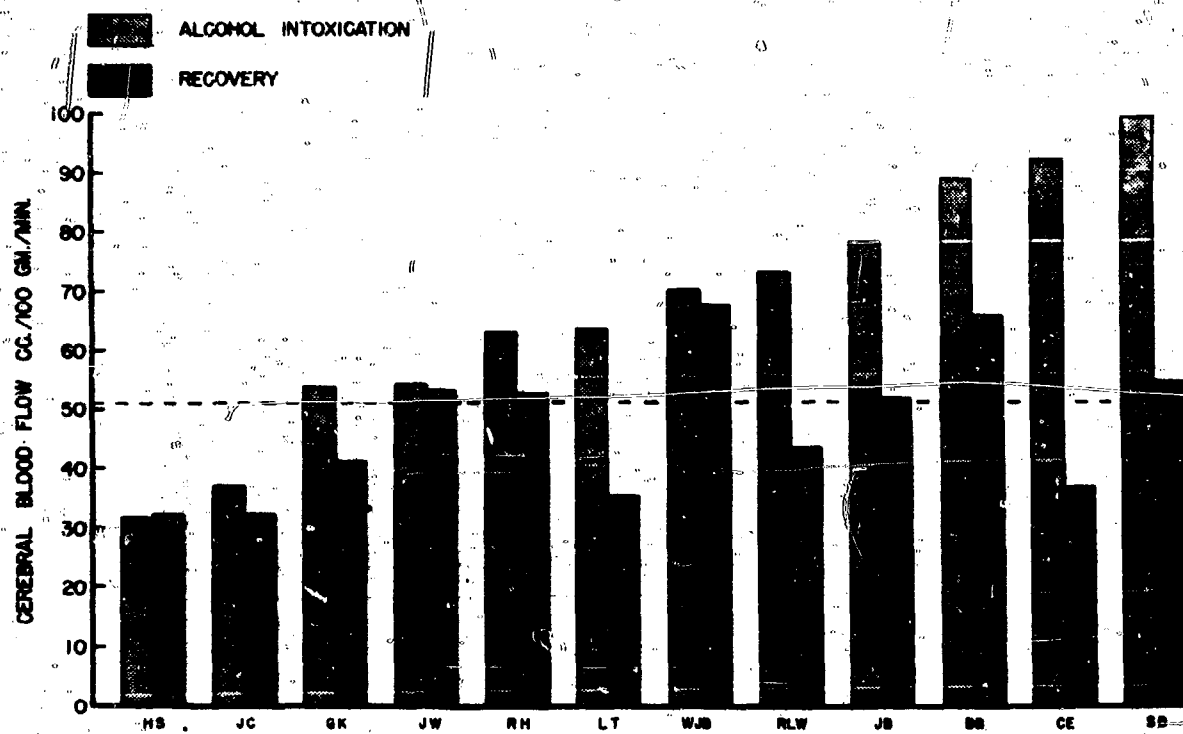


Fig. 1. The changes in cerebral blood flow in patients during severe alcoholic intoxication and following recovery. The broken line indicates the mean value in control subjects.

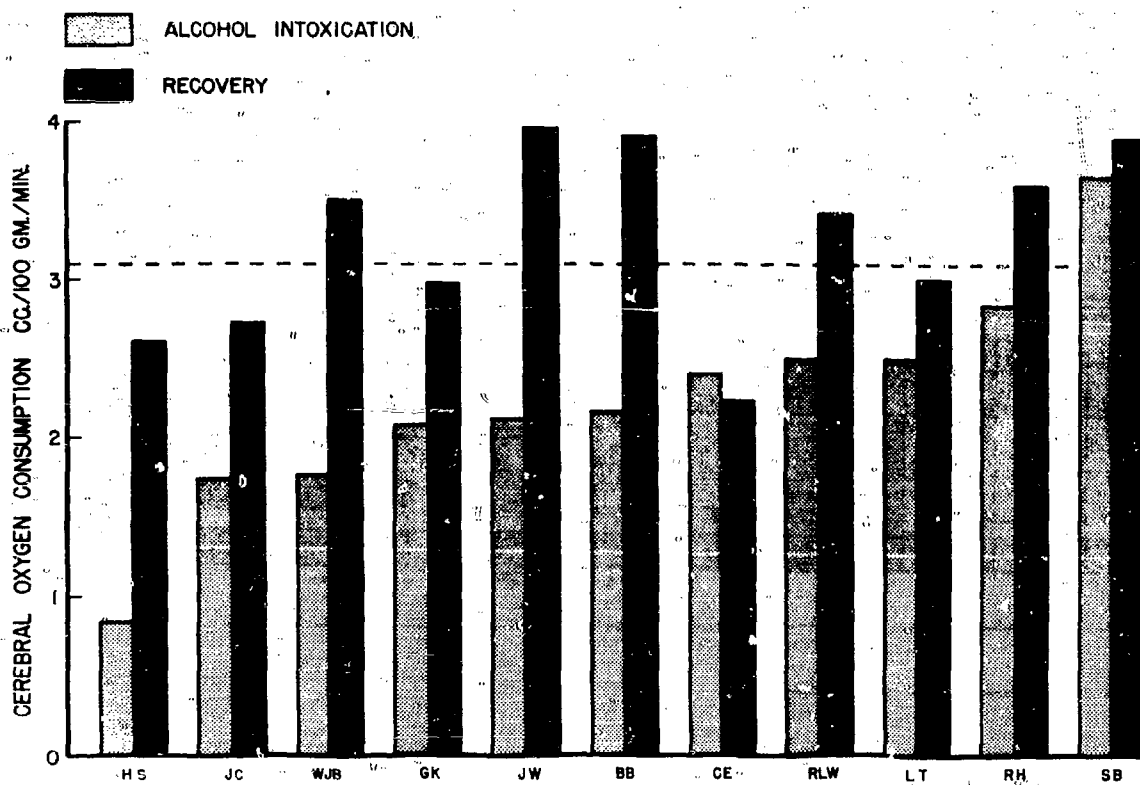


Fig. 2. The changes in cerebral oxygen consumption in patients during severe alcoholic intoxication and following recovery. The broken line indicates the mean value in control subjects.

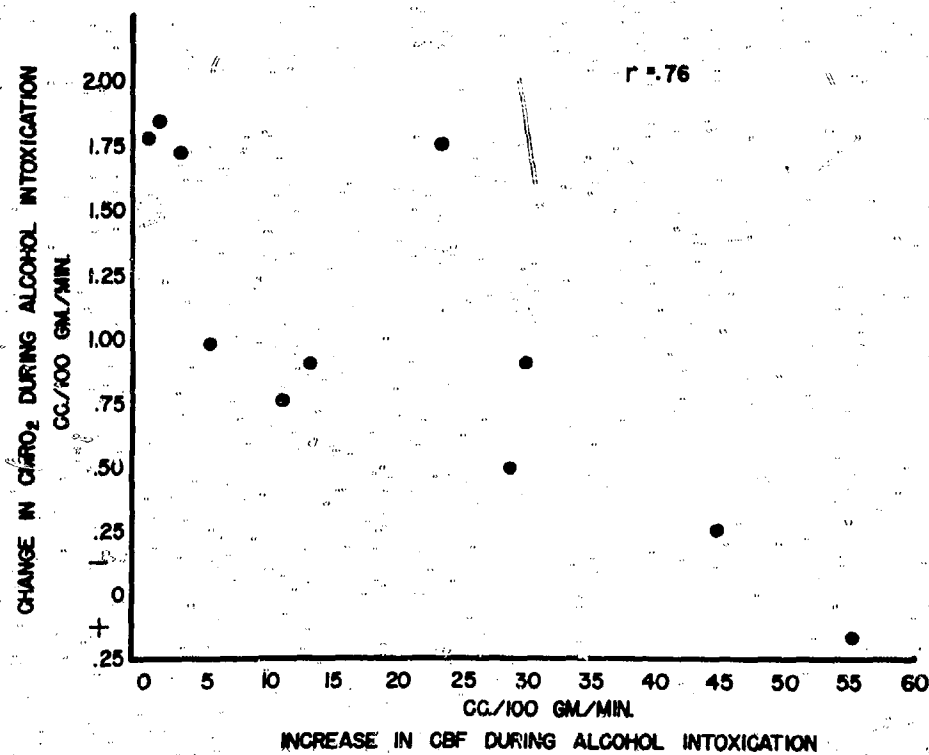


Fig. 3. The relationship between the increase in cerebral blood flow during alcoholic intoxication and the change in cerebral oxygen consumption.

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