The Hepatic Metabolism of Ethanol in Patients with Cirrhosis of the Liver*

K. WINKLER, F. LUNDQUIST & N. TYGSTRUP
Third Medical Department and Department of Clinical Physiology, Kommunehospitalet,
Department of Biochemistry A, University of Copenhagen,
Medical Department B, Bispebjerg Hospital,
Department A, Hepatology, Rigshospitalet, Copenhagen

Winkler, K., Lundquist, F. & Tygstrup, N. The Hepatic Metabolism of Ethanol in Patients with Cirrhosis of the Liver. *Scand. J. clin. Lab. Invest. 23,* 59-69, 1969.

Splanchnic ethanol uptake was lower in cirrhosis compared to normals. The accelerating effect of fructose on ethanol metabolism was smaller in cirrhosis. From studies of portocaval shunts, it appeared that acetate, formed from ethanol, was not metabolized in the liver. The peripheral metabolism of acetate, glucose and lactate was diminished in cirrhosis.

Key-words: Ethanol; fructose; acetate; lactate; pyruvate; glucose intermediary metabolism; cirrhosis; portocaval anastomosis; liver function hepatic blood flow.

K. Winkler, M.D., Physiology Dep., Kommunehospitalet, Copenhagen, Denmark

The elimination of ingested ethanol mainly takes place in the liver (21). When the liver is affected by disease, changes in this function may be anticipated. The usefulness of the ethanol elimination as a liver function test has been considered repeatedly (25, 4, 5, 14, 16), mostly with negative results.

The purpose of the present work was to study if decreased liver function had metabolic consequences which could be detected when the liver was loaded with ethanol. This was done by examining the metabolic response of the splanchnic organs by liver vein catheterization during ethanol infusion in patients with cirrhosis of the liver. In a further group of patients the accelerating effect of fructose on the rate of ethanol elimination was determined. The results were compared with data from similar studies in patients without liver diseases.

MATERIAL

The material comprised 20 patients with cirrhosis of the liver. The sex and age, the possible etiologic factors, the basis of the diagnosis, and some clinical and biochemical observations are given in Table I. Patients No. 9 and 16 were slightly jaundiced. In patients Nos. 16-20 an end-to-side porto-caval anastomosis had been established as a treatment for portal hypertension; the interval between the surgery and the study was 2-5 years. None of the patients displayed clinical signs of malnutrition.

The control material consists of 20 experiments, published previously (20, 27), and 11

* Tables with full details of individual experiments can be obtained from the authors.

experiments performed during the same period as the examination of the cirrhotic patients. The control subjects were patients without clinical signs of liver disease.

METHODS

The hepatic veins were catheterized in the fasting patient (premedicated with 100 mg of phenobarbitone) via an antecubital vein. Arterial blood was taken from an indwelling needle in a brachial or femoral artery. In 3 patients (Nos. 16, 19, and 20) portal blood was obtained from the porto-caval shunt through a catheter introduced percutaneously via the femoral vein. The correct positioning of this catheter was ascertained by injection of contrast medium.

Hepatic blood flow was determined by the indocyanine-green (ICG, Cardio Green®, Hynson, Westcott & Dunning) infusion method (28). The priming dose was 10 mg, and the infusion dose on the average 475 μg/min in the patients with cirrhosis. In the control subjects the previously described procedure was followed (20, 27). Each study comprised two periods; in patients Nos. 1-9 and Nos. 16-20 the first period served as control, and ethanol was infused during the second period. In patients Nos. 10-15 ethanol was infused during both periods, and fructose during the second period. The amounts infused are indicated in Tables I and V. The infusions were preceded

Table I. Clinical and laboratory data of the patients

Patient No.	Sex	Age (years)	Body weight (kg)	Diagnosed by*	Etiology**	History of coma	Clinical hepatomegaly	S-GO-transaminase (units)**	S-albumin (g/100 ml)	S-γ globulin (g/100 ml)	ICG-clearance (litres/min) °	Wedged hepatic venous pressure (mm Hg)	Transhepatic resistance § (mm Hg/l/min)	Infusion of ethanol (mmoles/min)
1	M	51	73	LB	U	–	+	42	4.1	0.9	0.83	14	3.1	1.76
2	M	54	84	LB	A	+	+	630	2.6	1.6	0.10	27	13.7	2.22
3	F	68	58	LS	U	+	–	29	3.9	2.3	0.43	18	13.3	3.11
4	M	44	75	LB	A	–	–	44	2.8	1.8	0.34	16	6.9	1.98
5	F	72	58	LB	U	–	–	49	2.6	2.4	0.15	17	13.4	1.73
6	F	66	78	LS	U	–	–	79	3.6	2.2	0.28	18	3.4	1.90
7	M	41	62	LB	H	–	–	122	3.1	2.4	0.55	7	2.6	2.12
8	M	52	91	LB	U	–	+	37	4.5	1.0	0.55	12	1.6	2.39
9	F	75	59	LB	U	–	+	72	2.3	2.1	0.17	–	–	2.11
10	M	44	64	Cl	A	–	+	140	4.2	1.5	0.18	–	–	2.35
11	F	76	63	LB	U	–	+	21	2.4	2.1	0.14	21	12.4	2.33
12	F	56	58	LB	H	+	–	73	2.8	2.4	0.18	27	11.4	2.03
13	M	57	84	PM	U	–	+	180	2.5	5.0	0.10	16	4.3	2.36
14	F	56	56	LB	U	–	+	65	3.1	1.2	0.41	18	7.1	1.33
15	M	61	85	LB	U	–	+	73	5.1	1.3	0.33	23	13.0	1.85
16	M	68	76	PM	U	+	–	75	3.5	1.4	0.16	14	32.7	1.97
17	F	69	46	LB	U	+	–	156	3.1	1.8	0.14	5	8.5	1.78
18	F	72	74	LB	U	+	–	48	4.1	1.4	0.16	16	26.3	2.72
19	F	51	48	LT	U	+	+	87	2.0	3.8	0.29	–	–	2.83
20	M	40	80	LB	A	–	–	23	3.6	1.6	0.20	17	25.4	2.15

*LB: liver biopsy; LS: laparoscopy; Cl: clinical observation; PM: post mortem examination; LT: laparotomy.
**U: unknown; A: alcoholism; H: hepatitis.
** the upper normal limit is 34 units.
° ICG: indocyanine green. (Normal value from our laboratory: 660 ml/min).
§ wedged minus free hepatic venous pressure over hepatic blood flow.

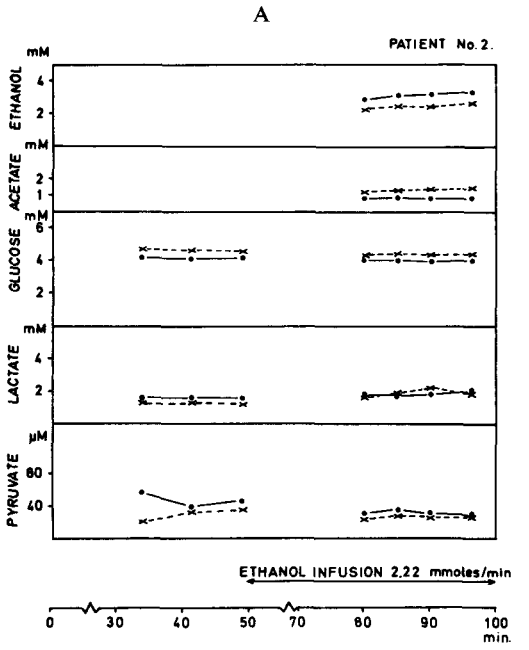
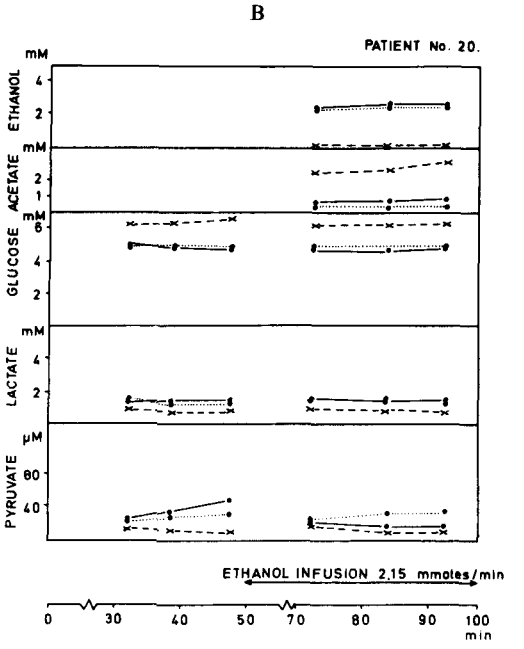
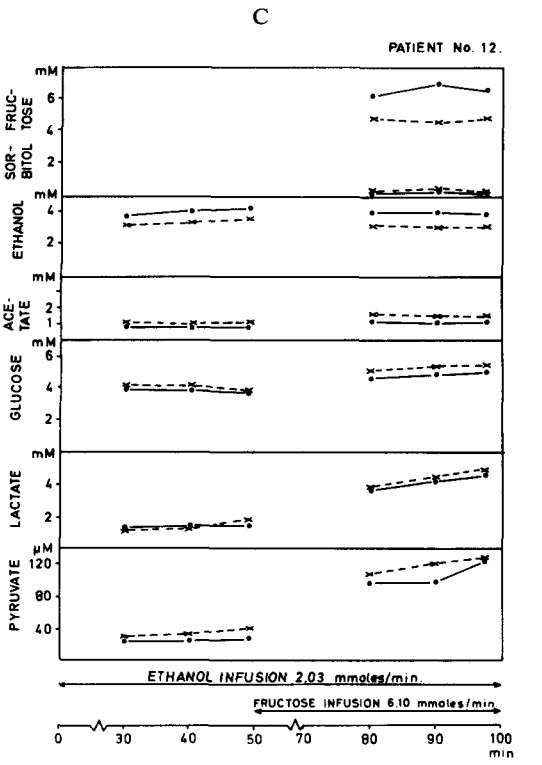


Fig. 1. Examples of the three types of experiment.
A shows patient No. 2
B " " No. 20
C " " No. 12
.——.: arterial concentration; .------.: hepatic venous concentration; .·····.: portal venous concentration. Patient No. 2: control and ethanol period; patient No. 20: control and ethanol period with sampling from end-to-side porto-caval shunt of portal blood; patient No. 12: ethanol and fructose-ethanol period.





by priming doses, 50 mmoles of ethanol and 180 mmoles of fructose, respectively.

The course of the experiments appears from the examples given in Fig. 1. Samples for determinations of blood oxygen and carbon dioxide (van Slyke) were drawn in the middle of each period. The following substances were determined by the methods indicated: ethanol (17), acetate (18), lactate (12), pyruvate (6), glucose (23), fructose (24) and sorbitol (27). For ethanol, acetate, lactate and pyruvate the plasma concentrations are given. Splanchnic uptake was calculated after conversion to blood concentrations.

RESULTS

Table II shows that the splanchnic uptake of ethanol was significantly reduced in the patients with cirrhosis, but the overlapping with the values found in the control subjects was considerable (Fig. 2). The reduction was most marked in the patients with porto-caval anastomosis (group B) but in one patient (No. 20) the elimination rate may not have been maximal, since the concentration of ethanol in the hepatic veins was zero.

The acetate production was also diminished, but in this case there was no significant dif-

Table II. Metabolic data during infusion of ethanol

		Ethanol		Acetate		Glucose		Lactate		Pyruvate		L/P	O_2	CO
	Hep. blood flow litres/min	art. conc. mmol/l	uptake mmol/min	art. conc. mmol/l	uptake mmol/min	art. conc. mmol/l	uptake mmol/min	art. conc. mmol/l	uptake mmol/min	art. conc. µmol/l	uptake µmol/min	Hep. vein ratio	uptake mmol/min	uptake
	(A) Cirrhosis													
N	15	15	15	15	15	15	15	15	15	15	15	15	15	1
mean	1.46	2.99	1.30	1.01	−0.92	4.64	−0.54	1.72	0.02	33	15	84	2.84	−0.7
range	(0.64-	(1.42-	(0.75-	(0.56-	(−1.73-	(3.28-	(−1.52-	(1.14-	(−0.16-	(11-	(−14-	(44-	(1.34-	(−1.6
	2.57)	5.81)	2.13)	1.92)	−0.41)	6.67)	−0.15)	2.17)	0.25)	72)	56)	219)	4.07)	0.9
SEM	0.13	0.30	0.09	0.10	0.09	0.26	0.09	0.07	0.04	4	4	16	0.21	0.2
	(B) Cirrhosis and porto-caval anastomosis													
N	5	5	5	5	5	5	5	5	5	5	5	5	5	
mean	0.45	4.38	0.79	0.87	−0.69	4.94	−0.43	2.01	0.09	53	14	108	1.45	−0.4
range	(0.28-	(2.49-	(0.62-	(0.68-	(−6.85-	(3.38-	(−0.57-	(1.52-	(−0.05-	(19-	(2-	(68-	(1.19-	(−0.6
	0.74)	6.17)	0.95	1.04	−0.55)	8.43)	−0.15)	2.63)	0.24)	88)	23)	163)	1.81)	−0.1
SEM	0.08	0.47	0.06	0.06	0.05	0.70	0.06	0.19	0.05	12	4	18	0.12	0.1
	(C) Controls													
N	31	31	31	31	31	21	21	21	21	21	21	21	31	2
mean	1.50	3.74	1.61	0.85	−1.18	4.00	−0.67	1.29	−0.04	24	16	162	2.97	−1.4
range	(0.95-	(1.24-	(0.87-	(0.59-	(−0.69-	(3.57-	(−0.29-	(0.84-	(−0.21-	(5-	(−2-	(31-	(1.35-	(−2.0
	2.24)	7.52)	2.29)	1.26)	−1.74)	5.21)	−1.15)	2.04)	0.17)	52)	58)	617)	5.75)	0.1
SEM	0.06	0.27	0.07	0.04	0.06	0.11	0.05	0.06	0.02	3	3	28	0.17	0.2
p A-C	−	−	+	−	+	+	−	+++	−	−	−	+	−	
p B-C	+++	−	+++	−	+++	+	−	+++	+	++	−	−	+++	
p A-B	+++	+	++	−	−	−	−	−	−	+	−	−	++	

Negative uptake means output. L/P is the lactate/pyruvate concentration ratio in hepatic venous blood. The p-valu refer to the significance of the difference between the means of the groups indicated (t-test).
−: $p > 0.05$; +: $p < 0.05$; ++: $p < 0.01$; +++: $p < 0.001$.

Table III. Changes in metabolic data from control to ethanol period

	Hep. blood flow litres/min	Glucose art. conc. mmol/l	Glucose uptake mmol/min	Lactate art. conc. mmol/l	Lactate uptake mmol/min	Pyruvate art. conc. µmol/l	Pyruvate uptake µmol/min	L/P Hep. vein ratio	O_2 uptake mmol/min	CO_2 uptake mmol/min
	(A) Cirrhosis									
N	9	9	9	9	9	9	9	9	9	8
mean	−0.10	−0.20	0.14	0.44	−0.19	−12	7	3.3	−0.11	0.51
range	(−0.47- 0.30)	(−0.43- 0.01)	(−0.32- 0.55)	(0.20- 0.89)	(−0.43- 0.35)	(−27- − 1)	(−11- 50)	(1.5- 6.1)	(−1.67- 1.30)	(−0.77- 1.65)
SEM	0.07	0.05	0.10	0.08	0.08	3	6	0.5	0.32	0.33
p	−	++	−	+++	+	++	−	+++	−	−
	(B) Cirrhosis and porto-caval anastomosis									
N	5	5	5	5	5	5	5	5	5	5
mean	0.05	0.37	0.02	0.55	−0.12	−18	− 3	2.4	−0.01	0.13
range	(−0.06- 0.18)	(−0.94- 1.56)	(−0.17- 0.22)	(0.12- 1.21)	(−0.38- 0.08)	(−22- −12)	(−15- 4)	(0.9- 3.2)	(−0.89- 0.78)	(−0.16- 0.38)
SEM	0.04	0.41	0.08	0.18	0.08	2	2	0.4	0.20	0.10
p	−	−	−	+	−	+++	−	+++	−	−

The changes are given as ethanol-(second period) minus control-(first period) value, or ethanol- over control-value (the L/P ratio). A negative value in the uptake columns thus may mean a decreased uptake or an increased output during the ethanol infusion. The p-values indicate if the mean change is significantly different from zero.

The symbols are explained in Table II.

ference between patients without (group A) and with (group B) porto-caval anastomosis. The ratio acetate output/ethanol uptake was 0.70 (SEM 0.05) in group A and 0.88 (SEM 0.05) in group B. The latter value is not significantly different from 1.00, but significantly greater than the former value.

The arterial concentrations of glucose and lactate were significantly elevated in cirrhotics during infusion of ethanol, but the splanchnic output of these substances was not increased. (The lactate/pyruvate concentration ratio (=P) in hepatic venous blood was significantly smaller in the cirrhotics (group A) than in the control subjects, but again the overlapping was great, and there was no correlation between this ratio and the splanchnic ethanol elimination rate in the cirrhotic patients ($r = +0.32$).

The oxygen uptake was correlated with the splanchnic blood flow ($r = +0.75$). It was only significantly decreased in patients with shunts (group B). The respiratory quotient was on the average 0.38 in group A, 0.31 in group B, and 0.58 in the control group. The difference between the groups was not statistically significant. The respiratory quotient was only calculated in patients with a splanchnic carbon dioxide output (omitting Nos. 11, 12, and 14).

Table III illustrates some effects of the ethanol infusion. The slight fall in hepatic blood flow was not significant in the patients with cirrhosis, in contrast to control subjects (20). Control data were not available for most of the other values. There was no significant difference between group A and B regarding these observations.

In group A there was a significant fall in the arterial glucose concentration, despite in unaltered splanchnic glucose output. In both group A and B the arterial concentration of lactate rose and that of pyruvate fell. There

was a small rise in the mean splanchnic output of lactate which did not correlate with the rise in the arterial concentration. Only an insignificant part of the increased lactate output could be accounted for by a decreased output of pyruvate.

The lactate/pyruvate concentration ratio in hepatic venous blood increased materially, except in patient No. 20 where the concentration of ethanol in the hepatic venous blood was zero.

The change in oxygen uptake and carbon dioxide production was not statistically significant.

As shown in Table IV the infusion of fructose increased the elimination rate of ethanol in 5 of 6 patients with cirrhosis, as it does in control subjects, but the effect was significantly smaller. The mean increase in acetate production was almost equal to that of the ethanol uptake.

The rise in arterial concentration and splanchnic output of glucose was less pronounced than in the controls. Arterial lactate concentration rose more, and splanchnic output less, than in the control material. The pyruvate response was much more variable in the cirrhotic patients. In most of the patients more pyruvate was released from the splanchnic area, in the control subjects the opposite was the case. This caused a significant fall in the lactate/pyruvate concentration ratio in the hepatic venous blood, which was not found in control subjects when fructose was added to an infusion of ethanol.

The cirrhotic patients showed a significantly smaller splanchnic uptake of fructose under these conditions (Table V). The fructose uptake did not correlate with the pre-fructose ethanol uptake, nor with the increase in ethanol uptake during fructose infusion. The proportion of fructose eliminated in the splanchnic area was slightly but not significantly diminished relative to other parts of the body. The pro-

Table IV. Changes in metabolic data from ethanol to fructose-ethanol period

		Ethanol		Acetate		Glucose		Lactate		Pyruvate			O_2	CC
	Hep. blood flow litres/min	art. conc. mmol/l	uptake mmol/min	art. conc. mmol/l	uptake mmol/min	art. conc. mmol/l	uptake mmol/min	art. conc. mmol/l	uptake mmol/min	art. conc. µmol/l	uptake µmol/min	Hep. vein L/P ratio	uptake mmol/min	uptake
	(A) Cirrhosis													
N	6	6	6	6	6	6	6	6	6	6	6	6	6	
mean	0.11	–0.16	0.38	0.33	–0.36	1.17	–0.13	2.93	–0.42	78	–34	0.51	1.14	–0.
range	(–0.23- 0.63)	(–0.57- 0.26)	(0.02- 0.74)	(0.00- 0.78)	(–0.98- 0.17)	(0.75- 1.62)	(–0.56- 0.47)	(2.33- 3.73)	(–1.09- –0.02)	(–9- 130)	(–115 3)	(0.22- 0.84)	(–0.55- 1.69)	(–1. –0.0
SEM	0.12	0.14	0.11	0.13	0.18	0.13	0.17	0.22	0.15	20	18	0.12	0.22	0.
p	--	–	+	+	–	+++	–	+++	+	+++	–	++	+++	
	(C) Controls													
N	10	10	10	10	10	10	10	10	10	10	10	10	10	
mean	0.40	0.09	1.23	0.58	–1.24	1.98	–1.31	2.16	–0.70	45	37	0.84	1.67	0.
range	(–0.15- 0.81)	(–0.84- 1.75)	(0.58- 2.20)	(–2.38- 0.92)	(–1.63- –0.68)	(1.03- 3.30)	(–4.10- –0.37)	(1.51- 2.86)	(–1.20- –0.27)	(20- 68)	(–3- 71)	(0.30- 1.32)	(0.48- 3.86)	(–1. 2.
SEM	0.09	0.32	0.13	0.06	0.09	0.22	0.34	0.15	0.10	5	7	0.16	0.35	0.
p	+++	–	+++	+++	+++	+++	+++	+++	+++	+++	+++	–	+++	
p A-C	–	–	+++	–	+++	+	+	+++	–	++	+++	–	--	

The changes are given as fructose-ethanol- (second period) minus ethanol- (first period) value, or as fructose-ethan over ethanol-value (the L/P ratio). The p-values in bottom line indicate difference between cirrhosis and control gro

Table V. Fructose metabolism during ethanol infusion

	Fructose				Sorbitol	
	Infusion mmol/min	art. conc mmol/l	uptake mmol/min	uptake infusion	art. conc mmol/l	uptake mmol/min
	(A) Cirrhosis					
N	6	6	6	6	6	6
mean	6.29	6.58	1.67	0.26	0.73	−0.06
range	(5.85-8.17)	(5.62-8.28)	(1.08-2.77)	(0.18-0.47)	(0.23-1.79)	(−0.33-0.07)
SEM	0.38	0.43	0.29	0.04	0.14	0.07
	(C) Controls					
N	10	10	10	10	9	9
mean	8.44	6.47	2.90	0.35	1.47	−0.62
range	(7.02-10.86)	(4.50-8.77)	(2.07-3.69)	(0.23-0.49)	(0.29-1.92)	(−1.23-−0.08)
SEM	0.43	0.35	0.08	0.02	0.27	0.16
p A-C		−	++	−	+	+

The p-values are given as in Table IV.

duction of sorbitol from fructose was significantly reduced in the patients with cirrhosis. The splanchnic oxygen uptake rose significantly during fructose infusion but did not differ from that of normal subjects.

The mean arterio-portal concentration differences during the control and ethanol periods in patients No. 16, 19 and 20 are shown in Table VI. Absolute values for uptake and output cannot be given, since the flow rate was not measured. In one patient (No. 19) there was a moderate output of glucose, possibly due to absorption of sugar taken despite the prescribed fast. The differences in lactate and pyruvate were small, whereas the concentration differences of oxygen and carbon dioxide were considerable, and the same was true of the acetate uptake in the extrahepatic splanchnic organs during the ethanol period.

DISCUSSION

Ethanol elimination in cirrhosis. On average, the hepatic elimination of ethanol is only slightly reduced in patients with cirrhosis, and most determinations are found within the

Table VI. Mean arterio-portal (shunt) concentration differences (mmol/l)

Case No.	Glucose	Lactate	Pyruvate	Ethanol	Acetate	O_2	CO_2
			CONTROL PERIOD				
16	−0.13	−0.03	−0.002	–	–	1.47	−0.63
19	−0.36	0.09	0.027	–	–	1.07	−0.71
20	−0.03	0.02	0.008	–	–	0.71	−0.49
			ETHANOL PERIOD				
16	−0.21	−0.13	0.001	−0.10	0.33	2.36	−1.87
19	−0.32	0.03	−0.005	0.01	0.17	0.58	−0.54
20	0.00	0.06	−0.012	0.08	0.33	0.85	−0.40

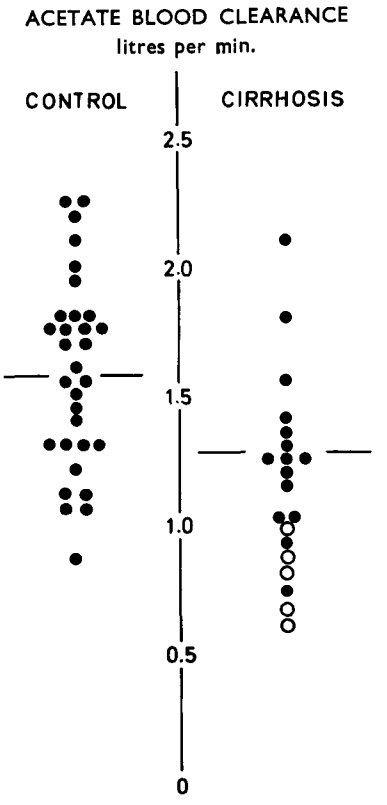


Fig. 2. Splanchnic ethanol elimination rates in control subjects and in patients with cirrhosis of the liver. o: patients with porto-caval anastomosis.

range of the control values. The overlapping is not reduced by relating the elimination rate to body weight or surface area. The cause of the great variability in the hepatic capacity for ethanol elimination is unknown. It is assumed that the elimination is maximal in all the subjects examined, with the exception of No. 20 (this assumption cannot be definitely proved by the present experiments). The variability should thus be sought in the process which limits the elimination rate, but it is still uncertain which process has that effect in vivo. It has been suggested that the limiting process is the removal of the hydrogen equivalents formed in the extramitochondrial cytoplasm by the oxidation of ethanol. The removal is thought to depend on 'shuttle'-mechanisms, consisting of red-ox systems like alfa-glycerophosphate hyphen dihydroxyacetone-phosphate or oxaloacetate-malate which carry the hydrogen through the mitochondrial membranes (10). Saturation of the mechanisms will result in a high NADH/NAD concentration ratio in the cytoplasm. An impression of the ratio is obtained by determination of the lactate/pyruvate concentration ratio in the medium (11), i.e. in the hepatic venous blood. In the cirrhotics the lactate/pyruvate ratio is smaller during ethanol elimination than in the control material, indicating that the 'shuttle'-mechanism is functioning relatively well in the cirrhotic livers, or that another mechanism is active in the transport of reducing equivalents into the mitochondria. Other factors may

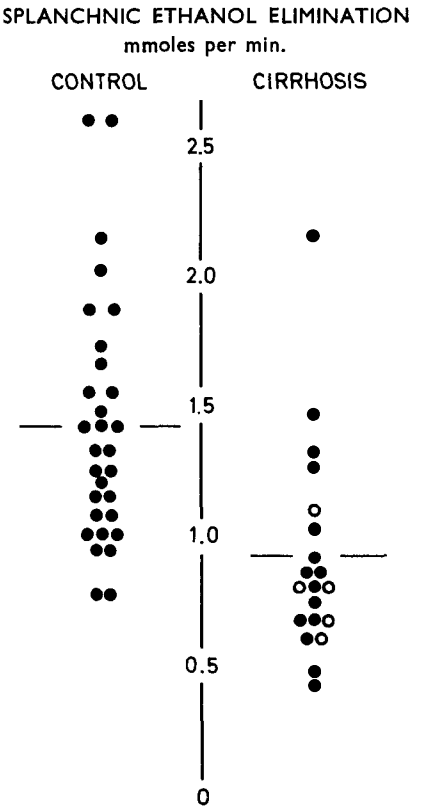


Fig. 3. Acetate 'blood clearance' (splanchnic acetate production over mean arterial acetate concentration) in control subjects and in patients with cirrhosis of the liver. o: patients with porto-caval anastomosis.

therefore limit the elimination rate of ethanol in these patients. One factor may be a reduction of the amount of alcohol-dehydrogenase (ADH) in the liver. Cytochemical studies have demonstrated a lowered activity of ADH in liver biopsy specimens from cirrhotic patients (8, 3).

Fructose effect on ethanol elimination. The accelerating effect of fructose on ethanol elimination indicates that the amount of ADH is not the limiting factor in normal subjects (27). The much smaller fructose effect seen in the cirrhotic patients, together with the drop in the L/P ratio in hepatic venous blood, suggests that the ADH activity is relatively reduced and may be limiting for the ethanol elimination under these conditions. The smaller elimination of fructose in the cirrhotic liver can only account for a minor part of the diminished fructose effect, since the 'extra' elimination of ethanol per mmole of eliminated fructose in the cirrhotic patient on the average is 0.23 mmole, against 0.42 mmole in the control subject.

Correlation with clinical and laboratory findings. The elimination rate of ethanol was not significantly larger in patients with hepatomegaly, but this does not exclude that it depends on the functional liver mass, which may be small in enlarged livers. Significant correlations between ethanol elimination and the conventional liver tests (serum albumin, gamma-globulin, GO-transaminase and prothrombine concentration) could not be demonstrated. It was correlated with ICG-clearance ($r = + 0.48$) but the correlation may be 'false', since it depends on inclusion of the patients with porto-caval anastomosis. The results do not settle the question whether the ethanol elimination rate in cirrhosis reflects the functional capacity of the liver, because the reference values are too uncertain. A correlation between ethanol elimination and serum bilirubin could not be established, since most of the patients were unjaundiced. Bilirubin has been found to inhibit ADH both in vitro (9) and in vivo (13).

The rise in transhepatic resistance is due to the disturbance of the lobular architecture, and it may therefore be considered a measure of the extent of the cirrhotic process in the liver. The transhepatic resistance was significantly correlated with the ethanol elimination rate ($r = - 0.75$), indicating a causal relationship, unless both resistance and elimination rate are directly influenced by the hepatic blood flow.

The metabolic effects of ethanol on the cirrhotic liver did not differ qualitatively from those seen in normal livers, and only minor quantitative differences were observed.

Extrahepatic splanchnic metabolism of ethanol and acetate. In liver vein catheterization studies it is generally impossible to distinguish between hepatic and extrahepatic splanchnic metabolism. This uncertainty is eliminated in studies of patients in whom portal blood bypasses the liver via an end-to-side porto-caval shunt, as in our patients No. 16—20. The exclusion of influence from extrahepatic splanchnic organs explains the difference between group A and B in blood flow and oxygen uptake, and in the ratio acetate output/ethanol uptake. In the operated patients this ratio is not significantly below unity, confirming that free acetate is only metabolized by the liver to a minor degree when ethanol is present (19).

The difference in ethanol elimination rate in unoperated (group A) and operated (group B) patients can hardly be explained by extrahepatic splanchnic removal of ethanol in the former group. It is doubtful whether these organs contain appreciable ADH-activity, and the experiments shown in Table VI do not reveal any consistent arterio-portal extraction of ethanol.

As a positive correlation between ethanol uptake and hepatic blood flow in the entire group of patients with cirrhosis is apparent from Table II ($r = 0.71$), we must consider whether the rate of ethanol removal is determined by the magnitude of the flow rather than by cellular function. Flow-dependent

elimination means that the elimination mechanism is not saturated. This is obviously the case in patient No. 20, where the hepatic venous concentration of ethanol is zero, and therefore ethanol is removed in one passage through the liver. In the remaining cases the extraction of ethanol is less than 100 per cent. In normal persons this will indicate that the elimination is saturated, but in cirrhotics it could be explained by intrahepatic shunts (22, 26). Admixture of blood from the shunts could obscure complete, and thus flow-dependent, extraction of ethanol from an effective 'non-shunt' proportion of the hepatic blood flow. The distribution between assumed effective and shunted flow may be estimated. If the actual shunted flow is smaller, extraction cannot be complete from the effective flow, and saturation is likely.

The maximum value of the shunted flow can be estimated on the assumption that Indocyanine Green is extracted one hundred per cent from the effective flow. In 7 of 19 patients the maximum shunted flow is too small to explain the hepatic venous concentration of ethanol as admixture of shunted blood alone, and saturation of the elimination can be assumed.

Thus, though the present experiments do not show that the elimination rate of ethanol is maximal and limited by hepatic cellular function, indirect evidence favours this concept. The correlation between ethanol uptake and hepatic flow must be caused by a common factor, e.g. the severity of the cirrhotic process.

Extrasplanchnic metabolism. Some of the observed differences between the cirrhotic patients and the control subjects indicate disturbances of the extrahepatic metabolism of the patients. Thus the mean arterial concentration of acetate in the cirrhotics is slightly higher than in the controls, despite a significantly lower splanchnic acetate output, indicating that the peripheral break-down of acetate is reduced. From the splanchnic acetate output and the arterial concentration which is practically constant during the experiments, an acetate 'blood clearance' may be calculated (Fig. 3). In the controls it amounts to 1.43 litres per minute, and in the cirrhotics to 0.92 litres per minute. The difference is statistically significant ($p < 0.005$). The arterial concentrations of glucose and lactate are also significantly higher in the cirrhotic patients, whereas the concentration of pyruvate is only significantly increased in the patients with porto-caval anastomosis. Elevated concentrations of lactate and pyruvate in cirrhotics have been observed by previous workers (1, 2).

The experiments of Lang, Goldstein & Levine (15) showed that the uptake of glucose in peripheral tissues was enhanced by some unknown liver-factor. A diminished peripheral utilization of glucose in patients with cirrhosis, demonstrated by Creutzfeldt (7), may be due to lack of this factor, and it is conceivable that it is also responsible for the inhibited elimination of acetate found in our patients.

ACKNOWLEDGEMENTS

These studies were performed at the Angiographic Clinic, the Radiology Department, Kommunehospitalet, and at the Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen. We wish to thank Professor Flemming Nørgaard and Dr. Niels Lassen for their hospitality and helpfulness in placing their facilities at our disposal. The work was supported by the Danish State Research Foundation.

REFERENCES

1. Alslev, J. Vergleichende Untersuchungen über den intermediären Galaktose- und Dextrosestoffwechsel bei Gesunden und Leberkranken. *Z. ges. exp. Med. 121,* 1, 1953.
2. Amatuzio, D. S. & Nesbitt, S. A study of pyruvic acid in the blood and spinal fluid of patients with liver disease with and without hepatic coma. *J. clin. Invest. 29,* 1486, 1950.
3. Asada, M. & Galambos, J. T. Liver disease, hepatic alcohol dehydrogenase activity, and alcohol metabolism in the human. *Gastroenterology 45,* 67, 1963.

4. Bauer, H. A. Der vereinfachte Alkoholtest als Leberfunktionsprüfung. *Gastroenterologia (Basel) 74,* 341, 1948-49.
5. Bernstein, A. & Staub, H. Zur funktionellen Leberprüfung mit Alkohol. *Helv. med. Acta 15,* 494, 1948.
6. Bücher, T., Czok, R., Lamprecht, W. & Latzko, E. Pyruvat. p. 253 in H. V. Bergmeyer (Ed.) *Methoden der Enzymatischen Analyse,* Weinheim/Bergstr. Verlag Chemie 1962.
7. Creutzfeldt, W. Personal communication.
8. Figueroa, R. B. & Klotz, A. P. Alterations of liver alcoholdehydrogenase and other hepatic enzymes in alcoholic cirrhosis. *Gastroenterology 43,* 10, 1962.
9. Flitman, R. & Worth, M. H., jr. Inhibition of hepatic alcohol dehydrogenase by bilirubin. *J. biol. Chem. 241,* 669, 1966.
10. Hassinen, I. Hydrogen transfer into mitochondria in the metabolism of ethanol. *Ann. Med. exp. Fenn. 45.* In press.
11. Hohorst, H. H., Kreutz, F. H. & Bücher, Th. Über Metabolitgehalte und Metabolit-Konzentrationen in der Leber der Ratte. *Biochem. Z. 332,* 18, 1960.
12. Hohorst, H. J. L-(+)-Lactat. p. 266 in H. V. Bergmeyer (Ed.) *Methoden der Enzymatischen Analyse. Weinheim/Bergstr. Verlag Chemie,* 1962.
13. Kiessling, K. H. & Pilström, L. The effect of bile obstruction on the oxidation rate of ethanol in the rat. *Acta physiol. scand. 69,* 187, 1967.
14. Kuple, W. & Mallach, H. J. Zur Tauglichkeit der Alkoholbelastung als Leberfunktionsprüfung. *Z. klin. Med. 156,* 432, 1961.
15. Lang, S., Goldstein, M. S. & Levine, R. Influence of the liver on uptake of glucose by extrahepatic tissues. *Amer. J. Physiol. 177,* 447, 1954.
16. Lieberman, F. L. The effect of liver disease on the rate of ethanol metabolism in man. *Gastroenterology 44,* 261, 1963.
17. Lundquist, F. The determination of ethyl alcohol in blood and tissues, p. 217 in Glick, D. (ed.) *Methods of Biochemical Analysis.* New York, Interscience *7,* 1959.
18. Lundquist, F., Fugmann, U. & Rasmussen, H A specific method for the determination of free acetate in blood and tissues. *Biochem. J. 80,* 393, 1961.
19. Lundquist, F., Svendsen, I. & Hyltoft Petersen, H. The metabolism of ethanol in rat liver suspensions. *Biochem. J. 86,* 119, 1963.
20. Lundquist, F., Tygstrup, N., Winkler, K., Mellemgaard, K. & Munck-Petersen, S. Ethanol metabolism and production of free acetate in human liver. *J. clin. Invest. 41,* 955, 1962.
21. Lundsgaard, E. Alcohol oxidation as a function of the liver. *C. R. Lab. Carlsberg, Ser. chim. 22,* 333, 1938.
22. Nakamura, T., Nakamura, S. & Tokita, K. Measurement of the intrahepatic shunted flow of blood in cirrhosis of the liver. *Nature (Lond.) 186,* 243, 1960.
23. Raabo, E. & Terkildsen, T. C. On the enzymatic determination on blood glucose. *Scand. J. clin. Lab. Invest. 12,* 402, 1960.
24. Roe, J. A colorimetric method for the determination of fructose in blood and urine. *J. biol. Chem. 107,* 15, 1934.
25. Serianni, E. & Lolli, G. Vorschlag einer neuen functionellen Untersuchungsmethode der Leberfunktion. *Dtsch. med. Wschr. 64,* 258, 1938.
26. Shaldon, S., Chiandussi, L., Guevara, L., Caesar, J. & Sherlock, S. The estimation of hepatic blood flow and intrahepatic shunted blood flow by colloidal heat-denatured human serum albumin labeled with J-131. *J. clin. Invest. 40,* 1346, 1961.
27. Tygstrup, N., Winkler, K. & Lundquist, F. The mechanism of the fructose effect on the ethanol metabolism of the human liver. *J. clin. Invest. 44,* 817, 1965.
28. Winkler, K. & Tygstrup, N. Determination of the hepatic blood flow in man by Cardio-Green R. *Scand. J. clin. Lab. Invest. 12,* 353, 1960.

Received 10 July 1968
Accepted 20 November 1968

K. Winkler, M. D.
Dept. of Clinical Physiology,
Kommunehospitalet, Copenhagen K,
Denmark