HEPATIC CIRCULATION AND HEPATIC FUNCTION DURING ANAESTHESIA AND SURGERY III CHLOROFORM-INDUCED LIVER INJURY

A GALINDO, M D, L D MACLEAN, M D,
R G B GILBERT, M B, CH B, F F A R C S, F R C P (C), AND
G FRED BRINDLE, M D, F R C P (C)*

HEPATIC HAEMODYNAMICS under surgery and anaesthesia have been studied,^{1,2} but the significance of these changes in the development of post-surgical hepatic injury is unknown. The present study attempts to correlate the hepatotoxic effect of chloroform with the observed hepatic circulatory effects.²

METHOD

Sixty-five dogs were used in these experiments. Hepatic haemodynamics and liver function were studied in the acute preparations. Hepatic function and liver histology were studied in chronic ones.

Acute

Nineteen dogs were studied in this group. Anaesthesia and surgical preparation have previously been described in detail.¹ Chloroform anaesthesia was administered in 11 experiments using a Fluotec vaporizer. Depth of chloroform anaesthesia was standardized when the normal corneal reflex had disappeared and the mean systemic blood pressure was depressed 30 per cent of the control value. This depth was maintained for 1 to 3 hours. In 8 experiments, no anaesthesia was given, and hypotension was induced by bleeding. In this unanaesthetized group a 30 per cent reduction in mean blood pressure was likewise maintained for 1 to 3 hours. In both groups a bromsulphthalein retention test (BSP) was done before the experiment and during the last 45 minutes of observation (5 mg/Kg i.v. injection, 45 minutes test period). SGOT serum levels were determined at the same time. Hepatic artery and portal vein blood-flow, mean arterial blood pressure, and the pH, pO_2 , and pCO_2 of simultaneous arterial and portal vein blood samples were determined as previously described. The effects of high pCO_2 were compared in the two groups of animals.

Chronic

Forty-six dogs were studied in this group. Anaesthesia and artificial respiration were induced as in the acute preparations. A femoral catheter was placed in the left femoral artery for recording of pressure and for blood sampling. These

*Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute and Hospital, and the Department of Surgery, the Royal Victoria Hospital

experiments were divided into two main groups. The first group acted as controls, while chloroform anaesthesia was given to the second. The total experimental time was 48 hours, with the first three hours constituting the experiment proper. Blood gas analyses were performed with the Micro-Astrup instrument using the S A (Siggaard-Andersen) nomogram. BSP retention tests were performed with a Beckman electrophotometer, 5 mg /Kg of BSP being administered intravenously and a blood sample being withdrawn 45 minutes later. The first BSP test was performed before each experiment, a second test during the final 45 minutes of the three-hour experimental period, and a final test just prior to sacrifice of the animal 48 hours later. SGOT determinations were made simultaneously with the BSP retention test in several animals. All animals were sacrificed with an intravenous administration of 90 mg /Kg of sodium pentobarbital. Samples of liver from two different lobules were fixed in 10 per cent formalin for histological study. The pathological findings in the liver were graded 0 to 4, indicating a range from no injury to severe hepatic injury.

In certain experiments the dogs were placed in a cage after three hours of the experiment and a six- to ten-hour recovery period was started. This consisted in maintaining the dogs under 100 per cent O_2 for one or two hours immediately following the experiment and then in an oxygen tent at an O_2 concentration of 40 per cent for six hours. Other animals had no post-experimental care during the recovery period.

Six dogs were maintained under severe hypoxia, i.e. with an O_2 arterial blood saturation of from 30 to 70 per cent. This group had no recovery and was considered the control group for the chloroform anaesthesia experiments. It also provided an indication of the effects of acute severe hypoxia on liver function and liver pathology.

Chloroform anaesthesia was administered to twenty dogs under three different conditions: (a) with atmospheric air (six dogs), (b) with 100 per cent O_2 at one atmosphere of pressure (four dogs), and (c) with 100 per cent O_2 at two atmospheres of pressure (ten dogs). Twenty more dogs were studied using the same experimental preparation, but some died immediately after the experiment, and in some no histological study of the liver was carried out. Chloroform was not administered to them. The effect of hypercarbia was studied in five, haemorrhage was noted in six, and straightforward control of the experimental preparation for a three-hour period was observed in nine.

RESULTS

The results from the acute preparations are compared in Figure 1 and Table I. Chloroform anaesthesia depresses hepatic blood-flow and portal pO_2 . These changes are greater than the modifications observed during a similar systemic blood-pressure reduction obtained by blood loss. The portal pCO_2 under these circumstances is higher in the group administered chloroform than in the control group. The effect of high arterial pCO_2 on the hepatic artery blood-flow is opposite in the two groups. Hepatic artery flow increases in the animals which did not have chloroform, while in the chloroform experiments the flow is further reduced.

FIGURE 1 Carbon dioxide increased hepatic artery blood-flow in control experiments while it reduced it under chloroform anaesthesia

TABLE I

COMPARISON BETWEEN CHLOROFORM AND HAEMORRHAGIC ARTERIAL BLOOD-PRESSURE REDUCTIONS, AND THEIR EFFECT ON PORTAL BLOOD-FLOW AND ARTERIAL TO PORTAL pO_2 , pCO_2 GRADIENTS

Control					Chloroform			
Experiment	P B F	PpO_2	ΔpCO_2	B P	P B F	PpO_2	ΔpCO_2	B P
58	500	97	12	140	100	51	35	105
59	550	73	4	165	200	48	17	100
60	400	61	2	130	300	63	13	120
64	450	596	5	130	100	78	15	100
65	500	334	11	140	200	160	11	100
66	800	172	12	170	400	68	38	80
Chloroform hypotension (%)								
P B F = -60.2								
PpO_2 = -72								
ΔpCO_2 = +75								
B P = -31								
Control					Hypotension			
Experiment	P B F	PpO_2	ΔpCO_2	B P	P B F	PpO_2	ΔpCO_2	B P
52	1300	280	14	130	1000	160	6	95
54	900	90	16	130	500	63	6	105
55	60	85	8	130	200	67	9	75
49	800	184	7	140	600	52	7	120
51	400	127	7	120	100	64	10	95
53	1300	80	14	130	400	25	22	90
56		90	16	130		54	12	90
57	500	76	5	115	200	40	15	105
Haemorrhagic hypotension (%)								
P B F = -44								
PpO_2 = -44								
ΔpCO_2 = 0								
B P = -28								

P B F = Portal vein blood-flow in flow units

PpO_2 = Portal pO_2 (mm Hg)

ΔpCO_2 = Arterial-portal vein blood pCO_2 difference in mm Hg

B P = Mean arterial blood pressure (mm Hg)

TABLE II
CORRELATIONS BETWEEN LIVER FUNCTION TESTS AND HEPATIC CIRCULATION

HABF (%)	BSP (%)		BP (%)	HABF (%)	PVBF (%)	BSP (%)		SGOT		BP (%)
	C	E				C	E	C	E	
Chloroform										
+10	2 6	14 5	-13	-77	-80	10 0	17 0	35	70	-25
-61	9 2	31 5	-35	-69	-46	3 4	31 5	38	68	-40
-63	5 3	31 2	-33	-70	-62	9 5	23 0	31	43	-44
-65	5 6	17 5	-39	-80	-42	6 2	37 8	43	54	-61
-80	4 5	27 5	-33	-87	0	6 0	10 6	35	61	-30
Control										
+43	2 5	3	—							
+33	3	7	—							
-10	3	7 5	—							
-15	2 5	4 2	—							
-16	4	7 5	—							
-37	6	16 5	—							
-50	7	12	—							

HABF = Hepatic artery blood flow Per cent change from control
 PVBF = Portal vein blood flow Per cent change from control
 BSP = Bromsulphthalein retention test C = control E = experiment
 SGOT = Serum levels of glutamic oxalacetic transaminase
 BP = Mean arterial blood pressure per cent change from control
 BSP showed a good correlation SGOT did not change significantly

TABLE III
CORRELATION BETWEEN LIVER FUNCTION TESTS
AND LIVER PATHOLOGY 48 HOURS AFTER THE
EXPERIMENT

LP	BSP (%)	SGOT
0	4	22
0	5 5	21
0	5	26
0	5	80
0	5	31
0 5	14	—
0 5	10	54
0 5	17 5	58
0 5	5 5	46
1	36	—
1	9	—
2	37 5	—
2	7 5	—
2 5	48 7	—
3	29 8	—
3	35 7	—
3	27 5	—
3	23	1600

LP = Liver pathology

CHLOROFORM and LIVER PATHOLOGY

FIGURE 2 The incidence of hepatic damage after chloroform anaesthesia was related to systemic hypoxia and hypercarbia A There was no correlation between liver pathology and the administration of 100 per cent oxygen during the anaesthetic period B There was some correlation when oxygen was administered during the immediate recovery period, and C there was a direct correlation between no recovery and hypercarbia and the incidence of hepatic injury

OXYGEN and LIVER FUNCTION

FIGURE 3 BSP retention test was related to the trans-anaesthetic oxygenation The immediate post-anaesthetic test had relative prognostic value for liver injury

BSP and SGOT results in both groups of animals are consistent with the circulatory changes (Table II)

The results of the experiments on the chronic group are summarized in Figures 2 and 3 and Table III. The liver function tests were consistent with the circulatory and pathological findings. In the control animals acute hypoxia and hypercarbia (3 hours) had no pathological effect on the liver (Fig 3). However, all hypoxic animals under chloroform anaesthesia had abnormal liver-function tests. When chloroform was given with 100 per cent O_2 at two atmospheres of pressure, BSP and SGOT were normal at the end of a similar period. Changes in hepatic blood-flow were similar in all chloroform experiments, and the only differences under hyperbaric oxygen were higher arterial and portal pO_2 values.

The final liver pathology was related to the oxygen administration during and after the period of anaesthesia as well as to the pCO_2 values during the administration of the agent (Fig 2). Experiments in which the arterial pCO_2 was normal or low and in which oxygen was administered during the anaesthetic as well as in the immediate recovery period, showed mild (2) to minimal hepatic injury (0.5).

DISCUSSION

All dogs submitted to three hours of chloroform anaesthesia developed hepatic injury. The severity and extent of this injury was dependent upon the oxygenation and ventilation of the animal. Control experiments in which hypoxia and hypercarbia were maintained for a similar period of time showed no hepatic damage. The effect of chloroform on the hepatic circulation persists after its administration² and might be related to the slow disappearance of chloroform from the liver.³

Whether chloroform depresses the hepatic circulation and secondarily injures the hepatic cell, or whether the circulatory impairment is the result of an initial cellular damage is unknown. In any event the administration of oxygen during and after chloroform anaesthesia reduces hepatic injury to a minimum. The pathological effect of high CO_2 concentrations during chloroform anaesthesia, noted in man by others,⁴ seems to be related to a further reduction in hepatic oxygen supply. High arterial pCO_2 did not produce liver damage in control experiments and is even considered as a protection during respiratory insufficiency.⁵ A biochemical effect of CO_2 during chloroform anaesthesia cannot be ruled out.

The liver function tests used (BSP and SGOT) were correlated with the pathological findings at the moment of sacrifice. It is suggested that a control determination of these two tests before surgery, followed by a second determination 48 hours after surgery, would indicate whether liver injury was present. The severity and prognosis of such a lesion could be determined with further studies.

GENERAL CONCLUSIONS

There are several causes of reduced oxygen supply to the liver during a surgical operation. Arterial hypotension, metabolic acidosis, trauma to the liver, and

anaesthesia, alone or combined, all depress hepatic blood-flow and portal oxygen tension. Under some circumstances this depression extends into the post-surgical period when other factors, yet unknown, may be added to prolong hypoxia of the liver. A normal liver can escape injury or is able to regenerate. However, previous liver disease, sub-clinical viral hepatitis, or the high incidence of post-blood-transfusion serum hepatitis⁶ may contribute, in a hypoxic liver, to the development of a severe injury. Therefore, post-surgical hepatic necrosis must be regarded as a syndrome in which anaesthesia is one factor. This could explain the difficulties reported in clinical studies which try to correlate anaesthesia with liver damage⁷⁻¹⁰. On the other hand, some anaesthetic agents such as chloroform contribute more than others to hepatic hypoxia, quite apart from their possible direct toxicity. Since it is impossible to prevent some physiological disturbances during surgery, it seems safer not to use such an agent. As for other anaesthetics, this study is being repeated with each one of them in order to establish the circumstances in which they may contribute to post-surgical hepatic damage.

Hyperbaric oxygen during surgery may be considered of therapeutic value in patients with marked liver dysfunction. Finally, it seems clear that in the development of hepatic damage, the immediate recovery period is as important as the surgical intervention itself.

REFERENCES

- 1 GALINDO, A. Hepatic Circulation and Hepatic Function during Anaesthesia and Surgery I. Hepatic Haemodynamics. *Canad Anaesth Soc J* 12: 262 (1965)
- 2 ——— Hepatic Circulation and Hepatic Function during Anaesthesia and Surgery II. The Effect of Various Anaesthetic Agents. *Canad Anaesth Soc J* 12: 337 (1965)
- 3 HELLENKANT, G. Distribution of Chloroform in Mice. *Acta pharmacol et toxicol* 21: 240 (1964)
- 4 SIMS, J. L., MORRIS, L. E., ORTH, O. S., & WATERS, R. M. The Influence of Oxygen and Carbon Dioxide Levels during Anesthesia upon Postsurgical Hepatic Damage. *J Lab & Clin Med* 38: 388 (1951)
- 5 REFSUM, H. E. Arterial Hypoxemia, Serum Activities of SGOT and SGPT and LDH and Centriobular Liver Cell Necrosis in Pulmonary Insufficiency. *Clin Sc* 25: 369 (1963)
- 6 HAMPERS, C. L., PRAGER, D., & SENIOR, J. R. Posttransfusion Anicteric Hepatitis. *New England J Med* 271: 747 (1964)
- 7 MUSHIN, W. W., ROSEN, M., BOWEN, D. J., & CAMPBELL, H. Halothane and Liver Dysfunction. A Retrospective Study. *Brit Med J* 2: 329 (1964)
- 8 LINDENBAUM, J. & LEIFER, E. Hepatic Necrosis Associated with Halothane Anesthesia. *New England J Med* 268: 525 (1963)
- 9 HENDERSON, J. C. & GORDON, R. A. The Incidence of Postoperative Jaundice with Special Reference to Halothane. *Canad Anaesth Soc J* 11: 453 (1964)
- 10 BUNKER, J. P. & BLUMENFELD, C. M. Liver Necrosis after Halothane Anesthesia. Cause or Coincidence. *New England J Med* 268: 531 (1963)