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Experimental Obstruction of Left Hepatic Vein in Dogs
II. Hemodynamic Changes

by

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Since 6 cases of CHIARI syndrome associated with inferior vena caval obstruction were treated in this department by KIMURA et al.,[1)2)] great interest has been aroused in the CHIARI syndrome or outflow obstruction of the liver. Accordingly, attempts have been made to experimentally produce this condition and thereby to study pathological and hemodynamic changes resulting from hepatovenous obstruction.

In a previous paper[3)] relatively simple methods were described for producing hepatovenous congestion on the left side of the canine liver while venous drainage of the other side was kept intact. As compared with other methods such as constriction of the thoracic inferior vena cava or occlusion of all the hepatic veins, this technique is inadequate for studies of ascites or portal hypertension. However, it has the advantage of allowing one to exclude the effects of venous congestion of the other organs, including the spleen, kidneys, adrenal grands etc. and also to compare changes of the veno-occluded lobe with those of the "open" lobe of the same liver.

Following the previous report on morphological changes of the liver, the present investigation was undertaken to study local and general hemodynamic alterations resulting from the obstruction of the left hepatic vein trunk.

MATERIAL AND METHODS

Adult mongrel dogs weighing 7 to 14 kg were used after overnight fast. They were anesthetized with pentobarbital (Nembutal) intravenously in a dose of about 30 mg per kg of body weight. If necessary, small doses were added during the operation. The animals were subjected to the obstruction of the left hepatic vein trunk in the manner described in a previous paper[3)]. Usually before and 1 hour after the obstruction the following measurements were carried out. Some of them were repeated at varying postoperative intervals.

Arterial pressure. The femoral artery was cannulated and connected to a mercury manometer by a polyethylene tube. The arterial pressure was continuously recorded on a kymograph. In this measurement the obstruction was usually created by the balloon technique so as to minimize operative intervention.

Response to intrahepatic injection of adrenalin. 0.1 cc of 0.1% adrenalin was injected into the parenchymal tissue of the left lateral lobe and the time required for the blood pressure to start rising as well as the maximal increase in blood pressure were measured. The injection was repeated three times to obtain a mean value. Because of

the inertia of the mercury manometer this method did not give absolute values.

Portal pressure. The portal trunk was punctured at its junction with the splenic vein by a needle which was directly connected to a silicon-rubber tube (1 mm in inside diameter) filled with saline. Before and after the pressure was read blood was allowed to regurgitate through the needle into the tube so as to confirm that the manometer was kept freely communicated with the venous lumen. For convenience the zero point of reference was adjusted to the level of the operating table. Thus, the figures obtained in this experiment were about 80 mm higher than those obtained in the usual manner in which the level of the portal vein was the zero point.

Portal vein and hepatic vein pressures in the left lateral lobe. This lobe showed the most severe changes after the obstruction of the left hepatic vein trunk. Both its portal and hepatic veins were accessible if the interlobar fissure between the left medial and left lateral lobes were opened by depressing the latter downwards. The pressure in each vein was determined in the same manner as described above.

Uptakes of radioactive rose bengal and gold colloid. About 20 μc of I^{131} rose bengal or Au^{198}gold colloid (Dainabott) was injected intravenously. Ten minutes thereafter about 1 gm of liver sample was removed simultaneusly from the edges of the left lateral lobe (occluded lobe) and of the right caudal lobe (open lobe). In one animal the samples were removed 10 min., 20 min. and 30 min. after the rose bengal injection which took place 1 hour after the left hepatic vein obstruction. After weighed each sample was put into a test tube containing saline solution, and its radioactivity was determined with a well-type scintillation counter. Then the concentration of the rose bengal or gold colloid in the occluded lobe was expressed as % of that in the open lobe:

$$\textit{Concentration in occluded lobe} = \frac{\text{cpm/mg of occluded lobe sample}}{\text{cpm/mg of open lobe sample}} \times 100$$

Later, this method was improved and a mixture of I^{125} rose bengal (Daiichi kagaku) and Au^{198} gold colloid was used for intravenous injection. The radioactivity of each sample was measured with a spectrometer (Shimazu) at two points at which the standard solution of I^{125} rose bengal showed a peak radioactivity while that of Au^{198} gold colloid gave low counts, and vice versa. Then the radioactivity of each isotope in a sample was calculated by solving the simultaneous equations of the first degree. To increase accuracy of I^{125} rose bengal value the measurement was repeated 2 weeks later when Au^{198} showed relatively very low radioactivity. This simultaneous analysis of the two isotopes allowed one not only to compare concentrations of an isotope between the occluded and open lobes, but also to compare rose bengal concentration with gold colloid concentration in a sample by the following expression:

$$\frac{I^{125}\text{ radioactivity/mg of sample}}{Au^{198}\text{ radioactivity/mg of sample}} \div \frac{I^{125}\text{ radioactivity of injected solution}}{Au^{198}\text{ radioactivity of injected solution}} \times 100$$

Portal flow and hepatic arterial flow. Both flows were directly measured with an electromagnetic flowmeter (Medicon) after isolation of the vessels. The portal flow was measured at the portal trunk proximal to its junction with the splenic vein; the hepatic arterial flow was determined at the common hepatic artery while the gastroduodenal and right gastric arteries were clamped.

Flow and protein content of thoracic duct lymph. The thoracic duct was exposed through a left cervical incision dividing the pectoral muscles. A thin polyethylene tube was inserted into the thoracic duct in a retrograde manner and its open end was kept at the level of the operating table. The lymph was continuously collected in a series of test tubes at 5 minute intervals. The volume of each sample was measured and the protein content determined with a refractometer. Since intra-abdominal manipulation was found to cause change in flow and nature of the lymph the obstruction of the left lepatic vein trunk was exclusively performed by the balloon technique.

Thromboelastogram. The Hellige thromboelastography was used. The blood sample was collected from a systemic vein and in a few instances from the left hepatic vein distal to the obstruction as well. The sample was immediately transferred to a cuvet of the instrument. The recording was started 2 minutes following the collection and continued for 150 minutes. In the thromboelastogram the following 5 parameters were measured and expressed as % of the preoperative value:

R: time required for the thrombocytographic oscillation to reach an amplitude of 1 mm from collection of sample.

R+K: time required for the oscillation to reach 20 mm.

φ: time required for the oscillation to reach the maximal amplitude.

MA: maximal amplitude.

F: ratio of 150th minute amplitude to maximal amplitude.

Hematocrite. The rest of the blood sample collected for the thromboelastogram was used for hematocrite determination. It was introduced into a heparinized capillary tube and centrifuged at 10,000 rpm for 5 min.

Determination of outflow tracts of the occluded lobe. Besides the above measurements an observation was made of outflow tracts of the left lateral lobe after measurement of pressure. About 2 cc of India ink was very slowly introduced into the portal vein or hepatic vein of this lobe through the silicon-rubber tube used for pressure measurement. The animal was sacrificed immediately thereafter. The liver was extirpated and examined for distribution of the dye to determine the direction of blood flow in each vein.

RESULTS

Arterial pressure. The arterial pressure always decreased during the obstruction of the left hepatic vein trunk (hereafter abbreviated as obstruction). Usually the pressure showed an abrupt fall immediately after the obstruction, followed by a slow, slight increase, then it reached a plateau, remaining lower than the control level (See Fig. 1.). When the obstruction was produced by the balloon technique under light anesthesia the mean decrease in pressure was about 20 mmHg as shown in Table 1. However, the decrease seemed to considerably vary with the depth of anesthesia, circulating blood volume, repetition of the obstruction etc.. In one dog (No. 17) the pressure fell by 93 mmHg at the first obstruction when the anesthesia was very deep. Another animal whose thoracic duct lymph had been continuously collected previous to the obstruction showed a pressure decrease of 74 mmHg.

Response to intrahepatic injection of adrenalin. Intrahepatic injection of 0.1 mg

adrenalin produced a abrupt rise in blood pressure as well as a prolongation of the respiratory pause. In the acute phase of the hepatic outflow obstruction there was still systemic response to adrenalin injection into the occluded lobe though it was considerably attenuated and delayed (See Fig. 1. and Table 2.). In one experiment the intravenous balloon was advanced to the peripheral portion of the left hepatic vein so that only the left lateral lobe was obstructed: The blood pressure likewise rose when adrenalin was injected into this lobe whereas this response completely disappeared when the innominate vein was also occluded with another ballon so as to prevent recirculation of thoracic duct lymph.

In two of the chronic survivors the mean response returned nearly to the control value; in another one it remained slightly attenuated and delayed. However, the responses to individual injecitons in the same animal varied widely with the site of the injection.

Pressures in the portal trunk, in the portal and hepatic veins of the left lateral lobe. These are illustrated in Fig. 2. During the control period the mean pressure gradient between the portal trunk and the portal vein of the left lateral lobe was 10 mm of saline while the mean gradient between the latter and the corresponding hepatic vein amounted to 66 mm, so that the portal trunk pressure was on an avarage 76 mm higher

Table 1. Arterial pressure before and immediately after left hepatic vein obstruction.

Dog No.	Mean pressure (mmHg) before obstruction	Decrease (mmHg) after obstruction
16	135	13
17	140	22
28	127	11
29	118	23
30	108	28
34	139	17
Mean	128	19

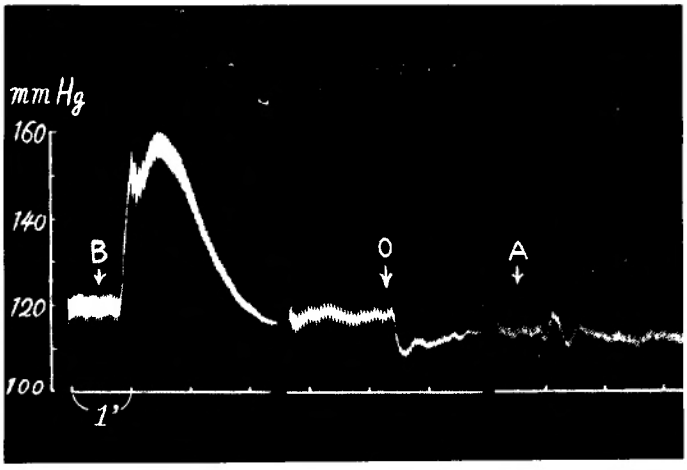

Fig. 1. Effect of intrahepatic adrenalin injection on blood pressure before (B) and shortly after (A) left hepatic vein obstruction (O).

Table 2. Blood pressure response to adrenalin injection into the left lateral lobe before and after left hepatic vein obstruction.

Dog No.	Before or after obstruction	Response time (second)	Pressure increase (mmHg)
25	Before	8.0	75
	1 hour after	9.6	19
28	Before	10.0	68
	1 hour after	16.1	8
29	Before	9.8	65
	1 hour after	21.0	10
31	Before	6.3	69
	1 hour after	13.2	8
38	Before	7.5	81
	1 hour after	9.3	3
70	53 days after	11.7	53
75	93 days after	12.1	50
76	92 days after	8.3	66
Mean	Before	8.3	72
	1 hour after	13.8	9

than the hepatic vein pressure of the left lateral lobe. Shortly after the obstruction these gradients were greatly decreased or even reversed as all the three pressures rose to a similar level exceeding 200 mm of saline. In all animals except one the difference between any two of these pressures was less than 15 mm. It must be noted that the hepatic vein pressure usually exceeded the portal pressure of the occluded lobe by about 10 mm, always rising more than 100 mm above the control level with a mean rise of 127 mm. The portal vein pressure of the occluded lobe in turn approximated very closely to the portal trunk pressure. The increase in portal pressure was less than 100 mm in all dogs.

In 6 dogs which survived the left hepatic vein ligation more than a month the portal trunk pressure returned to the control level. In 2 of them it was slightly below the pre-obstruction value. The mean pressure in the portal vein of the occluded lobe remained slightly higher, and the pressure gradient between the latter and the portal trunk was lower than the control values. The hepatic vein pressure of the occluded lobe again fell below the portal pressures. Its mean value, however, remained 46 mm above the control level.

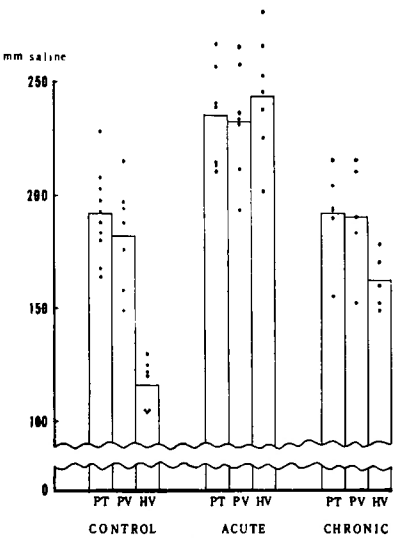

Fig. 2. Pressures in the portal trunk (PT), in the portal vein (PV) and hepatic vein (HV) of the left lateral lobe before and after left hepatic vein obstruction. The zero point is the level of the operating table. Acute, one hour after obstruction; Chronic, more than one month after obstruction.

Outflow tracts of the occluded lobe. In 5 dogs India ink was introduced into the

portal vein of the left lateral lobe shortly after the obstruction. In 4 of them this lobe was free from the dye, but only the right lateral and caudal lobes as well as the right edge of the right ventral lobe took dark colour of the dye. In one of these dogs the dorsal lobe was also stained. In the remaining one animal the left lobes including the left lateral lobe also turned dark. The typical result is seen in Fig. 3 where white ink

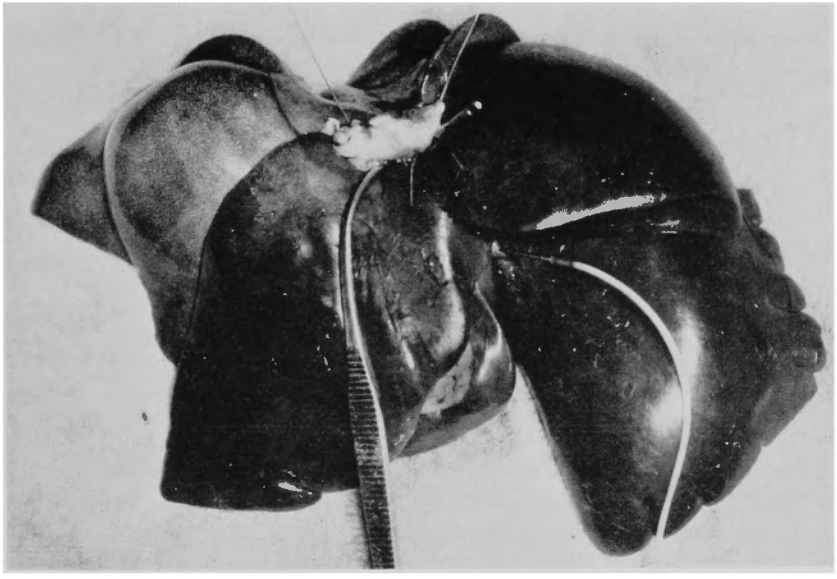

Fig. 3. Cranial view of the canine liver which was extirpated after white ink was injected into the portal vein of the left lateral lobe following ligation of the left hepatic vein trunk (under which a ligature carrier is passed). The white ink is localized to right lobes.

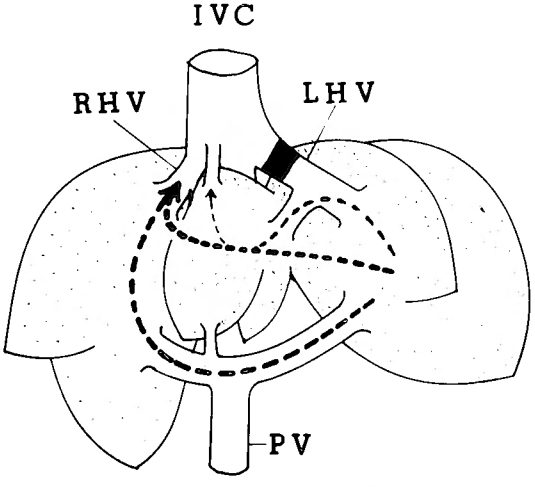

Fig. 4. Schematic representation of the outflow tracts of the occluded lobe in the acute phase of left hepatic vein obstruction. IVC, inferior vena cava; LHV and RHV, left and right hepatic veins respectively; PV, portal vein.

was used instead of India ink because the white colour and the liver contrasted more clearly in the photograph. These observations revealed that shortly after the obstruction the portal vein of the occluded lobe usually serves as an outflow tract along which the venous blood flows in a retrograde manner to enter the open lobes together with the portal blood from the splanchnic area.

In another 2 dogs India ink was injected into the hepatic vein of the left lateral lobe shortly after the obstruction. The dye was chiefly taken up by the left medial lobe and the central portion of the ventral lobes. Also some portion of India ink was recovered from the hepatic vein at the site of the injection. Consequently

the venous blood of the left lateral lobe can be partly drained through these areas lying between this lobe and the open lobes. Thus, the outflow tracts of the occluded lobe in the acute phase is diagrammatically illustrated in Fig. 4.

Two dogs surviving 3 months following the obstruction were also subjected to dye injection into the portal vein. In one of them only the ventral portions of the left lateral and medial lobes were exempted while in the other animal the India ink was irregularly distributed throughout the liver. The left lateral lobe appeared mottled, but again the ventral portion was relatively free from the ink.

Uptakes of radioactive rose bengal and gold colloid. It was disclosed in preliminary experiments that if radioactive gold colloid (hereafter referred to as GC) was injected into a mesenteric vein or into the common hepatic artery it was localized to limited lobes, depending on the site of injection, but that if a systemic vein was used for the injection all the lobes showed approximately equal radioactivity per unit weight although the central portion was slightly more radioactive than the peripheral area.

When injected intravenouly radioactive rose bengal (hereafter referred to as RB) was also uniformly distributed to all the lobes of a control dog. Repeated collection of samples at 10 minute intervals showed that the first samples or 10th minute samples gave the highest radioactivity followed by the 20th minute, and then the 30th minute samples. On the other hand, an external counting over the upper border of the liver recorded the maximal radioactivity about 20 min. after the injection.

In Fig. 5 are shown 10th minute concentrations of the radioisotopes in the occluded lobe in % of the open lobe value. Shortly after the obstruction the RB concentration in the occluded lobe ranged from 20 to 53% of that in the open lobe with a mean of 35%; The GC concentration in the occluded lobe was between 20 and 40%, avaraging 28% of the GC concentration in the open lobe.

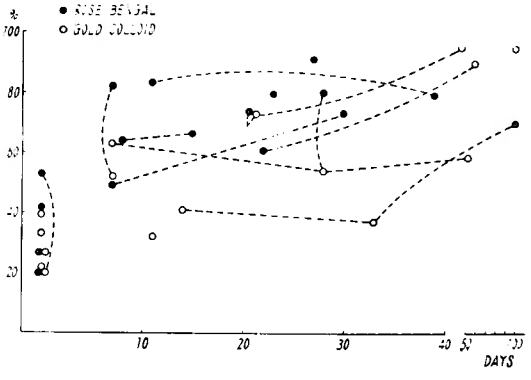

Fig. 5. Relative concentrations of radioactive rose bengal and gold colloid in the occluded lobe (expressed as % of those in the open lobe) after left hepatic vein obstruction. Samples were removed 10 min. after injection.

Circles connected with a broken line represent values of the same dog.

Thereafter, the RB concentration in the occluded lobe relatively increased, and from the 2nd week it was in a range of 60 to 90% of the open lobe value; The relative GC concentration in the occluded lobe remained lower than the corresponding RB value, usually being below 60% of the open lobe concentration for the first month. However, the GC concentration in the occluded lobe seemed to increase later since the GC concentration in the occluded lobe was over 90% of the open lobe value in three of four dogs which were studied 50 to 100 days after the obstruction.

Such a dissociation between the RB and GC concentrations in the occluded lobe was further confirmed in 4 dogs which recieved I^{125} rose bengal and Au^{198} gold colloid simul-

taneously and whose samples were analized for radioactivity of each isotope. As shown in Table 3, the relative RB concentration in the occluded lobe (% of the open lobe value) was higher than the corresponding GC value in all the 4 dogs which were studied 1, 3 and 4 weeks respectively after the obstruction. However, if the RB concentration was compared with the GC concentration of the same lobe the former was found to be always smaller than the latter in the 10th minute samples : In the occluded lobe the RB concentration was 57 to 83% of the GC concentration in the 4 dogs while in the open lobe the former was 29 to 56% of the latter. It was noteworthy that in the dog (No. 90) observed 1 hour after the obstruction the open lobe had an RB concentration as small as 29% of the GC concentration.

The dissociation of the RB and GC concentrations was also observed when instead of a hepatic vein a portal or hepatic arterial branch was ligated (See Table 3). However, in such cases the 10th minute concentration of rose bengal was absolutely higher than that of gold colloid in the occluded lobe.

In one dog whose samples were removed 10, 20, and 30 min. after the injection the rose bengal was found to increasingly accumulate in the acutely occluded lobe for 30 minutes of observation whereas in the open lobe the isotope reached the maximal concentration within 10 min. following the injection. (See Table 4).

Table 3. Relative concentrations of I^{125} rose bengal and Au^{198} gold colloid in the occluded and open lobes 10 minutes after their intravenous injection into dogs whose left hepatic vein (HV), portal branch (PV) or hepatic arterial branch (HA) was occlded.

Dog No.	Occluded vessel	Time after occlusion	$\frac{\text{Conc.* in occl. lobe}}{\text{Conc.* in open lobe}} \times 100$		$\frac{\text{Conc.** of rose bengal}}{\text{Conc.** of gold colloid}} \times 100$	
			Rose bengal	Gold colloid	Occl. lobe	Open lobe
86	H. V	28 days	80	54	83	56
88	H. V.	21 days	74	73	57	56
89	H. V.	7 days	82	52	82	51
90	H. V.	1 hour	53	20	77	29
91	P. V.	1 hour	75	40	124	66
92	H. A.	1 hour	79	52	130	85

* Cpm/mg of sample. ** Cpm/mg of sample/cpm of injected solution.

Table 4. Concentrations of I^{131} rose bengal in the open and occluded lobes after its intravenous injection following left hepatic vein obstruction (1 hour before injection)

Time after injection	Concentration (cpm/mg)	
	Open lobe	Occl. lobe
10 min	11.3	3.07
20 min	10.2	3.36
30 min	11.0	3.63

Portal flow and hepatic arterial flow. Although the direct measurement of blood flow with the electromagnetic flowmeter gave an accurate value of blood flowing at the moment of measurement, some unphysiological aspects involved by this method had to be taken into consideration : a) anesthesia, b) laparotomy, c) injury of nerve fibers accompanying the hepatic artery during its isolation, d) vasospasm at the placement of the sensor probe,

e) injury of lymph vessels and subsequent hemoconcentration during preparation of the portal vein and f) fall in body temperature during the procedure.

In Table 5 are listed flows of 5 dogs measured during the control period. The total hepatic flow ranged widely from 27 to 70 cc/kg/min. with a mean of 45 cc/kg/min., the hepatic arterial flow from 4 to 17 cc/kg/min. averaging 10 cc/kg/min. and the portal flow from 20 to 58 cc/kg/min. with a mean of 35 cc/kg/min. The ratio of the hepatic arterial flow to the portal flow was between 0.20 and 0.35 averaging about 3. Intravenous fluid administration appeared to significantly increase the hepatic flow.

As shown in Table 6, the portal flow was markedly decreased immediately after the obstruction, being around 30% of the pre-obstruction value whereas the hepatic arterial flow showed much less alteration, remaining more than 60% of the pre-obstruction value except in one dog (No. 73) which lost a considerable amount of blood during the operation. Consequently, with one exception the hepatic arterial flow made up about one third to one half of the total hepatic flow that reduced to less than one half the pre-obstruction value. It was noteworthy that in 2 dogs the arterial flow slightly increased after the obstruction.

These characteristic changes were attenuated or disappeared in the chronic group of

Table 5. Hepatic arterial flow, portal flow and total hepatic blood flow during control period.

Dog No.	Bd. wt. kg	H. A. F.		P F.		H. B. F.		H. A. F. / P. F.
		cc/min	cc/min/kg	cc/min	cc/min/kg	cc/min	cc/min/kg	
72	12.1	53	4.4	270	22.2	323	26.6	0.20
73	9.1	69	7.6	212	23.2	281	30.8	0.33
74	10.0	69	6.9	200	20.0	269	26.9	0.35
79*	11.3	136	12.0	660	58.3	796	70.3	0.21
80*	10.5	177	16.8	525	49.9	702	66.7	0.34
81*	13.9	189	13.6	545	39.3	734	52.9	0.35
82*	11.1	108	7.7	422	29.9	530	37.6	0.26
Mean	11.4	114	9.9	405	34.7	519	44.5	0.29

* Ringer's solution was intravenously administered during the operation.

Table 6. Hepatic arterial flow, portal flow and total hepatic blood flow shortly after left hepatic vein obstruction.

Dog No.	H. A. F.			P. F.			H. B. F.			H. A .F. / P. F.
	cc/min	cc/min/kg	%**	cc/min	cc/min/kg	%**	cc/min	cc/min/kg	%**	
73	7	0.8	12	30	3.3	14	37	4.1	13	0.23
79*	99	8.7	73	185	16.4	28	284	25.1	36	0.54
80*	188	17.9	106	178	16.9	34	366	34.8	52	1.06
81*	119	8.6	63	261	18.8	48	380	27.4	52	0.45
82*	110	7.8	102	140	9.9	33	250	17.7	47	0.79
Mean	105	8.8	71	159	13.1	31	263	21.8	40	0.61

* Ringer's solution was administered during the operation.
** % of control value.

Table 7. Hepatic arterial flow, portal flow and total hepatic blood flow 3 to 8 months after left hepatic vein obstruction.

Dog No.	Bd. wt. kg	Postop. months	H. A. F.		P. F.		H. B. F.		H. A. F. / P. F.
			cc/min	cc/min/kg	cc/min	cc/min/kg	cc/min	cc/min/kg	
57	8.8	8	135	15.4	223	25.3	358	40.7	0.61
63	13.1	6	105	8.0	270	20.6	375	28.6	0.39
67	11.0	4	110	10.0	350	31.8	460	41.8	0.31
75	7.0	3	76	10.8	213	30.5	289	41.3	0.36
76	10.3	3	166	16.1	330	32.1	496	48.2	0.50
Mean	10.0	5	118	12.1	277	28.1	396	40.1	0.43

5 dogs (Table 7) which were studied 3 to 8 months after the obstruction. As a matter of fact there was no statistical difference ($P > 5\%$) between this group and the control group in arterial flow, portal flow or total hepatic flow. However, in 4 out of 5 dogs the ratio of the hepatic arterial to portal flow was higher than 0.35 or the highest value of the control group. If the hepatic arterial flow of the chronic dogs were compared with that of the control dogs recieving no infusion, the former were all higher than the latter.

Flow and protein of thoracic duct lymph. Only acute changes were observed in fasted dogs whose left hepatic vein trunk was occluded by the balloon technique without laparotomy. As shown in Table 8, the control flow in 7 dogs weighing 7.8 to 14.0 kg ranged from 0.3 to 4.3 averaging 2.2 cc per 10 min. while the protein content was between 3.2 and 6.0 with a mean of 4.9 gm per 100 cc. After the obstruction the flow increased and in 10 to 20 min. reached a relatively constant value that was 2 to 5 times the pre-obstruction value with a mean increase of 3.1 times. The protein content of the lymph also rose about 1.2 times or by 1 gm/100 cc. Grossly the collected lymph remained clear although on standing red cells were visible in the sediment. After the obstruction was released one hour later, the flow and protein decreased but did not return to the control level for 30 min. of observation. In Fig. 6 is illustrated a typical result.

Table 8. Flow rate and protein content of thoracic duct lymph before and after left hepatic vein obstruction.

Dog No.	Body weight (kg)	Before obstruction		After obstruction		Increase	
		Flow (cc/10 min)	Protein (gm/100cc)	Flow (cc/10 min)	Protein (gm/100cc)	Flow (time)	Protein (gm/100cc)
37	7.8	1.0	4.9	4.5	5.9	4.5	1.0
38	12.1	0.3	4.7	0.6	5.6	2.0	0.9
42	10.1	4.3	3.2	8.9	4.1	2.1	0.9
43	8.0	1.6	4.3	4.1	5.7	2.6	1.4
50	14.0	2.8	6.0	14.5	7.3	5.2	1.3
55	8.5	2.9	5.9	6.8	6.3	2.3	0.4
59	11.0	2.2	5.2	6.6	6.1	3.0	0.9
Mean	10.2	2.2	4.9	6.6	5.9	3.1	1.0

Thromboelastogram The values of the five parameters showed a wide variation from dog to dog and also from time to time. In retrospect, this may be partly due to technical errors during the collection of blood sample, such as touching of the venous wall with the needle point, contamination of blood sample with extravascular blood and mixing of sample with air bubbles. All these factors tended to shorten r time and r+k time as well, so that decrease in these values seems to be of less significance than increase.

Fig. 7-11 summarize changes in the 5 parameters of the systemic venous blood obtained at various intervals following the obstruction.

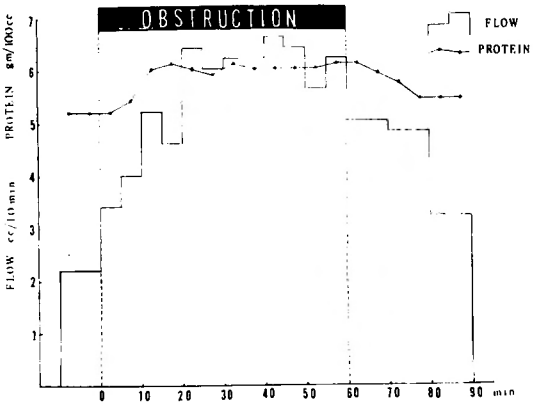

Fig. 6. Flow rate and protein content of thoracic duct lymph before and after left hepatic vein obstruction.

The r time was usually decreased shortly after the obstruction. However, blood samples collected in the subsequent few days showed longer r times than the preoperative samples. Thereafter the r time again decreased nearly to the control level or below it and remained in that range for the 2 months of observation.

The r+k time followed nearly the same trend as the r time. In most of the dogs it was decreased immediately after the obstruction and after the second week as well. However, between these periods some samples showed longer values than the preoperative ones, indicating a prolonged coagulation time.

The φ time increased shortly after the obstruction in parallel with the r time. Within a week it fell and remained below the control level for the 2 months of observation.

The ma value was decreased for several days following the obstruction. Then it returned to the preoperative level or slightly exceeded the latter, remaining there for the remaining observation period. The ma value and φ time showed inverse changes. It was presumed that fibrinogen or some other coagulation factor contributing to clot retraction was consumed and decreased for the early postoperative period but increased therafter.

The f value or the ratio of 150th minute amplitude to maximal amplitude showed no consistent change except in one animal in which it was markedly reduced 19 and 27 days after the obstruction, suggesting an increased fibrinolytic activity.

Comparison of the hepatic vein blood distal to the site of the obstruction with the simultaneously collected blood from a systemic vein revealed no remarkable difference between these two blood samples.

Hematocrite. The preoperative hematocrite value (before laparotomy) ranged from 32% to 41% with a mean of 36% in 10 dogs. The mean increased 1 hour and 2 hours following the obstruction, were 5% and 9% respectively. In this acute phase the hematocrite of the hepatic vein blood distal to the obstructiton was on an average 1% higher than that of the blood simultaneously collected from a systemic vein.

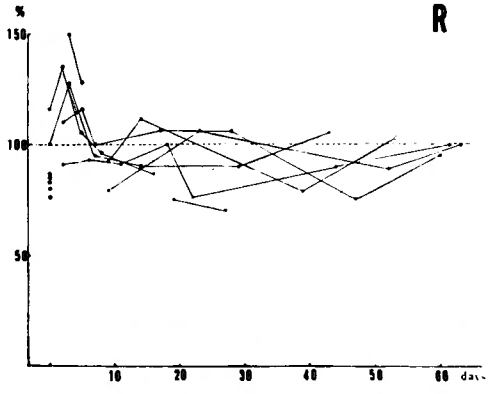

Fig. 7.

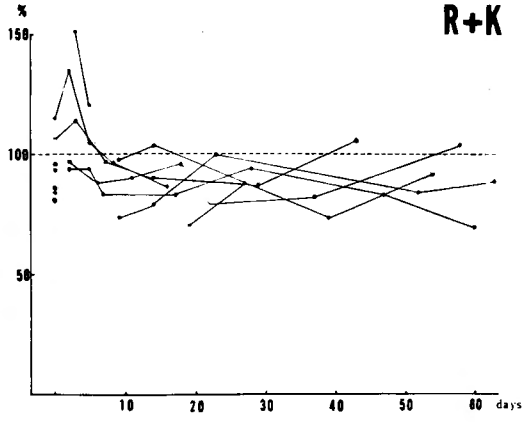

Fig. 8.

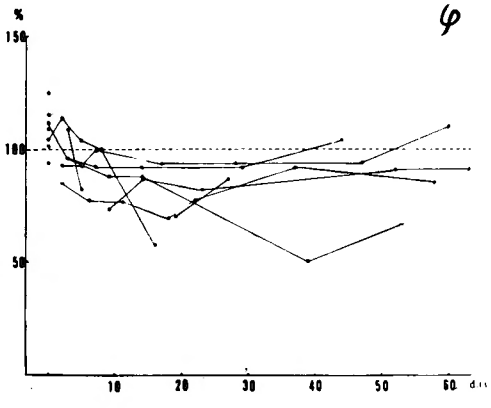

Fig. 9.

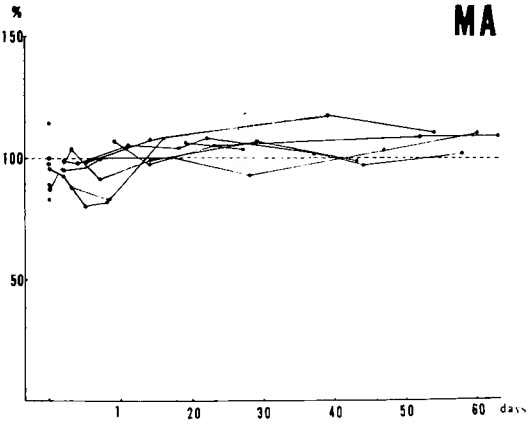

Fig. 10.

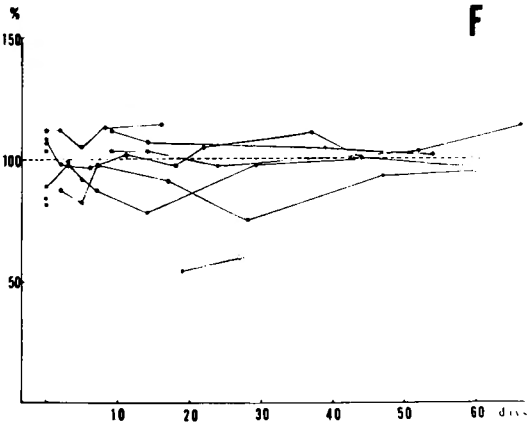

Fig. 11.

Fig. 7–11. Changes in thrombocytographic parameters after left hepatic vein obstruction (expressed as % of the control value).

Later changes are depicted in Fig. 12. In a typical case the acute increase after the obstruction was followed by a steep decrease, and in 2 days the hematocrit fell below the preoperative level, decreasing further for about a week to reach the lowest level. Thereafter, the hematocrit showed a slow, linear increase, but did not returned to the preoperative level for the 40 to 60 days of observation.

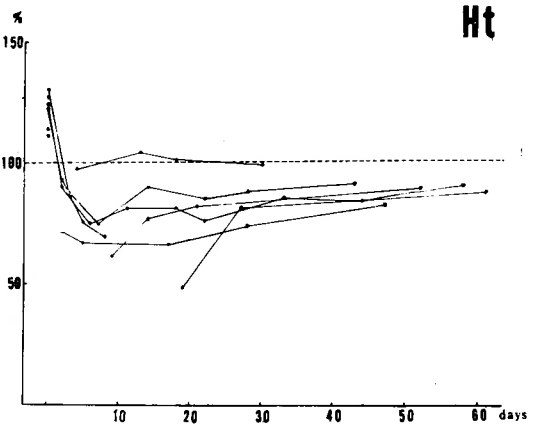

Fig. 12. Change in hematocrit value after left hepatic vein obstruction (expressed as % of control value).

DISCUSSION

The left hepatic vein trunk drains about 60% of the canine liver so that its acute obstruction causes intrahepatic pooling and consequent decrease in circulating blood volume. However, under light anesthesia and with minimal surgical intervention this decrease in blood volume seems to be compensated for by general vasoconstriction since the meen decrease in arterial pressure is only about 20 mmHg. This figure is smaller than the values obtained by BENDER and HORVATH[4]. It must be noted that in this experiment the obstruction caused a critical fall in blood pressure when the anesthesia was deep or other operative procedures were superimposed.

In spite of the acute obstruction of this physiological outflow tract the blood circulation is maintained to some degree in the occluded lobe. This is demonstrated by the observations a) that a rise in arterial pressure though attenuated and delayed is still seen when adrenalin is injected into the occluded lobe, and b) that this lobe takes up intravenously injected rose bengal or gold colloid. Obviously blood enters this lobe through the hepatic artery. The outflow tracts however are rather complicated according to the observations by India ink injection. Shortly after the obstruction venous blood of the occluded lobe was drained partly through the main portal branch in a retrograde manner and partly through the parenchymal bridge connecting the occluded lobe with the open lobes. Also, venous blood may regurgitate into hepatic vein tributaries draining the adjacent lobes to enter the open lobes (See Fig. 2). Of these channels the main portal branch appears to be a main outflow tract during the early period following the obstruction since the pressure in it is usually lower than that in the left hepatic vein and the India ink injected into the former is carried away more quickly than into the latter.

In the chronic stage the main portal branch no longer serves as an outflow tract; more peripheral portal branches and hepatovenous tributaries are competent enough to divert venous blood to the adjoining lobes or newly formed hepatovenous collaterals. In other words, prehepatic portal veins soon lose the role of outflow tract, which is taken over by intrahepatic vessels and posthepatic collaterals. Such shunts have been demonstrated in the previous paper[3].

GLIEDMAN and his coworkers[5] found that in ascitic dogs the radioiodinated serum

protein injected into the portal vein or hepatic artery was detected in the inferior vena cava below the liver prior to its recirculation whereas the animals which had spontaneously lost their ascites showed insignificant recovery of isotope from the same portion of the cava. Their results also might be explained by the similar process of "outflow shifting from prehepatic to intrahepatic and posthepatic levels."

On the contrary, if hepatovenous obstruction advances to a greater degree and extent for some reason (e. g. thrombosis), outflow tract may shift in the opposite direction, involving upper portal veins. Thus, portal veins supplying the occluded area sometimes serve as outflow tract snd sometimes as inflow tract. From this it follows that hepatovenous obstruction produces, if temporary, stasis not only in hepatic veins, but also somewhere in, and at some level of the portal system, whether the hepatic vein obstruction may be local (as in this experiment) or general; at a main trunk or at peripheral branches. This stasis may increase the risk of thrombosis which is otherwise favoured by increase in hematocrit and shortening of coagulation time in the acute stage of obstruction.

On the other hand, there may be teleologically some mechanism to prevent thrombosis. Thromboelastographic studies, however, failed to reveal such defense mechanism except that clotting time was prolonged in some dogs which were studied in early postoperative days.

It was thought that the degree to which blood circulation was maintained in the occluded lobe could be estimated by comparison of rose bengal or gold colloid uptakes between the occluded and open lobes of the liver. For example, if Au^{198}gold colloid was injected intravenously the occluded lobe showed 10 minutes thereafter a radioactive concentration of 20 to 40% of the open lobe value and this figure was regarded as indicating the degree of blood circulation in the occluded lobe. However, if rose bengal was used instead of gold colloid its 10th minute concentration in the occluded lobe was, at least for the first month, higher than when gold colloid was used. In other words the difference in rose bengal concentration between the occluded and open lobes was smaller than that in gold colloid concentration.

Similar dissociation was observed by TERADA[6]. According to him hepatic clearance of gold colloid reduced after experimental constriction of the thoracic inferior vena cava whereas BSP clearance remained nearly normal over a long postoperative period.

Since the veno-occluded lobe of the liver was found to be mainly supplied by the hepatic artery this dissociation seemed to be explained by the concept that the hepatic artery mainly supplied parenchymal cells with rose bengal or BSP, so that uptake of these substances was not so much affected in the occluded lobe. ANDREWS et al.[16] observed that BSP is removed more completely by the perfused canine liver when it is administered into the hepatic artery than into the portal vein. RABINOVICI et al[7]. found that after injection of RISA into the hepatic artery or portal vein its uptake by the liver was different between the two routes of injection and stated that the arterial blood is perfusing the parenchymal cells of the liver.

Such concept of selective supply of rose bengal by the hepatic artery however had to be discarded after supplementary experiments in which instead of the hepatic vein the hepatic arterial branch or portal branch supplying the left lateral lobe was ligated. In

either case the 10th minute concentration of rose bengal was markedly higher than that of gold colloid in the occluded lobe.

It was also disclosed in another experiment that in the veno-occluded lobe the rose bengal concentration continued to rise for 30 minutes following injection while in the open lobe the maximal concentration was reached within 10 minutes. This result clearly revealed the fact that in hepatovenous obstruction excretion of rose bengal was markedly impaired whereas its uptake remained relatively unaffected so that this substance accumulated in the occluded area.

Similar result was reported by TEZUKA[8] with constriction of the suprahepatic inferior vena cava in rabbits. By means of external counting he observed a prolongation of rose bengal excretion in early postoperative months, followed only later by delayed uptake.

Such dissociation between the uptake and excretion of rose bengal by liver cells does not seem to be characteristic of outflow or inflow obstruction of the liver. It was also observed by TALPIN[17] and MEURMAN[9] in CCl_4-poisoned animals and by STERNBERG[10] in burned rabbits. BRAUER[11] divided bile constituents, endogenous or exogenous, into classes A, B and C, of which class B included BSP, rose bengal and other substances which were concentrated in passage from blood to bile. He also showed that in some toxic liver injury secretion of BSP is severely impaired, whereas storage remains effective. HANZON[18] observed liver cell secretion of uranin, a class B substance, by means of intravital fluorescence microscopy, and stated that the hepatic cell membrane facing the bile capillary was injured earlier at graded ultra-violet radiation than the one facing the sinusoid ; the latter membrane was affected by more severe injury. Thus, it may be said that delayed excretion of the above substances is one of the earliest reflections of various pathological processes of the liver including hepatovenous obstruction.

An unanswered question concerns the very low ratio of RB to GC concentration in the open lobe (No. 90 in Table 3) during the acute stage. One of the possible explanations is that the open lobe received from the occluded lobe venous blood containing relatively rich gold colloid.

One of the remarkable hemodynamic changes in the acute phase of hepatic vein obstruction is a marked increase in hepatic arterial-to-portal flow ratio. This is conceivable in view of pressure gradient change in both systems. As far as the systemic blood pressure is maintained an elevation of 127 mm saline or 9 mmHg in hepatic vein pressure causes only a slight drop of pressure head in hepatic arterial flow, whereas the portal-hepatic vein gradient is decreased to a far greater extent. However, the observation that in 2 dogs the arterial flow slightly increased after the obstruction must be explained by decrease in resistance of the hepatic arterial system. Although the hepatic vein pressure falls in chronic stage the hepatic arterial-to-portal flow ratio appears to be still slightly higher than the control value. This may be due to organic changes of both the portal vein and hepatic artery as are described in the previous paper[3].

As for the thoracic duct lymph the present investigation has confirmed the observations by SIMONDS[12] and VAN DER HEYDE[13] that hepatic vein obstruction causes a marked increase in its flow. VAN DER HEYDE and his coworkers who studied thoracic duct lymph flow following ligation of hepatic vein branches with variations in portal hemodynamics,

also demonstrated a portal branch acting as an outflow tract.

Since OPPENHEIMER's description of vascular occlusion in polycythemia vera many cases have been reported in which CHIARI syndrome occurs concomitantly with polycythemia. ARMSTRONG[15], who attempted to elucidate whether hepatic thrombosis was the cause of or secondary to polycythemia, found that anemia developed in dogs with hepatic vein ligation, suggesting that polycythemia preceeded hepatic vein thrombosis. The present investigation also revealed that the hematocrit value remained below the preoperative value in the chronic phase of obstruction. However, a marked rise was observed in the acute stage: The mean hematocrit rose from the preoperative value of 36% to 45% two hours after the obstruction. Assuming that the total blood cell volume in the circulating blood remains unchanged, this increase means that about 30% of the preoperative plasma volume escaped from the circulating blood in this period of time. The laparotomy may be partly responsible for the plasma loss, but without laparotomy BENDER[4] reported an increase of 2.5% in arterial hematocrit in 10 minutes following the obstruction. It is uncertain whether ascites and edma of the liver together account for the 30% plasma loss, or more or less generalized edema results from the left hepatic vein obstruction. Further studies into this problem are necessary.

SUMMARY

Hemodynamic changes resulting from obstruction of the left hepatic vein trunk (draining about 60% of total liver) in dogs are reported with the following results:

1) Immediately after obstruction arterial pressure shows slight decrease (about 20 mmHg) with minimal operative intervention under light anesthesia. Otherwise it may fall more deeply and occasionally to a critical level.

2) In acute stage (1 hour after obstruction) portal pressure, portal vein and hepatic vein pressures of the left lateral lobe (occluded lobe) rise to a nearly equal level; the hepatic vein pressure slightly exceeds the corresponding portal vein pressure, rising by more than 100 mm saline. In chronic stage (more than 1 month after obstruction) portal pressure returns to pre-obstruction value; hepatic vein pressure falls below the other pressures but remains higher than its control level.

3) In acute stage the portal vein of the occluded lobe acts as a main outflow tract, which is soon taken over by intrahepatic vessels and posthepatic collaterals. A possibility is suggested that stasis occurs not only in hepatic veins but also in portal veins of the occluded area, predisposing them to thrombosis.

4) Gold colloid uptake by the occluded lobe (per unit weight) is 20 to 40% of that by the open lobe in acute stage. This value gradually increases and may exceed 90% in a month or two. As compared with gold colloid concentration, 10th minute concentration of rose bengal in the occluded lobe is higher (or closer to the corresponding open lobe value) for the first month. This dissociation is explained chiefly by impairment of rose bengal excretion with relatively normal uptake by the occluded lobe

6) Follwing obstruction portal flow markedly reduces (30% of pre-obstruction value) whereas hepatic arterial flow shows smaller decrease (70% of pre-obstruction value) with consequent increase in hepatic arterial-to-portal flow ratio. Vascular resistance of the hepatic

artery appears to be lowered. In chronic stage each flow approaches the control value but hepatic arterial-to-portal flow ratio seems to remain above the control level presumably as a result of organic changes of both vascular systems.

7) Thoracic duct lymph shows a three-fold increase in flow rate and a rise of 1 gm/100 cc in protein content shortly after obstruction.

8) Thromboelastogram shows a shortening of coagulation time in acute stage followed occasionally by a temporary prolongation, while ma reduces acutely only to increase later.

9) Hematocrite is markedly increases immediately after obstruction, indicating that a considerable amount of plasma is removed from circulating blood. This increase is followed by a steep decrease, from which hematocrite recovers gradually but remains below the preoperative level for 40 to 60 days of observation.

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和文抄録

左肝静脈閉塞による実験的肝鬱血の研究

—Ⅱ 血行動態の変化について—

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前報に於て犬の左肝静脈を閉塞して，肝左側に撰択的に鬱血を起し，その際の組織学的所見や血管系の変化を追究した．本報に於ては同様にして犬肝臓の約60%の領域の静脈血を集める左肝静脈本幹を閉塞して，その際の肝臓及び全身性の血行動態の変化を追求して次の結果を得た．

1) 肝静脈閉塞直後の血圧下降は麻酔深度が浅くかつ手術侵襲を最小にとどめれば軽度（約20mmHg）である．しかし他の場合には血圧下降はこれより大で，時にはショック状態に迄達することもある．

2) 急性期（閉塞後1時間）では門脈圧及び左外側葉（閉塞葉）の門脈圧及び肝静脈圧は共に上昇して互に近似した値となる．しかし閉塞葉の肝静脈圧は100mm水柱以上増加して，閉塞葉の門脈圧をわずかに越える．慢性期（閉塞後1ヵ月以上）では門脈圧は術前値に復し，肝静脈圧も他の二者よりも低くなるが，なお術前値よりは高値を取る．

3) 急性期には閉塞葉の門脈はその主流出路となる．しかし間もなく肝内血管や肝後性の副血行路がその門脈に代つて流出路となる．この際閉塞葉の肝静脈のみならず，門脈内にも血流停止が起ることが考えられ，これが血栓の形成を助長することもあり得る．

4) 閉塞葉の単位重量当りの金コロイド摂取率は急性期では非閉塞葉の約20～40%であり，この値は次第に増加して1，2ヵ月後には90%を越えることもある．この数値は閉塞葉に於て血行が如何に保たれているかの指標となる．ところがこの金コロイドの数値に比して，閉塞葉に於ける注入10分後のローズベンガルの濃度は最初の1ヵ月では比較的高い．（即ち閉塞葉のローズベンガル濃度は非閉塞葉の濃度により近い値を取る）この金コロイドとローズベンガルの違いは，閉塞葉ではローズベンガルの摂取が比較的正常に保たれるが，その排泄が障害されることで説明される．

6) 肝静脈閉塞後，門脈血流量は著しく減少する（閉塞前の約30%）．しかし肝動脈血流量の減少はこれより少ない（閉塞前の約70%）．その結果肝動脈流量対門脈流量比は増加する．この際肝動脈の血管抵抗は減少すると思われる．慢性期では両流量共閉塞前値に近ずくが，肝動脈流量対門脈流量比はなお高いようである．これは両血管系に器質的変化が起きた為と考えられる．

7) 胸管リンパ流量は閉塞後約3倍に，その蛋白量は約1g/dl増加する．

8) トロンボエラストグラムでは急性期に血液凝固時間の短縮が見られ，これはその後一過性に延長する．又 ma 値は急性期に減少するが，間もなくやや高い値を取る．

9) ヘマトクリット値は閉塞直後急激な上昇を示し，かなり大量の血漿が循環血液より消失することが分る．しかしヘマトクリット値はその後急速に低下し，その後徐々に上昇するが，40～60日の観察期間では術前値に帰らない．