Experimental Study on the Effect of Increase in Splenic Blood Flow upon the Portal Pressure

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The changes of portal pressure were studied in adult mongrel dogs, while splenic blood flow was let increase in five steps from 0 to 350 ml/min. When intrahepatic portal circulation was left intact, there was no appreciable change in the portal pressure concomitant with changes of splenic blood flow, but in dogs with obstruction of intrahepatic portal branches by silica particles, increase in splenic blood flow caused a marked elevation of the portal pressure. The role of the increase in splenic blood flow and the obstruction of intrahepatic portal branches in the pathogenesis of portal hypertension in idiopathic splenomegaly was discussed.

In regard to the pathogenesis of portal hypertension, a number of investigators support the view that it is the result of 'passive congestion' of the portal system caused by cirrhosis of the liver or obstruction of extrahepatic portal vessels. According to this concept, splenomegaly which is frequently seen in association with portal hypertension is also nothing but a manifestation of congestion of the portal system.

Studies in recent years, including detailed histologic examinations of the enlarged spleen, the observation of cases in which portal hypertension is present without liver cirrhosis or extrahepatic portal obstruction and the observation that portal hypertension is sometimes accompanied with splenic arteriovenous fistula, have given rise to the opinion that an increased blood flow into the portal system is an important factor in the pathogenesis of portal hypertension.

In a previous publication¹ we have emphasized that portal hypertension in idiopathic splenomegaly (so-called Banti's syndrome) can be best explained as a consequence of the combination of two factors: An increase in splenic blood flow and obstruction of intrahepatic portal branches. In the present study, an attempt was made in dogs to determine experimentally under what condition an increase of splenic blood flow influences the pressure.

MATERIALS AND METHODS

Experiments were performed on 20 adult mongrel dogs weighing 17 to 20 kg. The animal was laparotomized under penthobarbital anesthesia. The splenic artery together surrounding nerves was cut at about 2 cm toward the spleen from its junction with the celiac artery and a cannula of 2 mm in diameter was inserted into it. Another cannula, with a diameter of 7 mm, was inserted into the right femoral artery which had been exposed and the two cannulae were connected with each other by means of a siliconized vinyl tube with a diameter of 10 mm. A roller-pump* was placed between the two cannulae (Fig. 1).

Fig. 1. Schema of splenic perfusion.

The pump was so adjusted by changing its rotation that splenic blood flow could be changed in five steps of 0, 100, 200, 300, and 350 ml/min. A tube with a diameter of 1 mm was inserted into the portal trunk through a branch of the superior mesenteric vein for both measurement of the portal pressure and injection of silica particle suspension† to obstruct the intrahepatic portal vessels, 1 g of silica particles being suspended in 40 ml of heparinized normal saline. Another cannula was inserted into the left femoral artery for a continuous measurement of the arterial pressure during the experiment.

The animals were divided into two groups and one of the groups served as the control. In the control group, splenic blood flow was gradually increased in five steps as described above, and the portal pressure at each step was recorded.

In the second group, while the splenic blood flow was held at 0, 2.5% silica suspension was injected through the catheter into the portal trunk. The portal pressure was measured each time when 10 ml of the suspension was injected, and the injections were repeated until a stable portal pressure of 150 to 170 mm H₂O was obtained. When 60–70 ml of the silica suspension were injected, many intrahepatic portal branches were obstructed, as shown in Fig. 2 and stable portal pressure was established. Splenic blood flow was then gradually increased and the corresponding changes in the portal pressure were continuously recorded. In order to check reproducibility of the results, splenic blood flow was reduced after its maximum value was attained and increased again to the maximum level, while measuring the portal pressure all the time.

* Manufactured by Natsume Co., Osaka, Japan.

† Wakogel Q-22 Mesh through 200, obtained from Wako-Junyaku-Kogyo Co., Osaka, Japan.

Fig. 2. Histology of the liver after injection of 2.5% silica suspension portal branches are partially obstructed by silica particles.

RESULTS

1) Control group

When the splenic blood flow was 0, the portal pressure was 110 to 130 mm H₂O. There was no appreciable change in the portal pressure when splenic blood flow was increased to 100 ml/min. When it was increased to 200 ml/min, the portal pressure increased by 5 to 6 mm H₂O. Even when splenic blood flow was increased to 350 mm H₂O, the increase in the portal pressure was only 10 to 15 mm H₂O in most of the time, amounting 30 mm H₂O at the maximum. As shown in Table 1 and Fig. 3, the increase in the portal pressure remained below

TABLE 1. *Change of portal pressure in control dogs*

Dog No.	Body weight and sex	Portal pressure (mm H ₂ O)				
		0*	I*	II*	III*	IV*
1	15kg ♀	120	120	125	130	130
2	13 ♀	105	105	105	110	110
3	14 ♂	110	110	120	130	130
4	13 ♀	110	115	115	120	130
5	14 ♂	110	120	120	120	120
6	16 ♀	115	120	125	120	130
7	17 ♂	130	130	120	125	130
8	16 ♂	120	125	120	130	140
9	18 ♀	110	115	120	120	130
10	19 ♂	120	120	130	135	145

* Splenic blood flow

0: 0 ml/min. I: 100 ml/min. II: 200 ml/min. III: 300 ml/min. IV: 350 ml/min.

Fig. 3. Relation between portal pressure and splenic blood flow in control and in portal branch obstruction.

30 mm H₂O as splenic blood flow was increased from 0 to 350 ml/min in the control group. Besides, there was no appreciable change in the arterial pressure or in the size of the spleen as splenic blood flow was changed.

2) Portal obstruction

The injection of silica suspension caused intrahepatic portal obstruction and maintained the portal pressure stable at 150 to 170 mm H₂O, while splenic blood flow was 0. As splenic blood flow was increased to 100 ml/min, there was an increase in the portal pressure by 10 to 15 mm H₂O. When splenic blood flow was increased to 200 ml/min, the portal pressure rose by 30 mm H₂O at the minimum and 90 mm H₂O at the maximum. When splenic blood flow was increased to 300 ml/min, the increase in the portal pressure amounted to 50 mm H₂O at the

TABLE 2. Change of portal pressure in dogs with portal branch obstruction

Dog No.	Body weight and sex	Portal pressure (mm H ₂ O)				
		0*	I*	II*	III*	IV*
11	15kg ♂	160	190	220	260	300
12	18 ♂	150	160	300	330	370
13	15 ♀	145	165	175	220	310
14	17 ♂	170	190	260	340	390
15	14 ♀	145	175	200	350	375
16	19 ♂	160	180	240	360	440
17	17 ♀	155	185	250	320	390
18	16 ♂	150	170	250	300	320
19	20 ♂	160	165	245	290	310
20	17 ♀	165	180	200	255	315

* Splenic blood flow

0: 0 ml/min. I: 100 ml/min. II: 200 ml/min. III: 300 ml/min. IV: 350 ml/min.

minimum and 190 mm H₂O at the maximum, and it was 140 mm H₂O at the minimum and 260 mm H₂O at the maximum when splenic blood flow was increased to 350 ml/min. As is shown in Table 2 and Fig. 3, the portal pressure was elevated as splenic blood flow was increased, and the rate of the increase in the portal pressure was more pronounced when splenic blood flow exceeded 200 ml/min. There was no appreciable change in the arterial blood pressure or in the size of the spleen with the change of splenic blood flow. Reproducibility of the portal pressure changes was proved by repeated changes of splenic blood flow in the manner described above.

DISCUSSION

In previous publications, we have reported on the results of measurements of splenic blood flow in idiopathic splenomegaly (Banti's syndrome) by means of dye dilution² and histometric³ methods. It was revealed that in idiopathic splenomegaly splenic blood flow was markedly increased to 500 to 1,500 ml/min in comparison with the value of 250 to 300 ml/min in control subjects. It was also found that in patients with increased splenic blood flow the portal pressure was elevated and the fall of the portal pressure after splenectomy was larger. These findings will suggest that an increase in splenic blood flow is an important factor in the pathogenesis of portal hypertension. Studies supporting this view were reported by Williams *et al.*⁴ and Ueda *et al.*⁵

It has also been established, however, that splenectomy does not always reduce the portal pressure to the normal level in patients with splenomegaly accompanied by portal hypertension. It appears, therefore, that, at least in the presence of established portal hypertension, impairment of portal blood flow in the liver also contributes to development of portal hypertension. In order to evaluate this hypothesis, we thought it would be relevant to compare the effect of changes of splenic blood flow upon the portal pressure with and without impairment of portal blood flow. Observations in patients with idiopathic splenomegaly have revealed that splenic blood flow was increased to about 1,000 ml/min, namely 3 to 4 times the normal value. In the present study, likewise, splenic blood flow was increased as much as 3.5 times the normal value in dogs, since splenic blood flow in normal dogs of the body weight used in the present study was around 100 ml/min.² Portal blood flow in normal dogs is approximately 20 to 30 ml/kg/min that is around 350 to 500 ml/min.⁶ Consequently, portal blood flow was increased 1.7 to 2 times the normal value in the present experiments. In the control group with intact intrahepatic portal circulation, there was no appreciable change in the portal pressure with increase in splenic blood flow. On the other hand, it was found in a previous work⁷ that in dogs after splenic ischemia, a 1.7 times increase in splenic blood flow did not cause any change in the portal pressure. These findings suggest that an increase in the portal flow of this degree is well compensated by normal hepatic circulation and does not cause any portal hyper-

tension. It is therefore possible that, when the lesion in hepatic tissue in idiopathic splenomegaly is slight, portal hypertension does not develop as the result of an increase in splenic blood flow. Patients in which such a situation is actually present are not infrequently found.⁸

On the other hand, when obstruction of intrahepatic portal branches was produced by silica particles, increases in splenic blood flow of the same degree as in the control animals caused marked increases in the portal pressure. Obstruction of portal branches produced by silica particles in the present study was not strong enough to cause marked elevation of the portal pressure by itself. The portal pressure was elevated by this procedure to 150 to 170 mm H₂O, when splenic blood flow was 0, and to 170 to 190 mm H₂O when splenic blood flow was at the normal level of 100 ml/min. An elevation of the portal pressure of this degree does not mean portal hypertension at normal splenic blood flow. When splenic blood flow was increased to twice the normal (200 ml/min), however, the portal pressure was increased above 200 mm H₂O in 5 of 6 dogs, and a three-fold increase in splenic blood flow (to 300 ml/min) brought about an elevation of the portal pressure above 200 mm H₂O in all of the dogs, or above 300 mm H₂O in half the dogs. When blood flow was 350 ml/min the portal pressure exceeded 300 mm H₂O in all the dogs.

As has been reported previously,⁹ in patients with idiopathic splenomegaly extrahepatic collateral circulation and other manifestations of portal hypertension were evident in all the patients with portal pressure exceeding 300 mm H₂O. It can be surmised, therefore, that the obstruction of intrahepatic portal branches of such a degree as to sustain normal portal pressure so long as splenic blood flow is normal may give rise to typical portal hypertension when splenic blood flow is increased to as much as 3 times the normal. Furthermore, this relationship between the amount of splenic blood flow and portal pressure is very similar to that observed in cases of idiopathic splenomegaly clinically.

Tisdale¹⁰ *et al.* reported on 5 cases of portal hypertension without obstruction of the intra- and extrahepatic portal system. The liver of his patients, however, exhibited histologically loss of parenchymal cells and fibrosis, although slight, around the portal vessel. Furthermore, intrahepatic portal branches were poorly visualized in splenoportography in these patients, indicating portal obstruction. Therefore, his assertion that there was no obstruction in the intra- and extrahepatic portal system in these patients might not be sustained so far as intrahepatic portal obstruction without liver cirrhosis is concerned.

Arterial hyperemia followed by marked vascular sprouts in the distal region of central arteries in Banti spleens has been noticed by Ono.¹¹ This finding seems to support the authors' concept that arterial factor in the spleen plays an important role in the development of portal hypertension with splenomegaly. Ravenna¹² also suggested primary lesions of the splenic arterioles as a cause of insufficient control of blood flow.

Splenic arterio-venous fistula is a typical example of the causes leading to

increased blood flow in the portal system. Johnston and Gibson¹³ have reported on 3 cases of this disease, in 2 of which esophageal varices were present and in one of them the portal pressure was found elevated to 290 mm H₂O, which was reduced to 190 mm H₂O after splenectomy. Absence of cirrhotic changes in the liver in these patients led the above authors to the conclusion that portal hypertension in these patients was due to an increase in portal blood flow. Experiments have been performed by many workers in which increases in portal blood flow was produced by various methods. Tomota¹⁴ perfused an extra-corporeal canine liver and spleen preparation with normal saline and investigated the pressure flow-relationship in the combination of liver and spleen. In this study, he found that more pronounced portal hypertention was produced by the perfusion in a preparation of normal spleen and damaged liver after tetrachlor carbon administration than in one of normal spleen and normal liver even at increased flow. He observed furthermore that increase in the portal pressure was of the same degree in a preparation of an enlarged human spleen and a normal canine liver as in one of a normal canine spleen and liver. Although his studies were performed on preparations of isolated organs perfused with normal saline and the condition was therefore far from physiological, it deserves attention that a combination of the liver and spleen was used including the liver having been subjected to pathologic effects. Shilling *et al.*¹⁵ produced in dogs arterialization of the portal vein by implanting a hepatic artery of less than 4 mm in diameter into the portal vein. No appreciable increase in the portal pressure was observed in these dogs, portal pressures in 3 of the dogs being 148, 165 and 200 mm H₂O one and a half years after the operation.

Siderys *et al.* achieved increase in portal blood flow in two ways. In the first method,¹⁶ the aorta was directly anastomosed with the splenic vein. In the second method,¹⁷ side-to-end portocaval anastomosis was made in the first step so that all of the venous return below the liver went into the portal vein, and, in the second step, the aorta was anastomosed with the inferior vena cava below the liver side-to-side. Portal hypertension was produced by both of these procedures. Four weeks after the operation of the first method, the increase in the portal pressure averaged 100 mm H₂O, and hepatic blood flow at that time was 162 ml/kg/min in the average, as compared to 33 ml/kg/min before the operation. After the operation of the second method, the portal pressure increased by as much as 160 mm H₂O and attained the level of 320 mm H₂O in one case. In this case hepatic blood flow was also markedly increased to 278 ml/kg/min, which is a more than 8-fold increase compared with that before the operation. Histology of the liver showed periportal lymphocytic infiltrations and fibrosis of varying degrees in all cases. It is to be noted in these experiments that, because of the direct anastomosis between the aorta and portal system, the aortic pressure was directly transmitted to the portal circulation and the normal blood pressure gradient was completely distorted. Although direct communication between the artery and portal system as in splenic arteriovenous fistula is present in some cases of portal

hypertension, this is a rare condition and does not account for the development of portal hypertension in general. In experiments by Siderys *et al.* a five-fold increase in hepatic blood flow was necessary in order to raise portal pressure by 100 mm H₂O in an average after aortoportal anastomosis. In clinical cases of portal hypertension, including idiopathic splenomegaly, a decrease, but not an increase in hepatic blood flow is the rule, and maintenance of hepatic blood flow at 5,000 ml/min (five times the normal amount) is well beyond the capacity of the cardiac output.

Furthermore, in experiments with arteriportal anastomosis, the increase in blood flow is most likely maximum immediately after the operation and declines gradually with time. In idiopathic splenomegaly, on the other hand, the enlargement of the spleen as well as the increase in portal and splenic blood flow progress gradually with aggravation of the disease leading to elevation of portal pressure. Consequently, there is a fundamental difference in the process of increased blood flow between clinical portal hypertension, especially in idiopathic splenomegaly, and experimental arterio-portal anastomosis. It is not justified to regard these two conditions as the same.

In the present study, arterial blood flow was directed into the portal system not directly but through the spleen, and the increase in blood flow was kept below 3.5 times the normal splenic blood flow. Portal and hepatic blood flow did not exceed twice the normal. As was discussed in the foregoing section, these procedures were effective in reproducing the situation in patients with idiopathic splenomegaly.

As has been discussed in previous reports,^{1,3} splenic arteriolo-sinal shunts are often seen in idiopathic splenomegaly. Since they represent a sort of arterio-venous fistulae, it might be assumed that the experimental condition of the present study using the spleen of normal dogs is not all together identical with clinical condition of idiopathic splenomegaly. However, the direct communications act toward a decrease of the resistance to splenic blood flow. It can be assumed therefore that in idiopathic splenomegaly the effect of increased splenic blood flow upon the portal pressure would be more exaggerated than would be expected from the present study.

No definite conclusion can be drawn from the present study upon the relationship between the increase in blood flow and obstruction of intrahepatic portal branches. In experiments of arterio-portal anastomosis by Shilling *et al.*,¹⁵ Siderys *et al.*^{16,17} and Miyao,¹⁸ dilatation of intrahepatic portal branches with thickened walls and periportal cell infiltration and fibrosis of varying degrees were observed. Rather and Cohn¹⁹ reported on necrotizing vasculitis of the intrahepatic portal vessel in which obstruction of portal branches was demonstrated. As has been discussed by Ueda *et al.*,⁵ these findings suggest the possibility that in portal hypertension, especially in idiopathic splenomegaly, an increase in blood flow causes obstruction of intrahepatic portal branches.

It is to be pointed out, however, that in experiments of arterio-portal

anastomosis, an extraordinarily large amount of blood flows into the portal system. The condition is evidently unphysiological and quite different from the clinical condition. It is questionable, therefore, whether the changes of portal pressure observed in the experimental condition can be regarded as corresponding to the process taking place in clinical cases. Consequently, the findings of these experimental studies do not afford conclusive evidence to the view that portal hypertension in idiopathic splenomegaly is a result of increased splenic blood flow.

Imanaga *et al.*²⁰ described in their studies on hepatic circulation in portal hypertension the condition in which impairment of blood flow was restricted to the intrahepatic portal system as a distinct entity. They have not elucidated the mechanism of impaired blood flow, and their view is not completely in accordance with ours in that they regard the development of splenomegaly as the consequence of passive congestion. We are in agreement with them, however, in that we consider obstruction of intrahepatic portal blood flow to be an important factor in the pathogenesis of portal hypertension. In the present study it was demonstrated that the effect of increase in splenic blood flow for elevating portal pressure was manifest only when obstruction of intrahepatic portal branches was present.

We have held the view²¹ that idiopathic splenomegaly or Banti's syndrome is a manifestation of hepato-splenitis. The same pathogenic factor gives rise to changes in the spleen and at the same time causes fibrosis in the liver. From this viewpoint, we have investigated and reported a positive relationship between obstruction of intrahepatic portal branches and portal pressure. It might be accepted that by intrahepatic portal block with silica particles we have succeeded in producing the same condition within the liver as in idiopathic splenomegaly in which intrahepatic portal block is caused by fibrotic process.

Under the present experimental condition, it was demonstrated that a combination of two factors, an increase in splenic blood flow and obstruction of intrahepatic portal pressure, brought about a marked elevation of portal pressure, while each of the two factors alone caused only a slight rise in the pressure. This finding seems to confirm the above-stated view of ours in regard to the pathogenesis of idiopathic splenomegaly.

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