EXPERIMENTAL STUDY ON CIRRHOSIS OF THE LIVER: WITH PARTICULAR REFERENCE TO THE INFLUENCE OF THE LIGATION OF THE HEPATIC ARTERY UPON THE PORTAL BLOOD FLOW IN THE DOG WHOSE HEPATIC VEIN HAD BEEN CONSTRICTED

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THE PORTAL BLOOD FLOW IN THE DOG WHOSE
HEPATIC VEIN HAD BEEN CONSTRICTED

By

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I. INTRODUCTION

Since RIENHOFF, BERMAN and others recently advocated that the ligation of the
hepatic artery was effective for the treatment of cirrhosis of the liver, many investigators reexamined this problem from various angles. They are, however, of a diversity of opinions about this procedure.

Author intended to investigate the effects of the ligation of the hepatic artery upon the blood flow in the portal vein in cases of the liver cirrhosis associated with or without ascites. By constriction of the hepatic veins in dogs, we succeeded to produce the conditions quite similar to those of the liver cirrhosis in human beings. In these dogs, the hepatic artery was ligated and changes in the portal blood flow were studied.

Herrick in 1907, through his perfusion test of the liver, suggested there was an interrelation between the blood pressure of the hepatic artery and that of the portal vein. Later McIndoe (1926), Dock (1942) and Taylor & Rosenbaum (1953) also performed the perfusion test of the liver in cases of the portal hypertension particularly of the liver cirrhosis and found an interrelation between the blood pressure of the hepatic artery and that of the portal vein. Also they studied the correlation between the volume of blood flow of the hepatic artery, portal vein and that of the hepatic vein. We, instead of perfusion on the removed liver, carried out similar kind of experiment, in vivo, with the use of “Thermostromuhr”.

II. METHOD AND MATERIAL

Mongrel dogs of 7.6-15.0kg body weight were used. These were divided into three groups, i.e. 1) dogs in normal control group, 2) dogs in which the constriction of the hepatic vein was not followed by the development of ascites and 3) dogs in which the marked ascites developed after the constriction of the hepatic vein. Both in group 2) and 3), the animals underwent a reoperation for the determination of the rate of blood flow in the portal vein on the 14th day after the constriction of the hepatic vein.

1) Constriction of the hepatic vein in dogs

Prior to the procedure the animal was kept away from food for 24 hours. Under general anesthesia with an intravenous injection of thiopental sodium in dose of 0.04g/kg, laparotomy was carried out with r-subcostal incision. Ligation or constriction of the individual hepatic vein was carried out according to the Tsuchiya’s method. In the present experiment, however, manipulation for the right hepatic veins was slightly simplified, i.e. the right hepatic veins were divided into two groups, superior and inferior, and veins in each group were ligated en masse.

During these procedures a particular care was taken not to constrict the abdominal inferior vena cava. For the middle and left hepatic veins, constriction or ligation of a individual vein was made following the Tsuchiya’s original method.

2) Determination of the rate of blood flow in the portal vein (shown in photograph)

“Thermostromuhr” was used for the determination of the rate of blood flow in the portal vein. “Thermostromuhr” consists of high frequency current generator, galvanometer and lampscale and trough type thermo-couple.
i) High frequency current generator (Fig. 1, 2)
This apparatus was made under the guidance of Mr. Yoshifumi Sunahara who is an assistant in the institute of applied physics, faculty of technical engg.

ii) Galvanometer and Lamp scale
The galvanometer used in the present study was:
- resistance of wiring line 803 ohms,
- critical resistance 66,000 ohms,
- sensitivity $2.4 \times 10^{-10}$ amperes,
- $160 \times 10^{-7}$ volts,
- period 7.3 sec.

iii) Trough type thermo-couple
In Fig. 3, the trough type thermo-couple which was used by Herrick et al., was shown. In our experiment, instead of the electric heater, a diathermy electrode was used and this was connected with the diathermy generator which is believed to be ideal for warming the blood. Also 110V A. C. was used instead of the battery, and the rubber plate was used in place of the bakelite plate in order to provide a better approximation to the wall of the blood vessel.
iv) Use of the "Thermostromuhr"

The dog was anesthetized with thiopental-sodium and laparotomy was carried out with upper midline incision. The portal vein was dissected from the surrounding tissue. Distally from the bifurcation with the splenic vein and as close as possible to the liver, the trough type thermocouple was applied to the wall of the portal vein, thus the rate of blood flow in the portal vein was measured. To minimize the errors in measurement by the manipulation of ligating the artery as much as possible, silk thread was wrapped previously around the artery as shown in Fig. 4. Then, blood through the portal vein was warmed with the use of diathermy. Scale of the galvanometer at a time when the blood through the portal vein was thus warmed and before the hepatic artery was ligated, was set at 0 point. Change in scale after the quick-ligation of the hepatic artery by the silk thread previously wrapped around the artery, was read and recorded.

3) Determination of the volume of blood flow in the portal vein
A piece of the portal vein with a considerable length was taken out from the experimental dogs in order to determine the volume of blood flow through the portal vein. The trough type thermocouple was applied to this piece of removed portal vein. Two canules were inserted into the both ends of the vein and one of which was connected with a graduated irrigator filled with the heparinized blood in it. Blood volume which dropped from the irrigator was measured and at the same time change in scale of the "Thermostromuhr" was read. Thus, from these two measured values, the volume of blood flow was determined. This experiment was performed at the room temperature.

4) Determination of the systemic arterial blood pressure

Systemic blood pressure was determined with the mercury manometer at the femoral artery.

III. RESULTS

Fig. 5 Changes before and after ligation of the common hepatic artery on normal dogs.
1) Changes in the rate of the portal blood flow after the ligation of the hepatic artery

Since it was difficult from various reasons to observe the animals for long period after the ligation of the hepatic artery, the experiments were limited within a period of 30 minutes. The interruption of the blood flow through the hepatic artery was carried out either by the ligation of common hepatic artery alone or the ligation of the three major arteries (common hepatic, gastroduodenal, and right gastric artery) in one time.

In dogs of the control group

As illustrated in Figs 5 & 6, right after the ligation of the common hepatic artery or ligations of three major arteries, the rate of blood flow in the portal vein increased markedly. Within 5 to 20 minutes, however, it returned to the pre-ligation level, then gradually decreased. It was found that the time required the rate of blood flow to return to the pre-ligation level was longer, in the case of the ligation of three major arteries than that of the common hepatic artery alone. Converting these values into the volume of blood flow, as shown in Tab. 1, similar increase or decrease in the volume of blood flow in the portal vein were noticed. The average value of the volume of blood flow through the portal vein in the normal dogs was 208cc minute.

ii) In dogs in which the constriction of the hepatic vein was not followed by the development of ascites
Table 1. Portal blood flow (cc per minute)

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<th>5min</th>
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<th>15min</th>
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Fig. 7 Changes before and after ligation of the common hepatic artery on non ascitic dogs.
As illustrated in Figs 7 & 8, in some cases, it took longer time the increased rate of blood flow after the hepatic artery ligation to return to the pre-ligation level, compared with that in control animals, or in other cases, after the rate of blood flow decreased beyond the pre-ligation level, it increased again, so the curve directed upwards. These results were equally obtained either in case of the ligation
of the common hepatic artery alone or that of three major arteries. In dogs of
this group, the average volume of blood flow through the portal vein before the
ligation of the hepatic artery was 210cc/minute (Tab. 1).

iii) In dogs in which the marked ascites developed after the constriction of the
hepatic vein

As shown in Figs 9 & 10, the increased rate in blood flow after the hepatic
artery ligation, though there was slight fluctuation, did not return to the pre-
ligation level and this increase in the rate of blood flow through the portal vein
was kept continued. This tendency was especially marked in dogs whose three
major arteries were ligated. Average value of the volume of blood flow through
the portal vein in dogs of this group was 168cc/minute (Tab. 1).

iv) Comments

As shown in Fig. 11, the increase in the rate of blood flow was most obvious
in dogs in which the constriction of the hepatic vein had been followed by the
development of the marked ascites, and was the second in dogs in which ascites did
not develop after the hepatic vein constriction and was the least obvious in dogs of
the control group. In the latter two groups, once increased rate of the blood flow
dropped beyond the pre-ligation level as the time elapsed. In the former, on the
other hand, the increase in the rate of blood flow continued and never returned to
the pre-ligation level.

2) Changes in the volume of the portal blood flow per 100g of the liver after
the ligation of the hepatic artery

Results were shown in Fig. 12 and Tab. 2.

In the normal dogs average value of the blood flow volume through the portal
vein before the ligation was 72cc per minute per 100g of liver. Whilst, in dogs
Fig. 11 Average value of each group.

Fig. 12 Average value of each group.
which had the hepatic veins constricted and without ascites it was 68 cc/m/100 g of liver, and in dogs with ascites after the hepatic vein constriction it was 49 cc/m/100 g of liver. As previously mentioned, the volume of blood flow in the portal vein per minute itself did not show any significant difference between in the normal control dogs and in dogs without ascites after the hepatic vein constriction. But calculating it in volume per minute per 100 g of the liver tissue, the volume of the portal blood flow in the dogs without ascites after constriction was smaller than that in the normal dogs. Furthermore, comparing the volume in normal dogs with that in dogs which had the hepatic vein constricted and with a development of ascites, the difference became more significant, i.e. it reached as large as 23 cc/m/100 g of liver.

3) Balance of the increase and decrease in the volume of the portal blood flow at 30 minutes after the ligation of the hepatic artery

After the ligation of the hepatic artery, the volume of blood flow in the portal vein was measured at every one minute for 30 minutes. Comparing these values to that of pre-ligation level, the difference between them, i.e. the values of increase or decrease of the volume of blood flow were calculated at every minute after the ligation. Now, these values of difference, either positive or negative, were arithm-
etically added to obtain the balance for the period of 30 minutes. As shown in Tab. 3, this balance was negative in dogs of the control group and in dogs without ascites after the hepatic veins constriction and in both of which the common hepatic artery alone was ligated. Whilst, it was positive in dogs of the control group and in dogs without ascites of the hepatic vein constriction, and in both of which three major arteries were ligated. It was also positive in dogs with ascites after the hepatic vein constriction, and in which either the common hepatic artery alone or three major arteries were ligated. Among these, however, the positive balance was most markedly observed in dogs which had marked ascites after the hepatic vein constriction and later underwent the ligations of the three major arteries. In these animals an increase in the volume of the portal blood flow for 30 minutes reached as large as 1,000 cc.

This fact, as will be discussed later, may suggest that the blood flow of the hepatic artery is working hemodynamically as a resistance upon the blood flow in the portal vein, especially it is true in dogs with ascites after the hepatic vein constriction. The values of increase and decrease shown in Tab. 3, were average

<table>
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<tr>
<th>Time</th>
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<td>Total</td>
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Fig. 13 Changes of systemic blood pressure influenced by hepatic artery ligation
values from many animals.

4) Changes in the systemic arterial blood pressure after the ligation of the hepatic artery

Arterial blood pressure was determined at the femoral artery before and after the hepatic artery ligation with the use of mercury manometer. Results were shown

in Fig. 13 and Tab. 4. Actually in all dogs, i.e. in dogs in which either the common hepatic artery alone or three major arteries were ligated, or in dogs either in the control group or those with constricted hepatic vein, the systemic arterial blood pressure rose 10-40 mm Hg, within 1-2 minutes after the ligation of the hepatic artery and it continued to rise for approximately 10 minutes. This rise in blood pressure seemed to be due to the neurorefelectoric mechanism, (Burtont, Opitz) and also it quite corresponded in time factor to the transient increase of the portal blood flow soon after the ligation of the hepatic artery. Thus, these two phenomena might have some interrelation with each other.

5) Long-term observation of the changes in the portal blood flow after the ligation of the hepatic artery in the normal dogs

As illustrated in Fig. 14, the simultaneous ligation of three major arteries in the normal dogs, was followed by the marked increase in the rate of blood flow within 1-2 minutes. It, however, decreased rapidly, and the rate which was registered at approximately one hour after the ligation did continue for 8 hours, thereafter, it further decreased gradually. This last decrease was considered naturally to be due to the general weakness by the operation, though the particular care was taken for the maintenance of the body temperature or the relaxation of the legs

<table>
<thead>
<tr>
<th>Dog No</th>
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Table 4. Changes of systemic blood pressure influenced by hepatic artery ligation.
etc. Exceptionally, as seen in No. 50, very marked decrease in blood flow was observed within an hour.

IV. STUDY WITH BUBBLE-FLOWMETER

For the determination of the volume of blood flow in the peripheral organs, so many different methods have been used. These, however, can be roughly divided into two, i.e. direct and indirect methods. In the present study, in order to confirm the results obtained by the “Thermostromuhr”, the bubble flowmeter which is rather primitive in principle but fairly accurate, was also used. This flowmeter was used for the first time by Soskin et al. in 1934 for the determination of the volume of
blood flow.

We, as shown in Fig. 15, used a vinyl tube with 5mm of inner diameter, 7mm of external diameter and with 15 cc of inner capacity. This tube was again surrounded with vinyl water jacket. At the distal portion of this tube, i.e. close to the liver, a T-tube was set so that the bubble injected could escape through it. The flowmeter we used was the one of spiral type with one circuit which was believed to be of the least resistance. The tube of this flowmeter was placed on the same level as that of the portal vein. In using this flowmeter particular cares were taken for the following matters; use of anticoagulant drugs, cleanliness of the apparatus and use of water jackets for warming the irrigated blood etc.

1) Method

The volume of blood flow through the portal vein was measured before and after the ligation of three major arteries in normal dogs. Animals were kept away from food for 24 hours before measurement. Under a general anesthesia with intravenous injection of thiopental-sodium, a laparotomy was carried out with right subcostal incision. The portal vein was dissected from the surrounding tissue and the splenic vein was ligated and cut for convenience of the manipulation. Heparin was injected through the mesenteric vein, the portal vein was interrupted transiently, the vinyl tube was inserted and the portal vein was reopened. From the proximal part of the tube approximately 0.1-0.2 cc of air bubble was injected and the time which was required for the bubble to pass between two points of the tube. These two points were previously marked, so as the inner capacity of the tube between these two points to be 15 cc. Thus, the volume of the portal blood flow was calculated.

2) Results

This method was adopted, as previously mentioned, to re-examine the data obtained by the “Thermostromuhr” from the different angle. By this method, the volume of the portal blood flow was determined before and after the ligation of

Table 5. Changes of the portal blood flow before and after ligation of the three major arteries, measured by the Bubble Flow Meter

<table>
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<tr>
<th>Dog No.</th>
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<th>Portal blood flow before ligation cc per 100 grams of liver per min</th>
<th>Portal blood flow after ligation cc per 100 grams of liver per min</th>
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</tbody>
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| Average | 54.9            | 24.57        | 23 23 22 25 24 27 24 20 28                                    | 27 28 24 27 22 24 25 24                                      |
Fig. 16 Changes of the portal blood flow before and after ligation of the three major arteries measured by the Bubble Flow Meter.

In 1949, Riennhoff performed the ligation of the hepatic artery to a patient of liver cirrhosis, and concluded that this procedure was worthwhile to try for the treatment of liver cirrhosis particularly with ascites. In 1951, Berman et al. also reported excellent results of this procedure for the treatment of liver cirrhosis with ascites.

Tsuchiya, in our laboratory, performed the constriction of the hepatic vein in dogs and could produce in them the conditions quite similar to those in human cases of liver cirrhosis. In these animals the common hepatic, gastroduodenal and right gastric arteries were ligated. He made it clear that in dogs which tolerated the procedure and survived for long, the blood pressure of the portal vein markedly decreased. From my study, it was confirmed that when the common hepatic, gastroduodenal and right gastric artery were simultaneously ligated in dogs with ascites, a continuous increase in the volume of the portal blood flow resulted. Also in case of the ligation of the hepatic artery alone, similar increase in the volume of
the portal blood flow, though it was less marked, was observed.

Concerning the mechanisms of the development of ascites, there are many different opinions. Among those, a theory that due to the anomalies of the intrahepatic vascular bed the venous congestion may take place, this, in turn, gives rise to the translation of the liver lymph into the intraabdominal cavity to become ascites, is believed to be most reasonable (RIENHOFF, MADDEN).

In 1873 Gad reported that the blood flow in the hepatic artery slowed down the blood flow in the portal vein, following his experiments on rabbits. In 1907, Herrick advocated that the hepatic artery worked as a resistance upon the portal vein, through his perfusion test on the human liver. Further, he found this was most markedly seen in the cirrhotic liver. In 1928, McIndoe also pointed out that there was a definite relationship between the blood pressure of the hepatic artery and that of the portal vein.

Thus, it can be easily imagined that the ligation of the hepatic artery will be effective in reducing ascites even when we think of only one factor that this procedure can mitigate the congestive state of the liver. In this viewpoint, our experimental data that the hepatic artery ligation resulted in increase in the volume of the portal blood flow, is quite understandable, since in the case of liver cirrhosis with ascites the blood flow of the hepatic artery acts as a more obstacle upon the portal blood flow than in the normal liver.

Thus, we are of the opinion that the increase in the volume of the portal blood flow will serve to improve the liver function of the ascitic dogs with liver cirrhosis.

VI. SUMMARY

In 29 mongrel adult dogs the hepatic veins were constricted and ascites was produced experimentally. In these animals the effects of the ligation of the common hepatic, gastroduodenal and right gastric arteries upon the flow of the portal vein and upon the systemic arterial blood pressure were observed for 30 minutes.

Results obtained were as follows;

1) In dogs whose hepatic vein was constricted and ascites did not develop, the volume of blood flow in the portal vein did not essentially differ from that in normal dogs.

2) In dogs which had ascites after the hepatic vein constriction, on the other hand, the volume of the portal blood flow reduced markedly.

3) The volume of the portal blood flow increased markedly within 1-2 minutes after the hepatic artery ligation either in normal dogs or in dogs which had the hepatic veins ligated.

4) After the hepatic artery ligation in dogs whose hepatic vein had previously been constricted, the most marked and continuous increase of the portal blood flow was obtained in dogs which had ascites and in which the common hepatic, gastroduodenal and right gastric arteries were all ligated, and similar increase was seen, though in the lesser degree, in dogs of same group and in which the common hepatic artery alone was ligated.
5) In dogs of two other groups, i.e. dogs in the control group and those which did not have ascites, the ligation of the hepatic artery was not followed by a significant change in the volume of the portal blood flow.

6) Data obtained with the use of bubble flowmeter were essentially the same as those obtained by "Thermostromuhr".

I do wish to express my deep appreciation to Prof. Dr. CHIYAKO ARAKI for his guidance and for his correcting paper. Also I am greatly indebted to Assistant Prof. Dr. ISHAIO HONIO for his kind and extended directions throughout the period of this experimentation.

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和文抄録
肝硬変症の実験的研究
---特に肝静脈狭帯犬における肝動脈結紮の門脈流に及ぼす影響について---

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最近 Rienhoff, Berman 等が肝硬変症の治療に肝動脈結紮が有功であることを提唱以来、諸家により本法は極めて追試検討されてきたが、いまだ定説を得ない現状である。著者は肝硬変症の場合に、特に腹水の有無と関連して肝動脈結紘が門脈血流に対して如何様に働くかを確かめるため、犬の肝静脈を狭帯し肝硬変類似の状態を作成し、これに肝動脈結紘犬の肝動脈血流通断をおこない、門脈流に対する影響を "Thermostromuhr" 及び Bubble Flowmeter を使用して検査した。

実験動物には7.6kg～15.0kgの雌犬を使用し正常犬、肝静脈狭帯犬で腹水の貯溜をきたさなかった犬及び肝静脈狭帯犬で腹水の貯溜をきたした犬及び肝静脈狭帯犬は腹水の有無にかかわらず肝静脈狭帯後14日目に再開腹し、門脈血流速度測定を実施した。肝静脈狭帯犬の作成には大略教室の土屋が行った方法を採用した。

"Thermostromuhr" 測定装置のうち、検温電対は Herrick 等の使用したものと大差はないが、ベーグライト板には、よりよく血管に接着させるためゴム板を、又血液加温には高温波発生装置を使用した、検温電対の門脈への装着は脛靜脈流入部より肝臓側でおこなった。門脈血流値の判明した検査犬について門脈血流値の測定には犬の剖出門脈片及び同一個体より採集したヘパリン加血液を使用した。全身動脈圧測定には、便宜上股動脈圧を水銀マンメーターで測定した。

実験成績
1）肝動脈結紘後の門脈血流速の変動
肝動脈血流通断には絶肝動脈単独結紘と、三大動脈
（緑肝動脈、胃十二指腸動脈、右胃動脈）同時結紮と
の両者を実施した。

1 正常犬群

緑肝動脈又は三大動脈結紮直後、門脈血流速度は著
明に増加するが5分～20分で結紮前の速度に近づき、
以後徐々に速度は低下する。門脈血流量に換算しても
同様の増減を認めるのは当然で、正常犬の門脈血流量
は平均208cc/分である。

ii 肝静脈狭窄犬で腹水の貯溜をきたさなかった犬群

正常犬群のそれと比較すると肝動脈結紮直後上昇し
た血流速度は結紮前値に戻る迄の時間が延長したり、
又一時結紮前値以下の速度に下降した曲線が再び上昇
する傾向を示す症例もある。この犬群の肝静脈結紮前
の門脈血流量は平均210cc/分である。

iii 肝静脈狭窄犬で腹水の貯溜をきたした犬群

肝動脈結紮後上昇した血流速度は多少の増減はある
が結紮前値で減少することなく、速度増加を示したま
いで推移する。この傾向は三大動脈結紮の場合に特に
著明であった。この犬群の門脈血流量は平均168cc/分
である。

2) 肝動脈結紮後30分間における各犬群の門脈血流
量増減総和について

各大群について肝動脈結紮前門脈血流量に対して結
紮後各分毎の増減量を加減した値を30分間で区切って
総計を求めると、正常犬及び肝静脈狭窄犬で腹水の貯
溜をきたさなかった犬群の緑肝動脈結紮例では負の値
を示し、他方正常犬及び肝静脈狭窄犬で腹水の貯溜を
きたさなかった犬群の3大動脈結紮例、及び肝静脈狭
窄犬で腹水の貯溜をきたした大群では緑肝動脈のみの
結紮例でも、3大動脈結紮例でも共に正の値を示し、
特に肝静脈狭窄犬で腹水の貯溜をきたした犬群の3大
動脈結紮例では30分間に約1000ccの門脈血流量増加を
示す。

3) 全身動脈圧の変動

緑肝動脈のみの結紮でも3大動脈の結紮でも、又正
常犬でも肝静脈狭窄犬でも結紮後1分～2分で10mm
Hg～40mmHg上昇し10分前後持続する。この肝動脈
結紮後の一時的動脈圧上昇と門脈流の一時増加とは
時間的によく一致する。

4) 肝動脈結紮による門脈流変動を長時間観察した
が、結紮後大略1時間前後の血流速度を約8時間保つ
た、その後実験犬の全身衰弱等により漸次減少した。

5) 又肝流量計による検討

正常犬群について3大動脈結紮後門脈血流量を
測定した。測定値は“Thermostromuhr”で測定した
値と大略同様であることを確かめた。