Symposium* on
Factors Circulatory and Respiratory Failure upon
Effects of Hepatic Circulation and Metabolism:
Shock and Hepatic Circulation

Chairman: Dr. Toshio Torii

1. Hepatic Circulation in Hemorrhagic and Anaphylactic Shock
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1. Hepatic Circulation in Hemorrhagic and Anaphylactic Shock†
   Its Bearing on Systemic Circulation

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In recently published papers, the hepatic circulation in hemorrhagic shock has been discussed on various aspects by Heinemann3, Bradley2, Selkurt3,4, Frank5 and others6.

However, the discussion made by those investigators has mainly been confined to the problem of hepatic circulation itself without consideration upon its bearing on the systemic hemodynamic alterations, but arterial pressure alone, which takes place simultaneously and inevitably in any form of shock, and the fact may be accountable for a source of discrepancy in the opinions regarded.

In view of the matter, this study was undertaken to elucidate some problems of the hepatic circulation in hemorrhagic and anaphylactic shock with particular emphasis upon its relation to the systemic hemodynamic events.

Hepatic Circulation in Hemorrhagic Shock

Fifty heparinized dogs were used under intravenous thio-pental sodium anesthesia.

The following are the summarized descriptions of the methods used and the results obtained in this series of experiments.

a) Relation between hepatic blood flow and cardiac output (Fig. 1, Fig. 2, Fig. 3)

By modified Frank's9 method, the hepatic blood flow rate was measured directly with a catheter closely held in a hepatic vein. The determination of cardiac output was made in rapid succession by standard indicator dilution technique with radioactive iodinated serum albumin (RIA).

Fig. 1 illustrates a typical case of hemorrhagic shock indicating the percentile changes in hepatic blood flow and cardiac output.

During initial decline in arterial pressure following hemorrhage, simultaneous and proportional reduction in hepatic blood flow and cardiac output is observed, indicating the fact that the hepatic blood flow in this condition may simply be determined by the status of cardiac

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output. In another experiment, blood reinfusion performed in this stage of shock is capable for complete restoration in arterial pressure, cardiac output and hepatic blood flow, as shown in Fig. 2. Therefore, this stage may be referred to "simple hypotension" characterized by reversible hemodynamics.

During the following stage of sustained hypotension, continuous fall in hepatic blood flow is observed, while cardiac output is apparently stabilized at a reduced level, thus exhibiting a significant difference or "gap" in percentile changes between hepatic blood flow and cardiac output, and, despite no further hemorrhage, the "gap" gradually increases.

In this stage, reinfusion of blood never causes the continuous recovery of hemodynamic alterations nor the recovery of the above-mentioned "gap", and finally the animal dies (Fig. 3). Therefore, this stage could be stated as "irreversible phase" of hemorrhagic shock.

It is of particular interest that the irreversibility of shock appears in close relation to the

Fig. 1. Relationship between hepatic blood flow and cardiac output during hemorrhagic shock.

Fig. 2. Changes in hepatic blood flow and cardiac output before and after blood reinfusion performed at the stage of simple hypotension of hemorrhagic shock.

Fig. 3. Same as in Fig. 2, but reinfusion performed at the irreversible stage of hemorrhagic shock.
Initiation of the gap between hepatic blood flow and cardiac output.

b) Separate determination of hepatic artery and portal vein flow (Fig. 4).

![Graph showing hepatic and femoral artery flow](image)

*INJECTED INTO ASCENDING AORTA*

Fig. 4. Typical indicator dilution curves at a hepatic vein (upper) and femoral artery (lower). RISA was used as an indicator. A. represents concentration peak corresponding to hepatic artery flow and P. to portal vein flow. Arrow indicates the time of indicator injection.

Separation of hepatic artery and portal vein flow was intended by utilizing an indicator dilution method originally described by Ueda. The method was improved in this laboratory, and RISA was used as an indicator with central injection into the ascending aorta. Time-concentration curves were recorded at the hepatic vein and the femoral artery by collecting blood samples through indwelling catheters into respective vessels.

Fig. 4 is a typical curve thus obtained, where two concentration peaks are observed, each corresponding to the hepatic artery (A) and portal vein flow (P) respectively.

However, in almost all the experiments, no clear-cut separation of those two concentration peaks made it difficult to obtain accurate quantification of both flows, despite by the best of our performance. Therefore, the conclusion still remains in suspicion that the ratio of hepatic arterial to portal flow appears essentially not altered throughout the entire course of hemorrhagic shock.

c) Circulation time and circulating blood volume in the splanchnic vascular bed (Fig. 5).

![Graph showing circulatory parameters](image)

Fig. 5. Trends in circulating blood volume and circulation time at splanchnic and systemic circulation before and during hemorrhagic shock.

Splanchnic and systemic circulation time was obtained from the RISA dilution curves as above mentioned. The circulating blood volume in the splanchnic bed and in systemic circulation was calculated by the usual manner, by multiplying the circulation time by the flow in respective circulatory system.

As shown in Fig. 5, splanchnic circulation time is prolonged proportionally to systemic circulation time throughout the stage of simple hypotension and subsequent irreversible phase of shock. As a consequence, the ratio of splanchnic to systemic circulating blood volume re-

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mains essentially unchanged in the former condition. However, in the subsequent irreversible phase, the extreme reduction in circulating blood volume is evident in the splanchnic vascular bed, resulting from the marked decrease in hepatic blood flow.

d) Red cell volume in splanchnic organs (Fig. 6).

The red cell volume in each organ was measured by a dilution method with the injection of $^{32}$P labeled red cells. The details of the method were described in a previous paper published from this laboratory.

![Diagram](image)

**Fig. 6.** Diagrammatic representation of total red cell volume in each organ before and during hemorrhagic shock.

As illustrated in Fig. 6, red cells in the splanchnic organs are markedly reduced at the initial stage of hemorrhage, but, with progress in shock, they again increase, especially in the small intestine, whereas the circulating blood volume remains extremely reduced in the splanchnic bed. The latter phenomenon may be accounted from the pooling of “not circulating blood” in the splanchnic bed.

It is of our opinion that this pooling of the blood may be an important anticipating factor in production of irreversible circulatory failure in shock.

e) Inferior vena caval and portal pressure (Fig. 7).

Inferior vena caval pressure is reduced significantly from the initial stage without the corresponding decline in portal pressure. Moreover,

![Graph](image)

**Fig. 7.** Changes in portal and inferior vena caval pressure during hemorrhagic shock (lower diagram). Arterial pressure, hepatic blood flow and cardiac output are illustrated for comparative purpose (upper and middle diagram).

when “gap” appears between hepatic blood flow and cardiac output, portal pressure tends to rise above the control values, suggesting the increase in vascular resistance in the liver.

f) Splanchnic vascular resistance (Fig. 8).

Vascular resistance was calculated by use of the ordinary method upon pressure-flow relationship. During the stage of simple hypotension, splanchnic vascular resistance increases in parallel with the rise in total peripheral resistance. In the later stage characterized by the
disproportional reduction in hepatic blood flow to cardiac output, splanchnic vascular resistance continues to rise till animal's death, while total peripheral resistance does not significantly increase or occasionally rather decreases.

g) Catecholamines in arterial blood (Fig. 8).
Catecholamines were determined fluorometrically by Bertler's method.

As shown in Fig. 8, the catecholamine concentration in arterial blood continues to rise till animal's death.

It seems justified that this rise in catecholamine concentration may correlate with the increase in splanchnic vascular resistance, and may play a role in producing the pooling of the blood in the splanchnic vascular bed.

h) Splanchnic oxygen utilization (Fig. 9).
Oxygen utilization was calculated by multiplying hepatic blood flow by the difference between arterial and hepatic venous oxygen contents. The oxygen content of blood was determined by oximetric method.

The results are diagrammatically shown in Fig. 9. During the initial stage of hypotension when hepatic blood flow is still maintained above certain extent, the oxygen supply to the liver and intestine may be sustained by the increase in A-V $O_2$ difference. However, when the reduction in hepatic blood flow becomes severe above a limit, the splanchnic oxygen utilization is extremely reduced, because no more compensatory action can be obtained from increase in A-V $O_2$ difference.

Reduced splanchnic oxygen utilization may serve an important factor for initiation of the irreversible state in hemorrhagic shock.

**Hepatic Circulation in Anaphylactic Shock**

In this chapter, the hepatic circulation in anaphylactic shock will be briefly discussed. Regarding to the general consideration of this type of shock, readers are referred to the previ-

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ous communications from this laboratory\(^8,9,10\), where the details of the experimental procedures have also been described.

Dogs were provoked to anaphylaxis by the intravenous injection of horse serum after sensitization. The same procedures as described in hemorrhagic shock were used for evaluation of the changes in hepatic and systemic circulation.

a) Relationship between hepatic blood flow and cardiac output.

As illustrated in Fig. 10, hepatic blood flow varies in parallel with the changes in cardiac output during the almost entire course of anaphylactic shock but a brief period immediately after the provocation. At the latter period, cardiac output is abruptly reduced with simultaneous but more pronounced reduction in hepatic blood flow, so that a "gap" can be observed in percentile changes between those two variables, as seen in the later stage of hemorrhagic shock.

In severe cases, death may occasionally be encountered at this state, however, in most of the cases, hepatic blood flow and cardiac output are gradually restored in the subsequent recovery stage.

b) Other physiological phenomena related to the foregoing events.

Simultaneously with the abrupt reduction in hepatic blood flow, there appears the increase in total peripheral resistance and portal vein pressure with the coincidental decline in inferior vena caval pressure as indicated in Fig. 11. All of those phenomena are probably resulted from the constriction of the hepatic vein sphincters which is said to be the most characteristic feature of the dog anaphylaxis.

The marked increase in arterial catecholamine concentration observed coincidentally with the abrupt decline in arterial pressure may play a role in establishing this sluice mechanism.

Splanchnic oxygen utilization is considerably reduced throughout the 2 hour observation period.

c) Red cell volume in splanchnic organs.

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*Fig. 10. Relationship between hepatic blood flow and cardiac output during anaphylactic shock. Thin solid line: hepatic blood flow, Hatched line: cardiac output.*

*Fig. 11. Trends in total peripheral resistance (middle diagram) and in portal and inferior vena caval pressure (lower diagram) during anaphylactic shock.*
Two hours after the provocation of anaphylactic shock, marked congestion and plasma extravasation are observed in the liver. The latter are particularly concerned with the prognosis of the shock as previously reported.

**COMMENTS**

The significance of the individual changes in hepatic circulation has already been mentioned in the corresponding section.

Accordingly, only general remarks will be given in this chapter regarding the possible importance of hepatic circulation in the shock problem.

As already mentioned, the features of hepatic circulation are mainly determined by the status of systemic circulation, even at the shock state. However, during certain periods of shock, this relation could not be accepted. For example, shortly after provocation of anaphylactic shock or in irreversible phase of hemorrhagic shock, there appears more enhanced reduction in hepatic blood flow than in cardiac output. This fact indicates that, in those periods, hepatic blood flow is no more determined by the status of cardiac output alone, but may mainly be determined by virtue of the vascular resistance in the splanchnic bed.

It is of particular interest that the evidence takes place in such a critical condition as in the period just after the provocation of anaphylaxis or in the irreversible stage of hemorrhagic shock. In the former condition, the increase in hepatic venous resistance may serve a primary importance to establish the circulatory collapse, by eliciting the hepatic sluice mechanism. In the latter condition, though the situation is more complicated, it is certain that the increase in splanchnic vascular resistance is closely related to the irreversible state. Catecholamines may be concerned with the matter, as already discussed.

Because the relationship between hepatic and systemic circulation is somewhat different in the critical and other remaining stage of shock, it is necessary to differentiate those two conditions whenever hepatic circulation is discussed in connection with shock. Some of the controversies seen in the literature may actually be ascribed from the fact that the discussion was made without noticing the above circumstances.

**SUMMARY**

1) Hepatic circulation in hemorrhagic and anaphylactic shock was studied upon dog experiments, with special emphasis on its relation to systemic circulation.

2) The results on hemorrhagic shock are diagrammatically summarized in Fig. 12. During the stage of “simple hypotension”, concomitant changes were observed in the main features of hepatic and systemic circulation, as indicated in the Figure. However, during subsequent irreversible phase, the changes in hepatic circulation were no more in parallel with systemic hemodynamic alterations. In particular, the more pronounced diminution was revealed in hepatic blood flow than in cardiac output with a resultant “gap” between those two variables. This gap seems to be the most characteristic feature of this critical state of shock, and may result from increased splanchnic vascular resistance. Other problems such as the significance of the blood pooling in the splanchnic bed were discussed in connection with the foregoing events.

3) During anaphylactic shock, the features of hepatic circulation varied in parallel with systemic hemodynamic alterations, except at a brief period just after the provocation to shock. At this critical period, hepatic blood flow was reduced pronouncedly with the accompanying but less pronounced diminution in cardiac output, and, there was a sharp rise in portal vein pressure, a marked increase in splanchnic vascular resistance, and a simultaneous fall in inferior vena caval pressure. All of these phenomena may be ascribed to “hepatic sluice mechanism” due to the constriction of the hepatic venous sphincters. Marked congestion and plasma extravasation was observed in the liver.

4) Splanchnic oxygen utilization became significantly impaired, in both types of shock, despite the increased arterio-venous oxygen difference.

5) Catecholamine concentration in arterial blood rised continuously throughout the course of hemorrhagic shock, but it rised temporarily in anaphylactic shock just after the provoking
injection. The possible role of the fact was discussed in connection with its action on splanchic vascular resistance.

The details of the present investigation will be submitted by our collaborators as separate publications.

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2. Hepatic Circulation in the Experimental Allergic Hepatitis†

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In order to clarify the pathogenesis of microcirculatory disturbances in the liver, hepatic changes of the rabbits were examined morphologically in the intravascular antigen-antibody reaction or anaphylaxis.

Based upon the Hamamoto's theory of "Intravascular Antigen-Antibody Reaction", anti-rabbit red cell guinea pig serum were injected intravenously through the hepatic artery and portal vein of rabbits in the reversed anaphylaxis.

In the active anaphylaxis, shock of the liver was induced experimentally by injecting the bovine erythrocytes into the hepatic artery and portal vein of the previously sensitized rabbits. Erythrocytic antigen were chosen as the most suitable antigen to produce intravascular antigen-antibody reaction, and Yoshimi has reported on the histological changes in the liver which were induced by this reversed anaphylaxis, and the those of the active anaphylaxis were described by Shirasu.

The most severe histological changes in these reactions were as follows: a) parenchymal necrotic foci, b) various degree of degeneration of liver cells, c) serous inflammation, d) thrombosis, e) fibrinoid swelling of arterial walls.

No significant changes were found in the control animals.

For the purpose of clarifying the genesis of these parenchymal necrotic foci and degeneration of liver cells, the fibrinoid staining were carried out. In general the thrombi were found in arterioles and sinusoid surrounding of necrotic foci. The fibrin thrombi in these cases are of a special nature and consist of strands of fibrin, in most instances occluding the lumen of the vessels.

It is suggested that the microcirculatory disturbances occur in this part and these intravascular fibrin deposition in hepatic arterioles is responsible for the necrosis and degenerations.

Then, an experiment was made to investigate these microcirculatory disturbances.

The 2% trypan blue solution was injected 3 hours after a single provocative injection of antiserum, when permeable activity of the blood vessel walls had been increased most remarkable

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