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Hemodynamic response to induced septic shock and Effect on Prostacyclin and Steroid

Hiroshi NAKAYAMA

1st Depertment of Surgery

Nagasaki University School of Medicine

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Experimental septic shock was produced by giving a suspension of live Escherichia coli intravenously in dogs, confirming the hemodynamic and the biochemical alternations related to shock.

The effects of prostacyclin (PGI_2) and steroid on hemodynamics in septic shock were evaluated.

In conclusion, it was evident that PGI_2 and/or steroid administration led to an increase in blood flow of the superior mesenteric vein (SMVB) in septic shock in spite of an increase in that of the hepatic artery (HAB) as well as cardiac output (CO) even at short interval. It was defined that tissue perfusion of the liver (HtB) was not improved, reflecting the impairment of microcirculation in the liver although that of the small bowel (SBtB) was raised.

This study, however, lends support to finding that administration of PGI_2 and steroid benefits the liver from protection against liver cell damage, keeping on increasing HAB, SMVB, SBtB, and CO even in short term.

INTRODUCTION

It is known that the prognosis for septic shock is very poor, leading to death in short period. It, however, has become possible to recover temporarily from shock state since great strides in the treatment of circulatory and ventilatory failures in septic shock had been achieved. Consequently it is defined that multiple organ failure (MOF) after recovery from shock follows. An useful therapy for clinical features at the end stage of MOF is not yet established. One must be aware of the fact that functions of the liver and the intestine, which plays a major role in metabolism, energy production and host defence despite marked depression in shock, are directly related to their prognoses.

The aim of this study is to clarify the influence of shock on the intestinal and hepatic

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functions and to verify the validity of PGI_2 and steroid used.

MATERIAL AND METHODS

Twenty-seven adult mongrel dogs, weighing between 10 and 24kg, were used for this study. These dogs were divided into four groups : control group (n=7), E. Coli administration group (n=8), PGI_2 administration group (n=5) and steroid administration group (n=7). The dogs were anesthetized with intraveously administered pentobarbital sodium (30 mg per kg of body weight), intubated and maintained on volume unit ventilator of HARVARD (Model 607) at room air. EKG was prepared for monitering during the experiment. The catheter used for fluid transfusion and drug infusion was introduced to the femoral vein.

Fluid transfusion was maintained at a speed of 5 ml/kg/h of Lactate Ringer solution. CVP was also monitored through the catheter introduced to the external jugular vein and systemic pressure was measured via the femoral artery. A Swan-Ganz catheter was also introduced to the pulmonary artery.

Laparotomy was made to expose the hepatic artery and the superior mesenteric vein. The probes (FB type , ϕ2 to 5 mm) of the electromagnetic flow meter (NIHON-KODEN MFV 2100) were placed on these vessels and the gastroduodenal artery was ligated.

The intrahepatic and intestinal submucosal blood flow was measured with H_2 clearance method using wire electrodes (UNIQUE MEDICAL UHE 201).

Cardiac output (CO) was directly measured by cardiac output computer (Kimray Model PHG 201) through a 5Fr flow directed thermister catheter (Kimray Co.) with use of thermodilution method. The biochemical parameters of GOT, GPT and LDH were also measured. These values were expressed in terms of percent change and Student's T-test was used for statistical analysis and P-values of less than 0.05 were considered to be significant. Hemodynamic changes were carefully observed at a steady state at interval of 15 min until a elapse of 180 min and at interval of 30 min following the 120 min, compared with the control prior to this experiment.

Septic shock model of the dogs was made by intravenous administration of $1.0\sim1.2\times10^{10}$/kg of live Escherichia coli organisms during an hour duration.

PGI_2 (supplied by ONO Drug Co.) was solved with glycin buffer (pH 10) and storaged in ice box. This solution was administered at a speed of 100ng/kg/min for 140 min by

using the infusion pump. Methylpredonisolone (supplied by UPJOHN Drug Co.) was also given at a rate of 30 mg/kg for 15 min.

These drugs were infused at 40 min after occuring septic shock in dogs to elucidate the effects of drugs in shock.

RESULT

Mean systemic pressure was gradually reduced following E. coli administration and it was significant from 60 min to 210 min after giving E. coli, showing a minimum of 66 ± 12 g as shown in Fig 1.

PGI_2 administration also provided low systemic pressure and it showed a significant reduction at 105 to 150 min as compared with that of E. coli administration group. In contrast, it markedly reverted at the end of PGI_2 administration.

Steroid administration was effective to prevent the systemic pressure from reduction by E. coli administration. The systemic pressure was maintained high as compared to that of E. coli group and it was significantly different at 180 min to 300 min in comparison with that of E. coli administration group.

CO increased during 30 min after E. coli administration, reflecting a hyperdynamic state induced by E. coli. Thereafter, it decreased as being a hypodynamic state following 210 min as shown in Fig 2.

By PGI_2 administration, CO was not remarkably influenced as compared with that of E. coli administration group. It, however, had a tendency toward an increase after PGI_2 administration.

Steroid administration was beneficial to avoid reducing the cardiac index and it was possible to raise it during 240 min.

Total peripheral vascular resistance (TPR) was gradually reduced by E. coli administration. Judging from this result, it was a reflection of hyperdynamic state as shown in Fig 3. Thereafter, TPR gradually reduced, demonstrating a conversion of hyper-to hypodynamic state.

In PGI_2 administration group, TPR was much more reduced than that in E. coli administration group. In contrast, it gradually increased after PGI_2 administration.

In steroid administration group, TPR showed almost a similar pattern to that of E. coli administration group. The blood flow of the hepatic artery (HAB) was increased after E. coli administration it was statistically significant at 105 to 300 min after giving E.

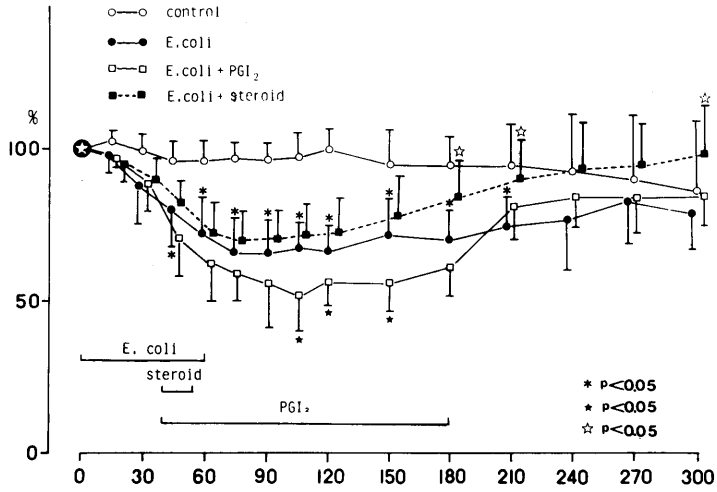

Fig. 1. Changes in mean arterial blood pressure among the four groups.

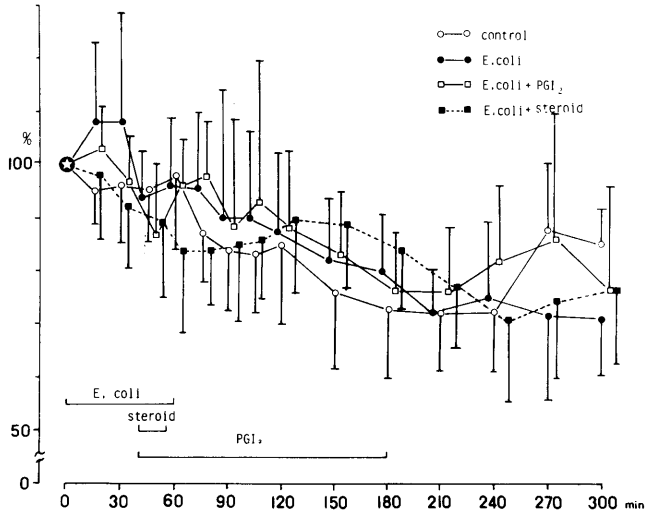

Fig. 2. Changes in cardiac index among the four groups.

coli as compared to the control and showed a maximum of 187 ± 36.

In PGI_2 administration group, HAB increased immediately after PGI_2 administration and it was statistically significant as compared with that of E. coli administration and reached a maximum of 448 ± 196.

In steroid administration, HAB was gradually increased immediately after giving and it was significant at 240 to 300 min after steroid administration. However, an increase in HAB from 133 ± 51 to 221 ± 108 was much slower as compared to that of PGI_2

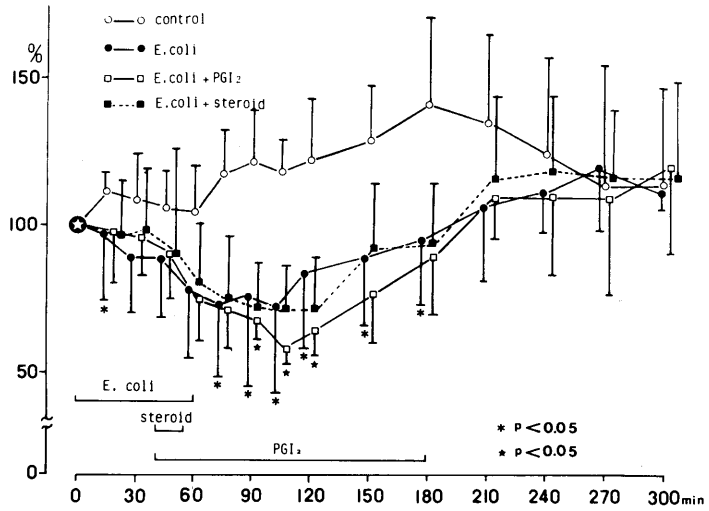

Fig. 3. Changes in total peripheral vascular resistance among the four groups.

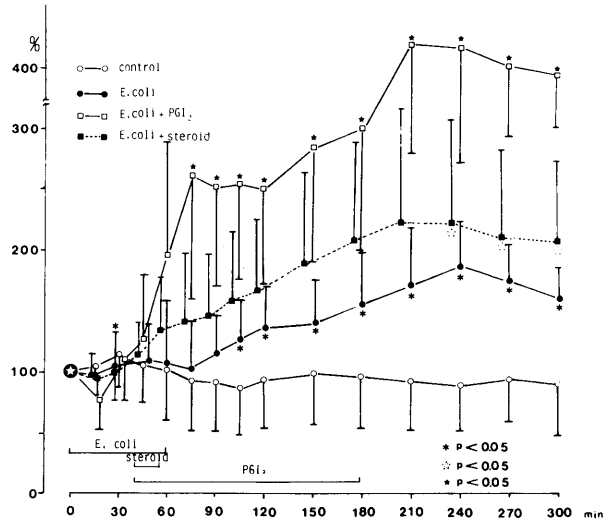

Fig. 4. Changes in hepatic arterial blood flow among the four groups.

administration.

The blood flow of the superior mesenteric vein (SMVB) was decreased 30 min after E. coli administration and it was significant during 180 to 300 min after giving E. coli as shown in Fig 5.

In PGI_2 group SMAB was markedly increased immediately after PGI_2 administration and continued to increase significantly during PGI_2 administration, showing a maximum of 137 $\pm$ 36. In contrast, SMAB was markedly decreased following the end of PGI_2

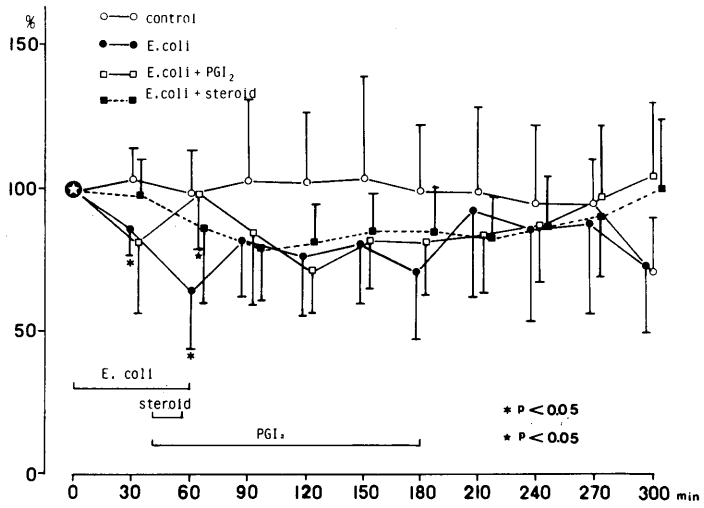

Fig. 5. Changes in blood flow of the superior mesenteric vein among the four groups.

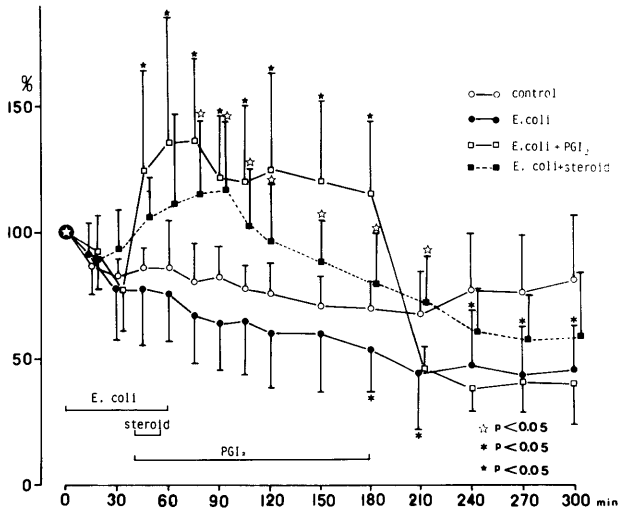

Fig. 6. Changes in tissue blood flow in the liver among the four groups.

administration.

In steroid group, SMVB was increased from 106 ± 19 to 111 ± 33 during a period from immediately after to 90 min and it was significant at 75 to 210 min as compared to E. coli administration. The hepatic tissue blood flow (HtB) was significantly decreased by giving E. coli but after a completion of giving E. coli, HtB was returned to the control level as indicated in Fig 6.

In PGI_2 adminirtsation group, HtB was rapidly returned to the normal, followed by

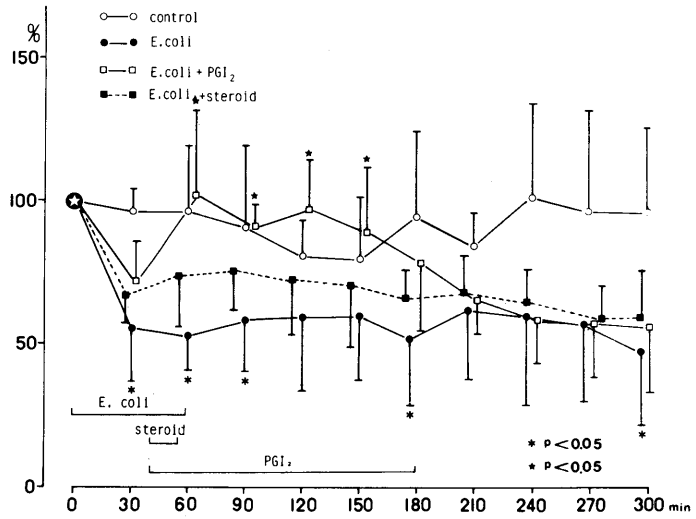

Fig. 7. Chasges in tissue blood flow of the small intestine among the four groups.

Table 1. Biochemical analysis prior to and 300 min after the exteriment.

Parameter	prior to the experiment				after 300 min after			
	control	E.coli	E.coli+PGI_2	E. coli+ Steroid	control	E.coli	E.coli+PGI_2	E.coli+ Steroid
GOT	n=5 33±17	n=6 37±14	n=5 44±16	n=5 50±29	45±14	* 140±87	57±15	* 116± 74
GPT	37±17	56±21	38±15	51±41	93±61	120±97	47±20	49± 30
LDH	118±56	182±56	165±34	180±76	180±68	* 470±30	* 304±101	274±140

*$p<0.05$

an decrease similar to that in E. coli group. An increase in HtB lasted between 180 and 300 min after PGI_2 administration.

In steroid administration group, there was no tendency toward decrease in HtB. Although it showed a similar change to that of E. colil administration group during a period from 90 min after giving steroid to 300 min. Thereafter, it changed into the increase for 300 min.

The tissue blood flow of the small bowel (SBtB) was remarkably reduced immediately after E. coli administration as shown in Fig 7. Thereafter, it was not so great a change, remaining a low level of 48 ± 26 to 61 ± 25. At 30 to 90 min after E. coli administration, a decrease in SBtB was significant as compared to that of the control.

In PGI_2 administration group, SBtB was significantly increased immediately after giving PGI_2 and remained high during a period of PGI_2 administration. When PGI_2

administration was discontinuecd, SBtB was decreased, demonstrating the same changes as E. coli administration group.

In steroid administration group, SBtB was gradually increased immediately after steroid administration. It was not so significant as that in PGI_2 group despite an increase in SBtB as compared to that of E. coli administration group.

On the basis of the results of biochemical evaluation GOT and LDH values represented the tendency toward shifting to deteriorate condition with time after E. coli administration as shown in Table 1. In contrast, GPT values were almost unchanged.

DISCUSSION

It is conceivable that at begining of shock state induced by endotoxin, the host makes a rule to exhibit defensive mechanisms such as raising the body temperature, increasing the cardiac output, and reducing the peripheral vascular resistasce, which is called hyperdynamic state, high flow state and/or warm shock.

On experiment concerning shock induced, the results presented until now raise the question about the animal species and/or the induced way to shock. Effort has been made that shock state similar to being seen in humans can experimentally be produced as reported by HINSHOW (1) with use of small amounts of endotoxin and cultured E. coli organism, by MACLEAN (2) and CLOWES (3) with peritonitis induced by ligation of the bowel and cholecystitis (4) introduced by exogenous bacterial organism and/or directly intravenous infusion.

In the present study, cardiac function and blood flow alterations of the bowel and the liver were evaluated in hyperdynamic shock dogs induced by giving a suspension of E. coli organism intravenously.

It is well known that endotoxin results in blood pooling to the peripheral vascular beds with hypotension and decreased cardiac output. HINSHAW pointed out that target organ in shock differs between various animal species used for shock experiments. It is speculative to say that portal stasis is specific in endotoxic shock in dogs. Evidence has accumulated from studies using different experimental models. The reasons for hypotension in shock is that constriction of the hepatic vein (5), elevation of the pressure of the portal vein, increased bowel weight due to increase in the vascular permeability of the bowel (6, 7), which were brought by shock, allow for a decline of circulatory blood volume.

LILLHEI (8) described that catecholamine plays an important role in reducing the

circulatory blood volume induced by contraction of the capillary and the vein. LEFER (9) and OKADA (10) pointed out the fact that pancreatic blood volume in shock is markedly lowered to one eighth of the normal in addition to activity of MDF released from demaged lysosome membrane of the pancreas.

CUEVAS (11) also postulated that circulating endotoxin causes constriction of the hepatic vein and intrahepatic circulatory failure due to damage to the liver cell, which results in splanchnic pooling.

In view of the intestinal blood flow in shock, MULLER (12) reported that blood flow of the liver remains unchanged in hemorrhagic shock in dogs and SWAN (7) also identified that blood flow of the bowel in shock is different from that in monkeys, the fomer is much more significantly reduced than the later. HINSHAW (13) also described a decrease in the blood presusre an increase in the portal pressure and a decline of the intestinal blood flow in dogs in contrast to a slight increase in the portal pressure and decrease in the intestinal blood on monkeys.

In baboons, it is certified the fact by SWAN (14) that the blood flow of the liver and the mesenterium is not so greatly changed in shock as that of the spleen. RUTHERFOOD (15) reported that in monkeys the blood flow of the kidney, lung and spleen is reduced in shock in contrast to an increase in those of the gastrointestinal tract and liver.

In the present study, TPR was gradually decrease after E. coli administration, showing a hyperdynamic state and 120 min later it began to revert to the previous level.

HAB also increased immediately after E. coli administration and decreased in SMVB as well as in SBtB. A decrease in HtB, however, was in contrast to an increase in HAB and there was no HtB response to an increase in HAB.

This result indicated that microcirculation failure of the liver by intravenous E. coli administration takes place and causes an opening of AV shunt. It, furthermore, seems worthwhile to document that HAB temporarily showed a rapid decrease immediately after E. coli administration, which was preceded by a drop of the systemic pressure, and quickly recovered, reflecting the fact of vasoconstriction of the hepatic artery via sympathetic nerve activity.

Emphasis should also be placed on the fact of autoregulation mechanism related to the portointestinal circulation in which an decrease in SBtB is reflectingly compensated by an increase in HAB.

There are many influential factors on hemodynamics in relation to the ensuing endotoxic shock such as sympathectomic state and/or release of vasoactive amins such as catecholamine, histamine and serotonin, and metabolic products including alteration of

blood coagulation activity. It has become well recognized that PGI_2 discovered in 1976 by VANE and MONCADA has a potent action on the inhibitions of platelete aggregation and of skeletal muscle tension to induce the relaxation. It, however, is unstable and converts into 6-Keto-$PGF_{1\alpha}$, which is chemically stable substance within about 7 min at 37°C and also has the special feature, not loosing an activation during a period of passage through the lung, which is metabolized in the liver as observed in the other kinds of derivates of prostaglandins.

SEELING (16) also cited that PGI_2 plays a key role in inhibition of increasing permeability of the pulmonary vessels and is effective in improvement of circulatory failure in sepsis. It is elucidated that PGI_2 acts as increase in cardiac output as reported by KRAUZ (17), increase in SMA blood flow and reduction release of cathepsin D and MDF as reported by LEFLER (18), promotion of protective activity for the liver damage by stabilization of the lysosomal membrane as described by ARAKI (19), protection of the liver cells from damage by promoting DNA synthesis as proposed by KATO (20).

In this study it is obvious that PGI_2 exerts on vasodilation to increase CO and reduce TPR at the begining of its administration. Consequently HAB and SMVB were markedly increased. Moreover, HAB continued to increase even after its administration and SMVB was gradually reduced in proportion to a decrease in SBtB. Such are assurance of PGI_2 efficacy to improve the intestinal blood flow in contrast to that not to improve the microcirculation failure of the liver caused by the liver cell damage.

SLOTMAN (21) postulated that release of TXB is rapidly increased accompanying high pulmonary artery pressure in septic shock in pigs and a decrease in CO follows since a blood return to the left ventricle is reduced. It is recognized that hypotension well correlates with increasing release of prostacyclin (22) and of TXA_2 and PGI_2 were continuously produced in septic shock in rats (23).

In contrast, OKADA (24) insisted on the aggravating effects of PGI_2, which led to vasodilation and increasing permeability of the vessel walls. The result in this series was not consistent with the above mentioned fact.

Steroid administration is effective in improving the cardiac ejection effect, promoting vasodilation activity as if α-blockers were given and stabilizing of the cell membrane transport (25) and metabolic process leading to the normal (26, 27).

In the present study, antishock effects of steroid was presented on the basis of a result of an increase in HAB and SMVB by administering steroid. It is known that steroid inhibits phospholipase A activity. It is an additive effect of steroid on improving the portointestinal circulation failure in shock.

In endotoxic shock, it is defined that an increase in S-GOT and ALP values represents the integrity of liver damage as reported by RANGEL (28) and also shows the degrees of respiratory failure of mitochondria and damage to the liver cells by endotoxin as described by SAKODA (29) in spite of evidence with ineffectiveness of steroid activity on liver dysfunction in septic shock in the present study.

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