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Experimental Study on the Intestinal and Hepatic Circulation Alteration by Superior Mesenteric Artery Occlusion

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The intestinal and hepatic circulations were experimentally studied on the state of the superior mesenteric artery occlusion (SMAO) in terms of duration of SMAO (30 min, 60 min and 180 min) and effect of PGI_2 administration.

1) In 30 min SMAO, systemic and hepatic hemodynamics were satisfactory sustained during occlusidon of the superior mesenteric artery (SMA) and after releasing. It is suggesive of fair prognosis for a 30 min occlusion of SMA.
2) In 180 min SMAO, the intestinal tissue perfusion, cardiac output (CO) and hepatic arterial blood flow (HAF) were significantly lowered. This is indicating that the prognosis is very poor even though adequate recirculation is established in the longer period of SMAO.
3) To judge as to whether the intestinal perfusion would be adequate or not, the assessment of GOT, GPT, LDH, CPK and CPK patterns was useful. The MM fraction of CPK was most valuable and total CPK increased in proportion to prolongation of SMAO.
4) PGI_2 administration enabled systemic hemodynamics and intestinal tissue perfusion to be adequate. In a 60 min SMAO, it is anticipated that satisfactory prognosis has been obtained by means of better reperfusion and PGI_2 administration. And also it is defined that PGI_2 has not necessarily led to an increase in the hepatic tissue blood flow.

INTRODUCTION

It is difficult to detect and diagnose the disease of SMAO clinically. It is also well known that its prognosis is very poor. With the aging of population in Japan SMAO is now increasing in number, accompanying an increase in heart and arteriosclerotic diseases.

This study was undertaken to clarify the systemic and the intestinal-hepatic circulatory changes after surgical repair of the occluded superior mesenteric artery.

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MATERIAL AND METHOD

Randomly-selected adult mongreel dogs of both sexes weighing 8 to 13kg were anesthetized with 30mg/kg pentobarbital, intubated and ventilated via HARVARD respirator (Model 607) with room air. Fluid transfusion during experiment was given at the rate of 5ml/kg/h of Ringer Lactate.

All animals were divided into three groups: control group of simple laparotomy procedure, ligation group of the superior mesenteric artery (SMA) composed of 30 min SMAO (a 30 min duration of ligation), 60 min SMAO (a 60 min duration of ligation), and 180 min SMAO (a 180 min duration of ligation) respectively. In 60 min SMAO-PGI_2 group, prostaglandin I_2 (PGI_2) prepared in glycin buffer(pH 10) and kept in refrigator (0°C) was given via drip at 30 min after SMAO for 120 min at a rate of 100ng/kg/min.

Enzyme activities of GOT, GPT, LDH, CPK and CPK isoenzyme were measured from blood samples obtained from the femoral vein. Mean systemic arterial pressure (MAP) was also continuously monitored through the catheter introduced to the femoral artery using the transducer and recorder (*NIHON-KODEN*). Cardiac output (CO) was measured by thermodilution method using SWAN-GANTZ catheter. Portal blood flow (PVF) and hepatic arterial blood flow (HAF) were measured by a electromagnetic flow meter(NIHON-KODEN MFV 2100) anchored on the portal vein and the hepatic artery after ligation of the gastroduodenal artery.

The tissue blood flows of the liver and the small intestine were measured at the site 3cm away from the hepatic margin and at the antimesenteric middle portion of the small intestine by H_2 clearance method using tissue flow meter (PHG 201 UNIK CO) under inhalation of H_2 gas (0.5 l /min) for 2 or 3 min and calculated according to Kety' equation as an absolute value of ml/min/100g.

RESULT

The obtained values in the present study were compared with the pre-study value and their alterations were expressed as percentage and analyzed by Student T test. P values of less than 0.05 were considered to be significant.

GOT was slightly elevated but did not significantly varied among the three groups during SMAO and after release of SMAO as shown in Fig. 3.

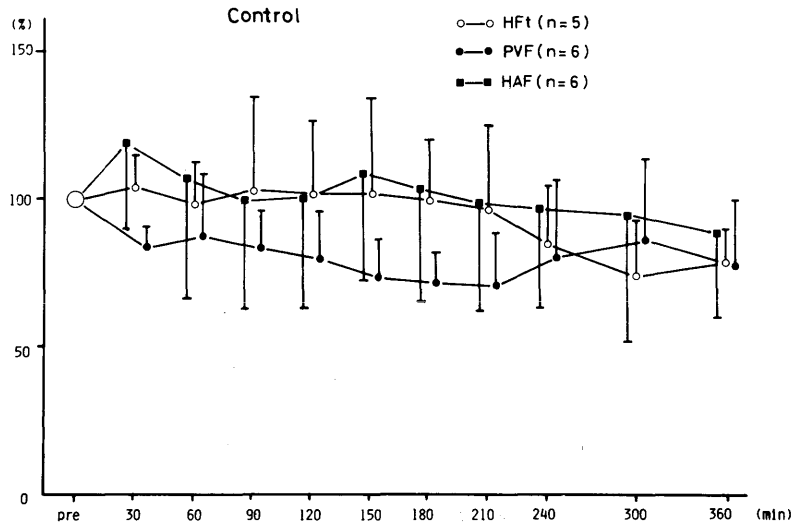

Fig. 1. Changes of the hepatic tissue blood flow (HFt), portal blood flow (PVF), and hepatic arterial blood flow (HAF) of the control group.

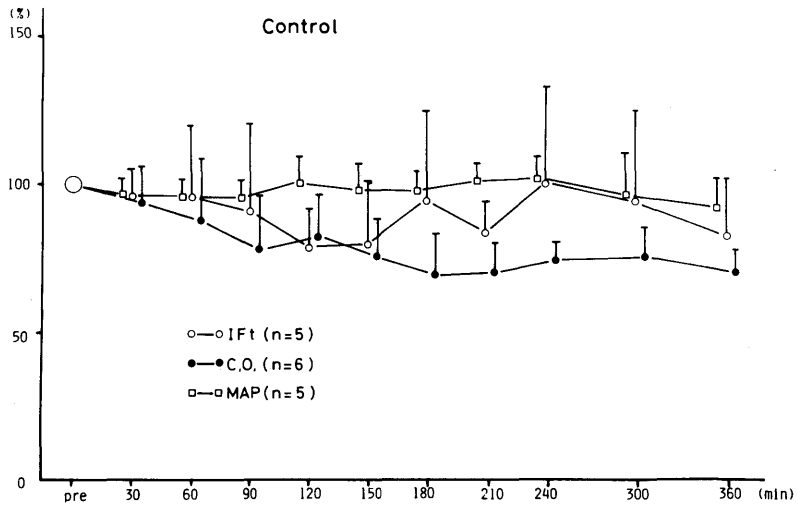

Fig. 2. Changes of the intestinal tissue blood flow (IFt), cardiac output (C. O.) and mean systemic arterial blood pressure (MAP) of the control group.

GPT also did not significantly changed, showing a slight increase, less than GOT as indicated in Fig. 4.

LDH fluctuated within normal range but elongation of SMAO time showed the tendency for LDH to rise as presented in Fig. 5.

Total CPK values were raised after release of SMAO.

These were almost constant in 30 min SMAO group, however, the longer ligation time of SMA, the higher the CPK values. The CPK isoenzyme pattern showed an increase in MM fraction as shown in Fig. 6.

MAP was gradually increased by 13 to 21% immediately after ligation of SMA as compared to that of the pre-study value and showed 95 to 104% values of the pre-study value during ligation. In contrast, MAP immediately after release of SMA ligation was significantly reduced to 83% of the pre-study value in a 30 min SMAO group, 80% in a 60 min SMAO without significant reduction in a 180 min SMAO. Thereafter, MAP in the three groups changed in 80 to 97% of the pre-study value as indicated in Fig. 7.

CO was increased by 3 to 13% of the pre-study value in the three groups immediately after ligation of SMA. There was not statistically significant. It, however, gradually reduced by 5 to 10% after release of SMA ligation. It wa noted that the longer the time of SMAO, the greater CO reduction after release of SMAO as shown in Fig. 8.

PVF was rapidly reduced up to 55 to 65% of the pre-study value following SMAO. The longer duration of SMAO led to significant reduction of PVF during ligation of SMA. The maximum of PVF reduction was observed in 180 min SMAO and reached a 45% reduction as demonstrated in Fig. 9. After releasing SMAO, PVF reverted to the control level in 60 min and 180 min groups despite demonstrating an increase in a 30 min SMAO.

Thereafter, there was not statistically significant difference among the three groups although PVF in a 30 min SMAO much more increased than those in another groups.

HAF was markedly increased immediately after ligation of SMAO and it remained high during SMAO. But at 180 min after ligation it was reduced. After releasing SMAO, it rapidly reduced and manifested in the 180 min SMAO group in relation to prolonged SMAO time as shown in Fig. 10.

The HFt values also kept high level after SMAO procedure as compared to the pre-study value. It, however, decreased to 95% of the pre-study value at 180 min. After releasing SMAO, it rapidly reduced by 85 to 90% and continued to decrease by 75 to 85% with time although not statistically significant as indicated in Fig. 11.

IFt was retured to 70 to 80% after releasing SMAO in the 30 min and the 60 min SMAO groups. In contrast, in the 180 min SMAO group, recovery of IFt remained at 50%

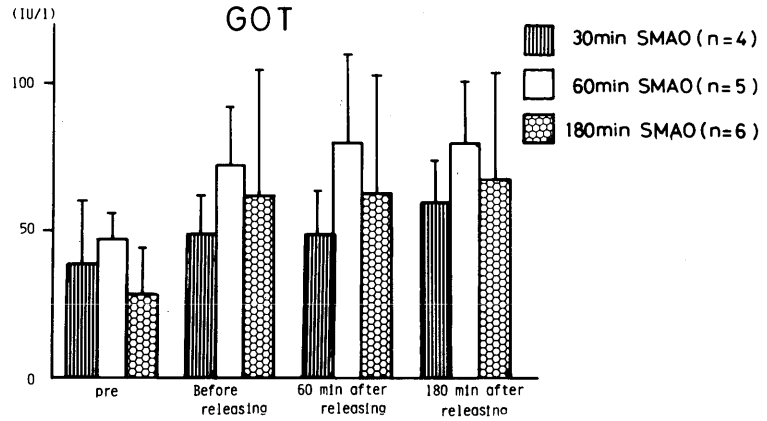

Fig. 3. Changes in the serum glutamic oxalacetic transaminase (GOT) among the three groups.

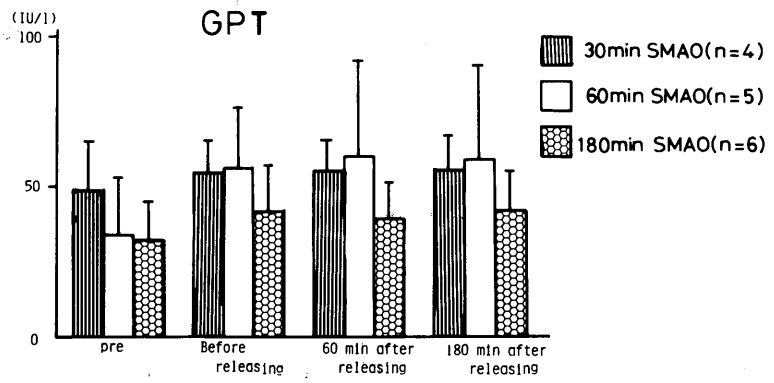

Fig. 4. Changes in the serum glutamic pyruvic transaminase (GPT) among the three groups.

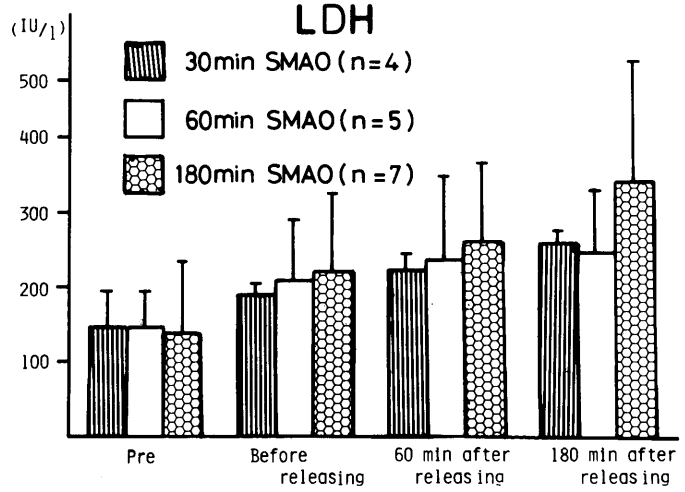

Fig. 5. Changes in the serum lactic dehydrogenase (LDH) among the three groups.

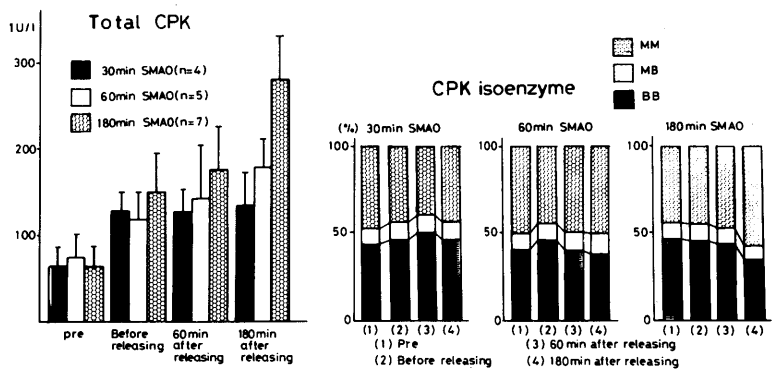

Fig. 6. Changes in the serum total creatine phosphokinase (CPK) and its isoenzemes among the three groups.

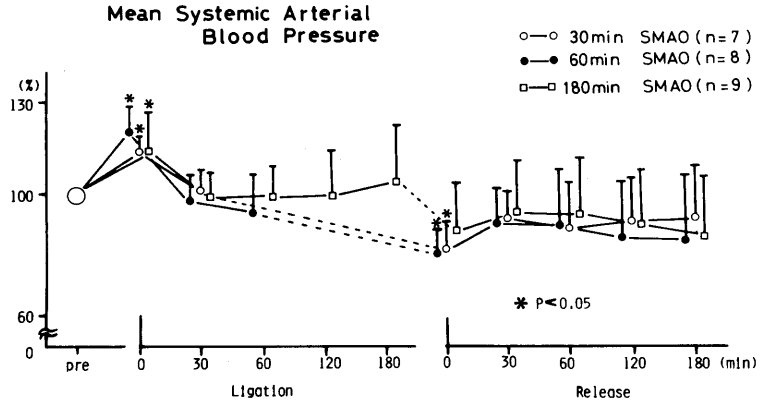

Fig. 7. Changes in the mean systemic arterial blood pressure (MAP) during ligation and after releasing of the superior mesenteric artery among the three groups.

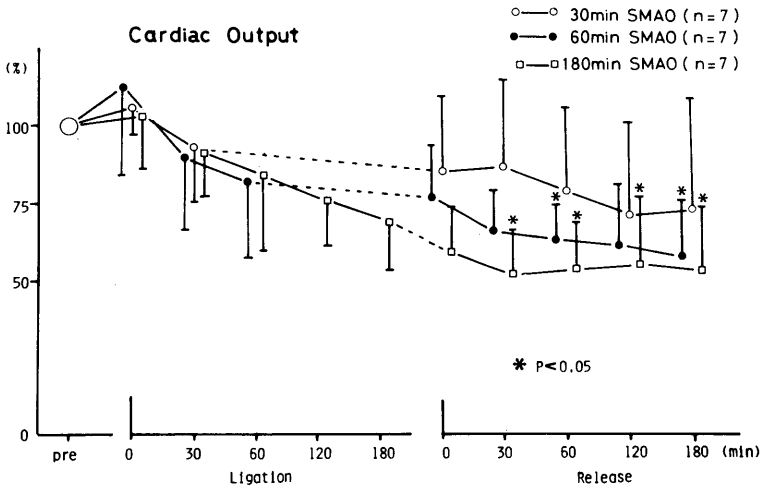

Fig. 8. Changes in the cardiac output (C. O.) during ligation and after releasing of the superior mesenteric artery among the three groups.

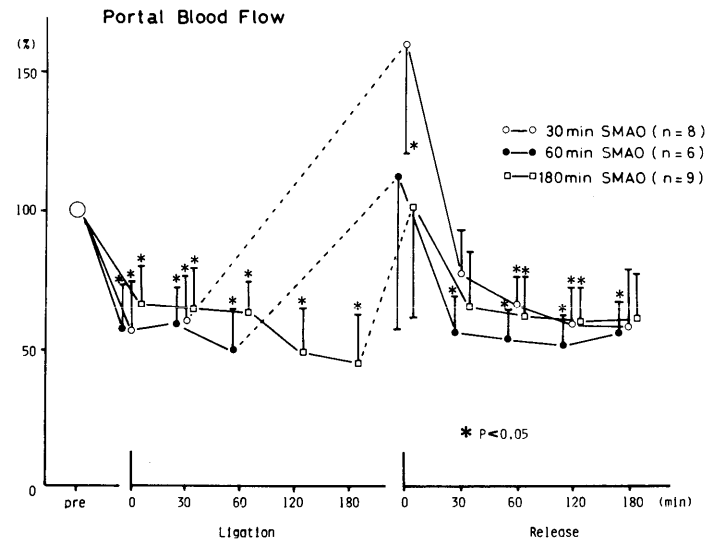

Fig. 9. Changes in the portal blood flow (PVF) during ligation and after releasing of the superior mesenteric artery among the three groups.

of the pre-study value. And then, it varied with a range of 65 to 80% of the pre-study value in a 30 min SMAO (not significant difference). However, it significantly reduced at 60 min SMAO group and immediately after in the 180 min SMAO group respectively. There were statistically significant as shown in Fig. 12.

In the 60 min SMAO-PGI_2 group, MAP showed a 10 to 20% decrease during administration of PGI_2 despite an excessive rise after interruption of administering PGI_2 (Fig. 13). CO also increased by 10% during administration of PGI_2 and showed a 15 to 20% increase after discontinuation of PGI_2 administration (Fig. 14).

HAF increased during SMAO by administration of PGI_2 but there was no significant difference after releasing SMAO in both groups (Fig. 15).

PVF remained high during and after releasing SMAO as long as PGI_2 was given. Such was statistically significant as compared to that in the non-PGI_2 group (Fig. 16).

HFt was lowered during a period of administration of PGI_2. After discontinuation of PGI_2 administration, there was no statistical difference between PGI_2 and non-PGI_2 groups (Fig. 17).

IFt increased during administration of PGI_2. At 180 min after releasing SMAO, IFt was returned to 56% when compared to the pre-study value in the PGI_2 group in contrast to a 25% in the non-PGI_2 group. It was statistically significant.

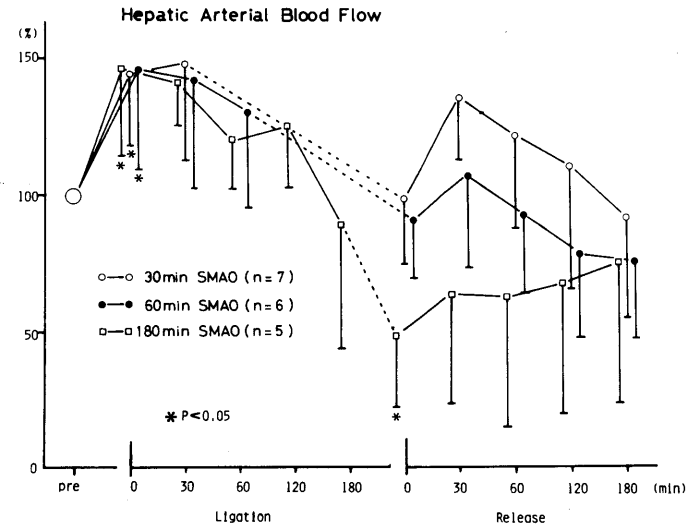

Fig. 10. Changes in the hepatic arterial blood flow (HAF) during ligation and after releasing of the superior mesenteric artery among the three groups.

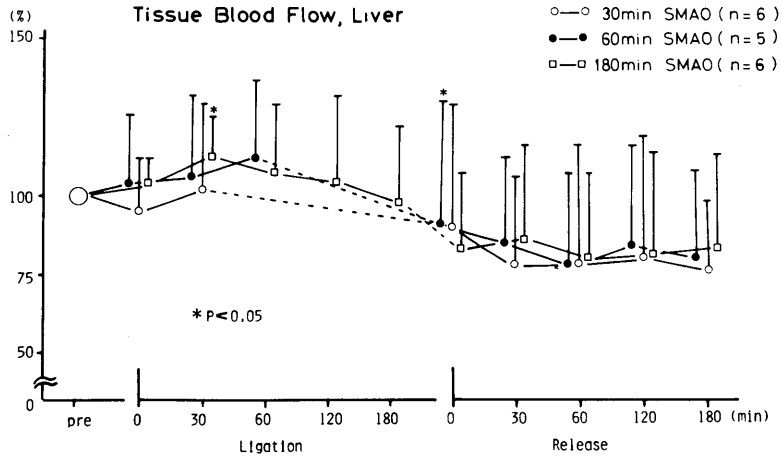

Fig. 11. Changes in the hepatic tissue blood flow (HFt) during ligation and after releasing of the superior mesenteric artery among the three groups.

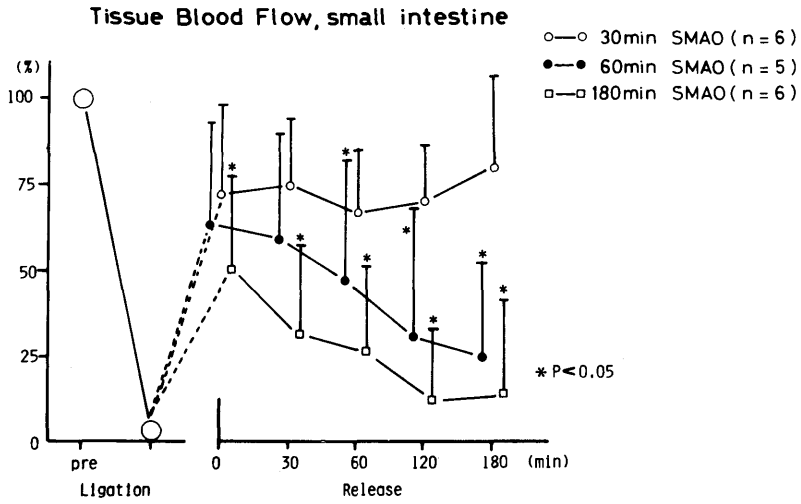

Fig. 12. Changes in the small intestinal tissue blood flow (IFt) after releasing occlusion of the superior mesenteric artery among the three groups.

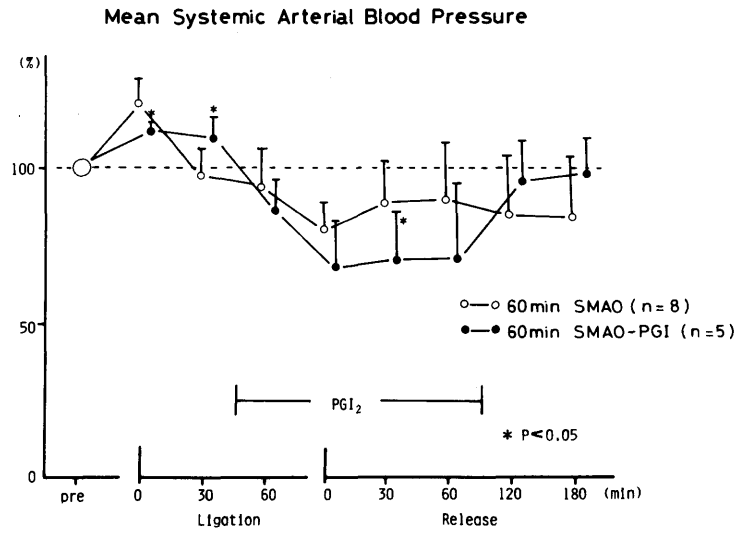

Fig. 13. Changes in the systemic arterial blood pressure (MAP) during ligation and after releasing of the superior mesenteric artery between the two groups.

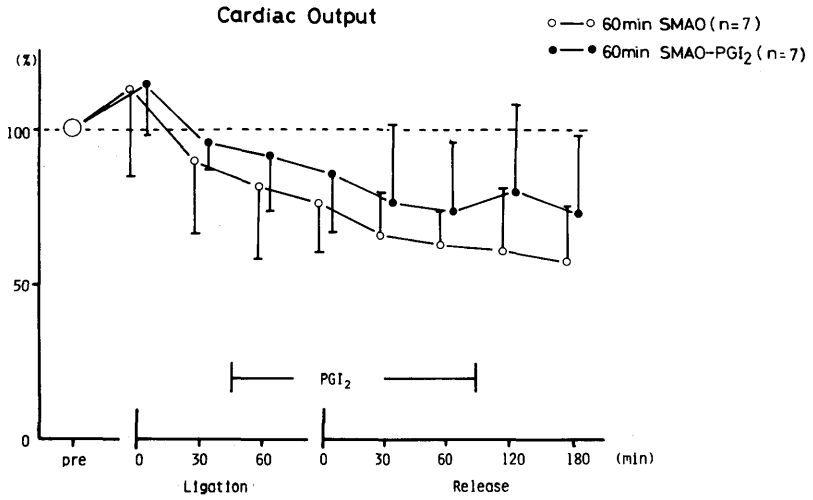

Fig. 14. Changes of the cardiac output (C. O.) during ligation and after releasing in the superior mesenteric artery between the two groups.

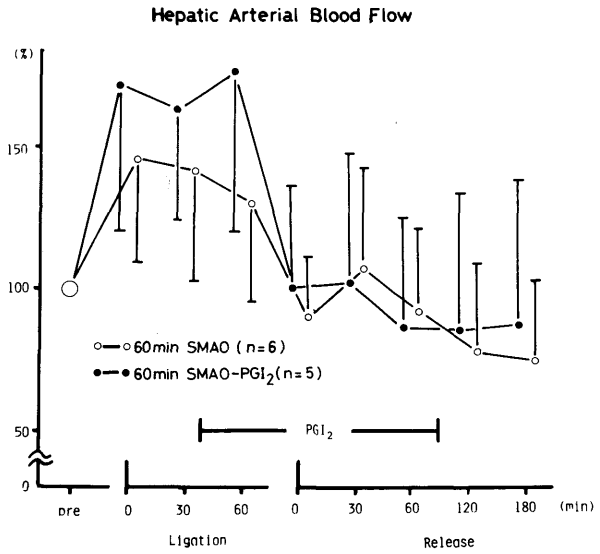

Fig. 15. Changes in the hepatic arterial blood flow (HAF) during ligation and after releasing of the superior mesenteric artery between the two groups.

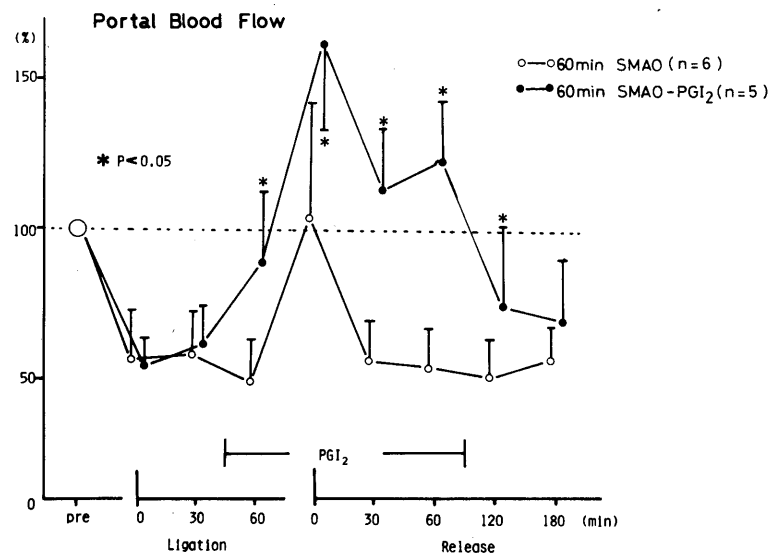

Fig. 16. Changes in the portal blood flow (PVF) during ligation and after releasing of the superior mesenteric artery between the two groups.

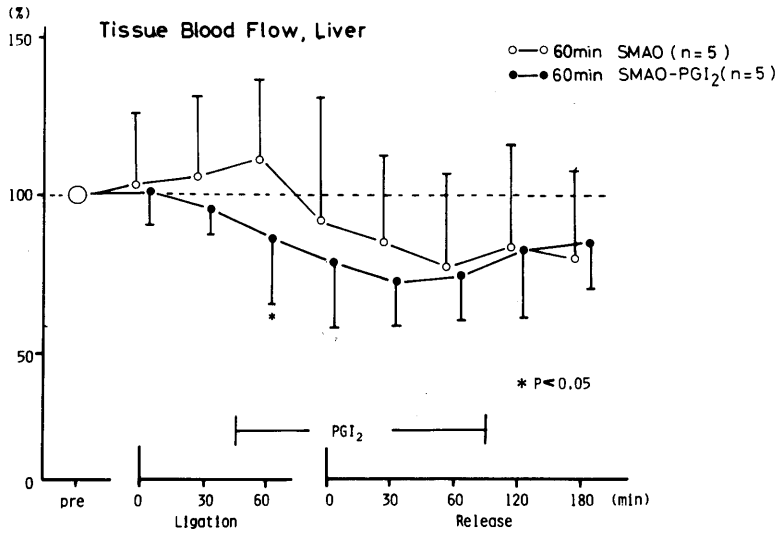

Fig. 17. Changes in the hepatic tissue bloed flow (HFt) during ligation and after releasing of the superior mesenteric artery between the two groups.

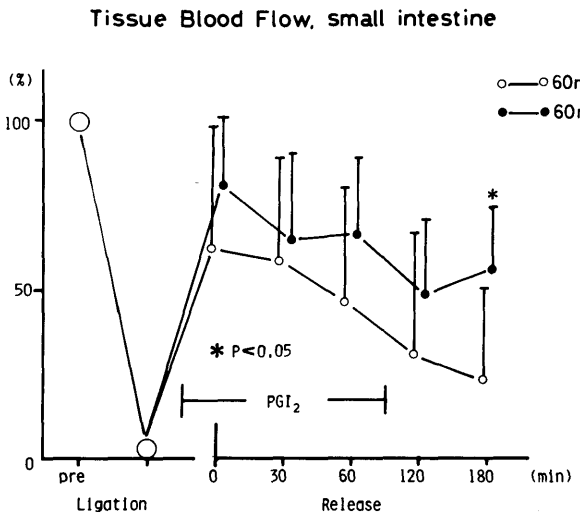

Fig. 18. Changes in the small intestinal tissue blood flow (IFt) after releasing occlusion of the superior mesenteric artery between the two groups.

DISCUSSION

It is well known that the intestinal blood flow corresponds to 30% of cardiac output and it is regulating by neural, humoral and hormonal factors[1]. And it is said that the blood flow in the small bowel coincides with 60% of the portal blood flow[2]. Severe systemic and portal circulatory failures ensue when the intestinal blood flow has become impaired.

Furthermore, recent data imply that the interruption of the blood flow to the superior mesenteric artery results in the release of endotoxin which occurs in a frequency of 90%[3]. It is taken into consideration that the impaired barrier function of the intestinal mucosa due to ischemia is a major factor to release endotoxin in addition to hypofunction of the reticuloendothelial system which produces the reticuloendothelial depressing substance (RDS)[4]. In general, the pancreas is more vulnerable to various shocks, not only endotoxic but also hemorrhagic and arfonad-induced shocks.[5] It is not infrequently noted that the blood flow of the pancreas was markedly reduced in shock.[6]

LEFER detected one of peptide releasing from the pancreas in shock and designated it myocardial depressant factor (MDF).

It is assumed that MDF acts as depressant of myocardial contraction in the heart and phagocytic activity in the reticuloendothelial system even when SMAO takes place.

In the present study, elevated MAP and increased CO during SMAO and/or reduced MAP and decreased CO after releasing SMAO were shown in shock, reflecting such a rapid hemodynamic changes.

During SMAO, CO gradually decreased in spite of showing high MAP. It is presumed that endotoxin released into blood helps increase the peripheral vascular resistance and inhibite the myocardial contraction.

After releasing SMAO, CO fairly returned to the control level in the 30 min SMAO group. In contrast, that in a 180 min SMAO was significantly lowered. It is a reflection of apparent vascular contraction and potent myocardial depression in the 180 min SMAO group rather than in the 30 min SMAO group. One felt confident that ominous hemodynamic responses to endotoxin were attributable to poor prognosis due to hypoperfusion to the vital organs.

To our knowledge, it is more likely that vital organs especially the liver necessitate better perfusion to keep the function satisfactory in shock.

It is of interest to note that the mechanisms of improved blood flow into the liver in shock are attributed to the genesis of increased blood flow of the hepatic artery[5)9)10)] and increased PVF/HAF ratio regardless of hypo-and hyperdynamic states caused by endotoxin[11)]. In the present study it is certain that improved hepatic blood flow is mainly based on increased HAF despite reduction of PVF.

It, however, is shown that in the 180 min SMAO group autoregulation mechanism of increasing PVF become inactive in addition to decrease in HAF.

After releasing SMAO, long-term interruption of SMA blood flow as seen in the 180 min SMAO group no longer regulates a fall of PVF so as to increase the hepatic blood flow in contrast to that in the 30 min SMAO group.

The PVF/HAF ratio, which is one of the most important factors to regluate hepatic blood flow, is infulenced by the hepatic artery itself, the degree of intrahepatic blood pooling, the vasodilator substance to the portal vein which may generate in situ,[12)] autoregulation mechanism inherent to the mesenterium[13)] and so on.

It is known that HFt in endotoxic shock is reduced by 20%.[11)] SAKODA[14)] also postulated that the hepatic tissue PO_2 is markedly decrease even at hyperdynamic state in which total hepatic blood flow is not reduced. The reason is that the intrahepatic A-V shunt is to be broaded. However, it is not suggestive of this fact in this study.

It is well known that A-V shunt also exist in submucosal plane of the gut[15)] as experimentally indicated by NUMATA.[16)]

In comparison of PVF and IFt between 30 min and 180 min SMAO groups, signifi-

cant difference between the two groups was noted in IFt in spite of no difference in PVF. This result seems to indicate that A-V shunt in the bowel and mesenterium is well functioning.

In 1976, VANE[17] discovered PGI_2 which is generated from the endothelial cells of the vessel and share some activities on antiaggregation of platelet, vasodilation, lysis of platelet aggregation[18][19] and cytoprotection of the heart.[20]

In the present study, PGI_2 activity was tested on condition that production of PGI_2 from the damaged endothelial cells of the vessel due to ischemia had been impeded.[21]

In the SMAO experiment, administration of PGI_2 was effective in lowering MAP, probably due to relaxation of the smooth muscle of the vessel wall within 10 min before metabolized to 6-Keto $PGF_{1\alpha}$[22] and CO also increased even after discontinuation of PGI_2 administration. It is a reflection of PGI_2 activity on peripheral vasodilation and myocardial cytoprotection. It is noted that the vasodilation activity of PGI_2 is not potent in the abdominal organ vessels[23] and different at the sites of the tributary vessels.[24] In this study, the hepatic arterial blood flow was not necessarily increased by PGI_2 administration during and after releasing SMAO. In contrast, PVF was significantly increased by PGI_2 administration. It is presumed that development of collateral blood flow is induced in addition to prevention from occurence of vasospasm and thrombus formation.

PVF was rapidly dropped after discontinuation of PGI_2 administration despite not remarkable changes in IFt and CO.

It is due to varying variety of development of collateral circulation. During administration of PGI_2, changes in PVF correlated well with those in HAF, showing the sustained satisfactory autoregulation mechanism of hepatic circulation.

HFt was lowered during PGI_2 administration as compared with that during non PGI_2 administration. It means that shunt effect in the presinusoid may be associated and PGI_2 administration is not beneficial to increase an effective hepatic blood flow.

It is defined that changes in GOT, GPT and LDH values reflect circulatory failure of the bowel.[25] In this study the sensitivity of the indices to slight ischemic damage to the bowel was GOT, GPT and LDH in the order. The changes in CPK and CPK isozyme pattern, MM fraction, correlated well with prolongation of SMAO time as reported by GEOFFREY.[26] It is defined that the smooth muscle contained MM, MB and BB fractions especially large amounts of BB. It is natural to consider that high BB may be dected when ischemic necrosis in the intestine occures. Of interest is the fact that half life of BB fraction is too short to detect it when the intestinal necrosis takes place. Consequently it is emphasized that an increase in MM fraction become evident.[26]

The measurement of BB fraction may help acertain a presence of the intestinal ischemia,[27] recognize a satisfactory resection on the basis of a result of BB disappearance after performance of surgery for the intestinal ischemia.[28] And it benefits from judgement of viability of the gut as well as diagnosis of SMAO.

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REFERENCES

1) GRANGER, D. N., RICHARDSON, P. D., KVIETYS, P. R., *et al.*: Intestinal blood flow. *Gastroenterology*, **78**: 837-863, 1980.
2) LUNDGREN, O.: Blood flow distribution and countercurrent exchange in the small intestine. *Acta Physiol. Scand. Suppl.* **303**: 1-42, 1968.
3) S. TAMAKUMA, M. D., R. ROJAS-CORONA, M. D., P. CUEVAS, M. D., *et al.*: Demonstration of a lethal endotoxemia of intestinal origin in refractory non-septic shock. *Annals of Surgery*, **173**: 219-224, 1971.
4) BLATTBERG, B., LEVY, M. N.: Detection of reticuloendotherial depressing substance in shock. *Am. J. Physiol.* **209**: 71-74, 1965.
5) I. KOSUGI, *et al.*: Sequential changes in the fractional distribution of cardiac output during hypotension induced by Arfonad in dogs. *Clinical Physiol* **3**: 613-619, 1973.
6) LEFER, A. M., GLENN, T. M.: Role of the pancreas in the pathogenesis of circulatory shock. *Adv. Exp. Med. Biol.* **23**: 311-335, 1971.
7) LEFER, A. M., GRADDOCK, G. B., COWGILL, R., *et al.*: Performance of papillary muscles isolated from cats in postoligemic shock. *Am. J. Physiol.* **211**: 687-692, 1966.
8) LEFER, A. M., BARENHOLZ, Y.: Pancreatic hydrolases and the formation of a myocardial depressant factor in shock. *Am. J. Physiol.* **223**: 1103-1109, 1972.
9) MULLER, W., SMITH, L. L.: Hepatic circulatory changes following endotoxin shock in the dog. *Am. J. Physiol.* **204**: 641-644, 1963.
10) GREENWAY, C. V., STARK, R. D.: Hepatic vascular bed. *Physiol. Rev.* **51**: 23-65, 1971.
11) M. TERANAKA, M. D.: Experimental studies on studies on liver circulation and function in shock state. *J. of Japan Surg. Society.* **79**: 216-230, 1978.
12) WAALKES, T. P., WEISSBACH, H., BOZICEVICH, J., *et al.*: Serotonin and histamine release during anaphylaxis in the rabbit. *J. Clin. Invest.* **36**: 1115-1120, 1957.
13) JOHNSON, P. C., INTAGLIETTA, M.: Contributions of pressure and flow sensitivity to autoregulation in mesenteric arterioles. *Am. J. Physiol.* **231**: 1686-1698, 1976.
14) K. SAKODA, H. GRAFELMANN, R. SCHOSSER, *et al.*: Pathophysiology of endotoxin shock in

hyperdynamic state. *J. of Japan Surg. Society*. 82 : 702-707, 1981.

15) SCHNITZLEIN, H. N. : Regulation of blood flow through the stomach of the rat. *Anat. Rec.* 127 : 735-748, 1957.

16) M. NUMATA. Hemodynamics of splanchnic organs during and after hypotension induced by endotoxin. *J. of Japanese College of Angiology*. 25 : 511-515, 1985.

17) S. MONCADA, R. GRYGLEWSKI, J. R. VANE, *et al.* : An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 263 : 663-665, 1976.

18) SINZINGER, H., FEIGL, W., SILBERBAUER, K. Prostacyclin generation in atherosclerotic arteries. *Lancet* 2 : 469, 1979.

19) S. MONCADA, M. D., J. R. VANE, M. D : Arachidonic and metabolites and the interactions between platelets and bloodmetabolites and bloodmetaboites and the interactions between platelets and the interactions between platelets and bloodvessel walls. *New Engl. J. Med*. 300 : 1142-1147, 1979.

20) ARAKI, H., LEFER, A. M. : Cytoprotective actions of prostacyclin during hypoxia in the isolated perfused cat liver. *Amer. J. Physiol*. 238 : 176-181, 1980.

21) S. MUROTA. : Thromboxanes and prostacyclin. *Proc. Symp. Wakan-Yaku* 14 : 136-144, 1981.

22) T. OZAWA., S. SUGIYAMA. : Biochemistry of prostacyclin. *Respiration and Circulation*. 33 : 839-844, 1985.

23) A. KUSABA. : Prostacyclin therapy for peripheral artery disease. *Respiration and Circulation*. 33 : 871-876, 1985.

24) ELLIS, E.F., WEI, E. P., KONTOS, H.A. : Vasodilation of cerebral arterioles by prostaglandins D, E, G and I. *Am. J. Physiol*. 237 : 381-385, 1979.

25) Y. TSUJI., T. SHIMOYAMA., T. KUGIMIYA. : Mesenteric vascular occlusion. *The Japanese Journal of Acute Medicine*. 5 : 749-756, 1981.

26) GEOFFREY, M.G., PATRICK, J. C., MICHAEL, J. R. : Changes in serum total creatine phosphokinase and its isoenzymes caused by experimental ligation at the superior mesenteric artery. *Ann. Surg*. 193 : 499-505, 1981.

27) M. ITANO, M. D. : The detection of CPK (BB) in serum. *Am. J. Clin. Pathol*. 65 : 351-355, 1976.

28) DORAN, G. M. : Appearance of creatine kinase BB isoenzyme in the serum of a patient suffering from infarction of the colon. *Clin. Chem. Acta*. 92 : 415-419, 1979.