**EFFECT OF ISOSORBIDE DINITRATE ON GASTRIC BLOOD FLOW
IN RATS WITH LIVER CIRRHOSIS DETERMINED
BY ANALYZING GASTRIC BLOOD FLOW,
PORTAL VEIN PRESSURE AND BLOOD GAS**

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Abstract: We investigated the effects of isosorbide dinitrate (IDN) on gastric blood flow (GBF), portal venous pressure (PVP) and blood gas of rats with liver cirrhosis (LC) accompanied by portal hypertension. Thirty male Wistar rats (LC in 17 and normal in 13) were used. Before and after IDN administration, GBF, PVP and blood gas in the femoral artery and portal vein were measured. Portal blood oxygen concentration was estimated by calculating the ratio of PO_2 in portal blood and that in arterial blood ($PpvO_2/PaO_2$) of each rat. The GBF in the LC rats was significantly lower than that in the normal rats. In the LC group, IDN administration significantly increased the GBF. The $PpvO_2/PaO_2$ value in the group with LC was significantly lower after IDN administration than that before IDN administration. In the investigation whether changes in PVP or Ppv/PaO_2 contributed more to the change in GBF after IDN administration, a significant correlation was found between rates of change in GBF and $PpvO_2/PaO_2$ were significantly correlated ($r = -0.733$, $p < 0.05$). The effect of IDN on changes in the stomach accompanying portal hypertension is mainly attributable to a decrease in preload, which suppresses inflow to the stomach, as reflected by a decrease in $PpvO_2/PaO_2$, rather than to a decrease in afterload on GBF, as reflected by a decrease in PVP.

Key words: Portal hypertension, Portal hypertensive gastropathy, Isosorbide dinitrate

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INTRODUCTION

Portal hypertensive gastropathy (PHG), first reported by McCormack *et al.* in 1985¹⁾, is now recognized as a distinct entity accompanying liver cirrhosis^{2,3)}. These lesions are characterized histologically by marked dilatation of the mucosal and submucosal vessels in the stomach⁴⁻⁶⁾. Whether these changes are the consequence of passive congestion induced by obstruction of gastric venous outflow or by increased gastric blood perfusion remains controversial⁷⁻¹⁰⁾. PHG causes gastric hemorrhage with frequency of approximately 30% in all upper gastrointestinal hemorrhage in patients with portal hypertension¹¹⁻¹⁵⁾. Endoscopic treatment for hemorrhage because of PHG is generally difficult because of the diffuse exudation of blood from the gastric mucosa^{16,17)}. Therefore, propranolol, somatostatin, octreotide and isosorbide dinitrate are usually used for treatment¹⁸⁻²³⁾. Organic nitrates have vasodilation actions^{24,25)}. Some vasodilators generate nitric oxide in a nonenzymic reaction with cysteine²⁶⁾. The consequent reduction in portal pressure seems to be associated with a reduction in arterial pressure and an increased heart rate. Nitrates might induce venodilation that engenders baroreceptor-mediated splanchnic vasoconstriction, a sympathetic response to vasodilation and venous pooling. The efficacies of both vasoconstrictors and vasodilators for treatment of PHG have been described^{18,23,27,28)}. However, the efficacy of organic nitrates for treatment of PHG and the mechanisms by which organic nitrates influence gastric blood flow (GBF) remain controversial.

In portal hypertension, the amount of oxygen partial pressure (PO_2) in portal blood (PpvO_2) increases because of systemic hyperdynamic circulation²⁹⁾. For that reason, the hyperdynamic state is thought to influence the pathogenesis of PHG. We speculated that PpvO_2 and portal venous pressure (PVP) respectively represent preload and afterload of gastric circulation. From this viewpoint, to address the mechanism by which organic nitrates affect PHG, we investigated effects of isosorbide dinitrate (IDN) on GBF, portal venous pressure (PVP) and PO_2 in arterial (PaO_2) blood and portal (PpvO_2) blood of rats with liver cirrhosis accompanied by portal hypertension.

MATERIALS AND METHODS

1. *Animals*

Thirty male Wistar rats aged 12 weeks or older and weighing 200–350 g were housed in an environment maintained at 22–23°C and 50–60% humidity and given food and water *ad libitum*. All experimental procedures in this study were conducted in accordance with standard procedures indicated in the Guide for Care and Use of Laboratory Animals published by the National Institutes of Health (NIH 86-23, revised 1985). This study was approved by the approval board of experimental

animal center in Fukushima Medical University.

2. *Induction of liver cirrhosis in rats*

Nodule formation and fibrotic changes in rats with liver cirrhosis induced by thioacetamide are more histologically remarkable than those induced by CCl_4 ³⁰⁾. Therefore, we induced liver cirrhosis in rats using three intraperitoneal injections of thioacetamide at a dose of 0.2 mg/g body weight per week for 8 weeks³¹⁾.

The rats were examined 3 months after the end of thioacetamide administration. Liver cirrhosis was confirmed by histological examination of Elastica Masson-stained hepatic tissue obtained by laparotomy.

To confirm changes in the gastric mucosa accompanying portal hypertension, the gastric wall was resected after completion of the experiments, stained with hematoxylin-eosin, and examined histologically.

3. *Experimental protocol*

The 30 rats, 17 and 13 rats with and without liver cirrhosis, respectively, were weighed in a fasting state and anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg body weight; 5.0% Nembutal injection; Dainippon Pharmaceutical Co. Ltd., Tokyo) for surgery. Sodium pentobarbital has the same hemodynamic effects in thioacetamide-induced cirrhotic rats as in controls³²⁾. Portal vein pressure, GBF and blood gases (portal vein: PpvO_2 , artery: PaO_2) were analyzed before and after administration of IDN to the anesthetized rats.

1) PVP measurement

After a middle abdominal incision, the portal vein was freed from surrounding tissue. A 24-gauge intravenous indwelling needle (Top Co. Ltd., Tokyo, Japan) was inserted into the portal vein near its point of confluence with the superior mesenteric vein; the plastic needle tip was positioned and fastened in the portal vein. The needle was connected to a water-filled glass tube used to measure portal blood pressure (Manometer tray; Toray Co. Ltd., Tokyo). The height of the portal vein reference point was set as the height of the hepatic hilus; the PVP was measured as water column pressure³³⁾.

2) GBF measurement

We used a laser Doppler flowmeter (ALF21R; Advance Co., Tokyo) to validate and estimate GBF^{34,35)}. Laser Doppler signals (ml/min/100 g) are useful to estimate GBF by integrating red blood cell contents and velocity. The principles governing the blood-flow measurements using laser Doppler are the following. A semiconductor laser probe has optical fibers. Only back-scattered light from moving red blood cells undergoes a shift in frequency. The nature of the Doppler shift from an illuminated tissue is dependent on the velocity and the number of moving red blood cells³⁶⁾. Scattered light is gathered from a 1-mm-wide and 1-3-mm-deep region.

After incising the abdomen, the greater omentum was carefully folded back and the laser Doppler probe was spread over as much of the serosa of the anterior wall of the lower corpus of the stomach as possible. Therefore, contact pressure between the serosa and probe was minimized and did not affect gastric blood flow. The output signal from the flowmeter was printed on a recorder. The GBF value was taken as the average of three measurements conducted when the output signal had become stable without motion artifacts for over 15 seconds. These measurements were taken at the corpus of the stomach because the blood flow was rich and the measured value was stable.

The measuring depth of the laser Doppler flowmeter is thought to correspond to the entire thickness of the gastric wall; the mucosal blood flow accounts for approximately 80% of the total gastric blood flow³⁷⁾. Consequently, GBF measured at serosa in this study was considered to accurately reflect gastric mucosal blood flow.

3) Blood gas analysis

After anesthetizing the rats, a small incision was made in the right or left femoral area, and the femoral artery was exposed. Before and after IDN administration, 0.8 ml of blood was collected from the femoral artery and from the portal vein to analyze PO_2 using a blood gas analyzer (ABL-330; Radiometer Trading KK). These procedures were performed after measuring PVP and GBF so as not to affect blood volume by sampling. Results showed that $PpvO_2$ differed from PaO_2 , which was affected by anesthesia and other manipulations. Therefore, portal blood oxygen concentration was estimated by calculating the ratio of PO_2 in portal blood and that in arterial blood ($PpvO_2/PaO_2$) of each rat.

4) Administration of isosorbide dinitrate (IDN)

Under anesthesia, a small incision was made on the right or left femoral area of each rat, and IDN (1.0% nitrol injection; Eisai Co. Ltd., Tokyo) was injected slowly into the exposed femoral vein at a dose of $50 \mu\text{g/kg}$. This dosage was decided referring to literatures^{38,39)}, on the basis of diameter of portal vein and related arteriovenous vessels in rat.

5) Measurements of PVP, GBF and blood gas analysis

Changes in PVP, GBF and $PpvO_2/PaO_2$ caused by IDN were investigated in rats with and without liver cirrhosis. Before IDN administration, PVP and GBF were measured as described above. Then, 0.8 ml of blood was collected from the femoral artery and from the portal vein for blood gas analysis. After administration, PVP and GBF were measured at 1, 3, 5, 7 and 10 min. At 12 min after administration, 0.8 ml of blood was drawn from the femoral artery and from the portal vein; then blood gases were analyzed.

4. Statistical analysis

The results are presented as means $\pm$ SDs. The Mann-Whitney U test for unpaired data was used to compare differences of the group means. Spearman's

Figure 1. Macroscopic findings showed roughness on the liver surface, dilation of the portal vein, and prominent development of collateral veins. These findings indicated liver cirrhosis with portal hypertension.

Table 1. Comparison of the portal vein pressure (PVP) and gastric blood flow (GBF) values between liver cirrhosis (LC) rats and normal rats.

	LC rats <i>n</i> =17	normal rats <i>n</i> =13	<i>p</i> value
PVP (mmH ₂ O)	155.0±42.94	118.7±15.44	<i>p</i> <0.05
GBF (ml/min/100g)	33.65±5.88	43.72±10.05	<i>p</i> <0.05

data expressed as mean±S.D.

correlation coefficient by rank test was calculated to estimate the linear association between two variables. A *p*-value of less than 0.05 was considered significant.

RESULTS

1. Pathological findings in rats administered thioacetamide (Figure 1)

Macroscopic findings revealed roughness on the liver surface, dilation of the portal vein, and prominent development of collateral veins in all of the rats that had been treated with thioacetamide. These findings were in agreement with the signs of liver cirrhosis with portal hypertension. Liver cirrhosis was confirmed histologically in all rats treated with thioacetamide. Vasodilation was observed in the gastric mucosal layer and submucosal layer of all rats given thioacetamide but in none of the rats of the control group.

Table 2. Comparison of the portal vein pressure (PVP) values before and 10 minutes after isosorbide dinitrate administration in liver cirrhosis (LC) rats and normal rats.

	PVP (mmH ₂ O)		<i>p</i> value
	before	after	
LC rats <i>n</i> =17	155.0±42.94	133.7±19.57	<i>p</i> <0.05
normal rats <i>n</i> =13	118.7±15.44	103.5±13.85	<i>p</i> <0.05

data expressed as mean±S.D.

Figure 2. Time course of gastric blood flow (GBF) ratio after administration of isosorbide dinitrate (IDN). In the cirrhotic group (*n*=9), GBF ratios had increased significantly after IDN administration of IDN in comparison with the ratio obtained before administration (ratio=1) (*p*<0.05). The GBF ratios of the liver cirrhosis (LC) rats at 3 and 5 min after administration of IDN were significantly higher than those of the normal rats. In normal rats (*n*=6), the GBF ratios did not change significantly.

2. PVP and GBF before IDN administration

Before IDN administration, PVP and GBF were measured respectively in 17 rats with and 13 rats without liver cirrhosis. Table 1 shows that the value of PVP in the group with liver cirrhosis (155.0 ± 42.94 mmH₂O) was significantly higher than that in the control group (118.7 ± 15.44 mmH₂O) (*p*<0.05). Furthermore, GBF in the former group (33.65 ± 5.88 ml/min/100 g) was significantly (*p*<0.05) lower than that in the latter group (43.72 ± 10.05 ml/min/100 g).

Before IDN administration, PVP and GBF in the group with liver cirrhosis were weakly and negatively correlated (*r*=−0.42, *p*<0.05). The values of PVP and

GBF in the control group were not significantly correlated.

3. Changes in PVP attributable to IDN administration

Table 2 shows that PVP in the group with liver cirrhosis 10 min after IDN administration (133.7 ± 19.57 mmH₂O) was significantly lower than that immediately before IDN administration (155.0 ± 42.94 mmH₂O; $p < 0.05$). Also, PVP in the control group at 10 min after IDN administration (103.5 ± 13.85 mmH₂O) was significantly lower than that immediately before IDN administration (118.7 ± 15.44 mmH₂O; $p < 0.05$).

There was no significant difference between the decreasing rates of PVP in the control group ($88.6 \pm 10.2\%$) and in the liver cirrhosis group ($89 \pm 8.5\%$).

4. Changes in GBF attributable to IDN administration (Figure 2)

The value of GBF before IDN administration was set at 1, and the percent changes in GBF thereafter were calculated. In the liver cirrhosis group, GBF after IDN administration was significantly higher than that before administration ($p < 0.05$). Moreover, the values of GBF in the liver cirrhosis group at 3 and 5 min after IDN administration were significantly higher than those in the control group ($p < 0.05$).

On the other hand, compared with the preadministration value, GBF in the control group did not change significantly within the first 10 min after IDN administration.

5. Portal blood oxygen partial pressure

Blood gases were analyzed respectively in 9 and 6 of the rats with and without liver cirrhosis. Therefore, PVP and GBF measurements and blood gas analyses were conducted simultaneously in those animals.

1) PaO₂ and PpvO₂ before IDN administration

Absolute values of PaO₂ were not significantly different between the group with liver cirrhosis (84.82 ± 11.25 mmHg) and the group without (91.15 ± 13.87 mmHg). Likewise, the absolute values of PpvO₂ were not significantly different in the two

Table 3. Comparison of the blood oxygen partial pressure in artery (PaO₂), portal vein (PpvO₂) and Ppv/aO₂ ratio between liver cirrhosis (LC) rats and normal rats.

	LC rats <i>n</i> =9	normal rats <i>n</i> =6	<i>p</i> value
PaO ₂ (mmHg)	84.82 ± 11.25	91.15 ± 13.87	ns
PpvO ₂ (mmHg)	56.78 ± 5.87	51.27 ± 7.67	ns
Ppv/aO ₂ ratio	0.679 ± 0.114	0.568 ± 0.078	ns ($p = 0.08$)

data expressed as mean $\pm$ S.D.

ns: not significant

Table 4. Comparison of the Ppv/aO₂ ratio in liver cirrhosis (LC) rats and normal rats before and after isosorbide dinitrate administration.

	Ppv/aO ₂ ratio		<i>p</i> value
	before	after	
LC rats <i>n</i> =9	0.68±0.11	0.46±0.14	<i>p</i> <0.05
normal rats <i>n</i> =6	0.57±0.07	0.52±0.20	ns

data expressed as mean±S.D.

ns: not significant

ns: not significant.

Figure 3. Correlation between the gastric blood flow (GBF) ratios and portal vein pressure (PVP) ratios in liver cirrhosis (LC) rats. No significant correlation was found between the GBF ratio and PVP ratio in LC rats ($r=-0.467$, $p=0.186$).

groups (56.78 ± 5.87 mmHg in the cirrhosis group vs. 51.27 ± 7.67 mmHg in the control group). The PpvO₂/PaO₂ value in the group with liver cirrhosis (0.679 ± 0.114) was higher than that in the normal group (0.568 ± 0.078), but the difference was not significant ($p=0.08$) (Table 3).

2) Differences in PpvO₂/PaO₂ values before and after IDN administration

The PpvO₂/PaO₂ value in the group with liver cirrhosis was significantly lower ($p<0.05$) after IDN administration (0.464 ± 0.137) than before IDN administration (0.679 ± 0.114). On the other hand, the values in the control group before and after IDN administration were not significantly different (Table 4).

Figure 4. Correlation between gastric blood flow (GBF) ratio and $\text{PpvO}_2/\text{PaO}_2$ ratio in liver cirrhosis (LC) rats. A negative and significant correlation was found between GBF ratio and $\text{PpvO}_2/\text{PaO}_2$ in LC rats ($r = -0.733$, $p < 0.05$).

6. Correlation of changes in PVP or $\text{PpvO}_2/\text{PaO}_2$ with GBF changes following IDN administration

We compared the correlation between the rates of change in GBF and in those PVP and $\text{PpvO}_2/\text{PaO}_2$ to determine which of changes in PVP or $\text{PpvO}_2/\text{PaO}_2$ contributed more to the change in GBF after IDN administration. A significant correlation was not found between rates of change in GBF and PVP following IDN administration ($r = -0.467$, $p = 0.186$) (Figure 3), but rates of change in GBF and $\text{PpvO}_2/\text{PaO}_2$ were significantly correlated ($r = -0.733$, $p < 0.05$) (Figure 4).

DISCUSSION

PHG is associated with portal hypertension regardless of the underlying disease. Although portal hypertension is known to play a major role in the pathogenesis of increasing PHG, it is not clear whether PHG is the consequence of passive congestion induced by the pressure load against the outflow of gastric circulation or the consequence of active congestion (overflow because of a hyperdynamic state) with passive congestion. Iwao *et al.*⁷⁾ reported that PHG is probably caused only by passive congestion because PHG is associated with increasing PVP and decreasing gastric perfusion. On the other hand, several investigators have found consistently that gastric blood flow is increased in experimental models of portal hypertension, either in the whole gastric wall or in the mucosal-submucosal layers⁴⁰⁻⁴³. These findings suggest that PHG is also caused by active congestion because of a hyperdynamic state. Although these conflicting findings might be attributable to differences in methods of measurement, the results of our study, in which Laser Doppler flowmetry was used, showed decreased perfusion of the gastric mucosa in

rats with portal hypertension. Thus, increasing of perfusion in the gastric mucosa by administration of vasoactive agent will be treatment for PHG.

PHG has been treated with vasoconstrictors such as propranolol and somatostatin. Hosking *et al.*¹⁸⁾ reported that propranolol is effective in arresting hemorrhage associated with severe gastropathy. On the other hand, the mechanism by which vasodilators affect gastric mucosal hemodynamics in PHG has remained controversial. Noguchi *et al.*²³⁾ evaluated the hemodynamic changes of PHG after administering nitroglycerin using the hemoglobin index (IHB) and the oxygen saturation index (ISO₂). They suggested that nitroglycerin helps reduce portal pressure and congestion of the gastric mucosa in patients with portal hypertension caused by liver cirrhosis. In addition, they reported that gastric mucosal blood flow decreased as a result of reflux splanchnic vasoconstriction produced by nitroglycerin.

Nitrates reduce PVP by several possible mechanisms: reduction in portal inflow by relaxation of arterial smooth muscles, which lowers arterial blood pressure and triggers high-pressure arterial baroreceptors to cause reflex splanchnic vasoconstriction; dilation of collateral vessels; and vasorelaxation at the sinusoidal level leading to reduced intrahepatic resistance. Noguchi *et al.*²³⁾ reported that nitroglycerin reduces PVP in cirrhotic patients, particularly by dilation of the major portal-systemic collaterals. In the present study, however, PVP was decreased significantly in rats both with and without liver cirrhosis after IDN administration; the rates of decrease in the two groups were not significantly different. Our findings suggest that either the above-mentioned first or the third mechanism is the main mechanism by which IDN reduces PVP in rats.

In the present study, PVP and PpvO₂/PaO₂ were used as parameters for evaluating the mechanism by which IDN acts on GBF. Changes in these parameters in rats with and without liver cirrhosis after IDN administration are shown in Table 5. High portal pressure might be an obstacle to efferent blood flow from the stomach into the portal venous system. The increasing PVP might be regarded as an afterload on the GBF. On the other hand, blood flow into the portal venous system from the splanchnic circulation might increase because of increasing arterial contents of the portal venous system. The reported values of PpvO₂ and oxygen saturation in portal venous blood of patients with liver cirrhosis are high⁴⁴⁾.

Table 5. Summary of change in gastric blood flow (GBF) and portal vein pressure (PVP) values and Ppv/aO₂ ratio after isosorbide dinitrate administration in liver cirrhosis (LC) rats and normal rats.

parameters	LC rats	normal rats
GBF	increased	stationary
PVP	decreased	decreased
Ppv/aO ₂ ratio	decreased	stationary

Therefore, increasing $PpvO_2$ might indirectly indicate an increase in splanchnic circulation. Therefore, $PpvO_2/PaO_2$ might be regarded as an index of preload on GBF. In the following, the mechanism by which IDN acts on GBF is discussed from the viewpoint of preload and afterload on GBF.

PVP as afterload: Results of the present study showed that the GBF rate was lower in the cirrhotic rats than in the normal group. Moreover, despite the fact that PVP decreased significantly in both groups after IDN administration, GBF increased only in the cirrhotic group. In addition, GBF in the cirrhotic group at 3–5 min after IDN administration was significantly higher than that in the normal group. These findings suggest that the reduction of afterload with decreased PVP is involved in the improvement in GBF by IDN in liver cirrhosis. However, because these changes were evident in both groups, the decrease in PVP might not be the specific mechanism of IDN-induced improvement in GBF in portal hypertension.

$PpvO_2/PaO_2$ as preload: Results of the present study showed that $PpvO_2/PaO_2$ did not decrease in the normal group after IDN administration, but it was significantly decreased in the cirrhotic group. The portal vein collects blood flow from splanchnic organs such as the gastrointestinal tract. Therefore, a decrease in $PpvO_2$ would mean that either the amount of oxygen uptake in each organ had increased or that the amount of arterial blood flowing into each organ had decreased. Vasodilators will not alter intestinal oxygen uptake unless they affect oxygen metabolism. The IDN does not influence oxygen metabolism directly⁴⁵⁾. Therefore, it is thought that a reduction in arterial blood flow induced by baroreflex-mediated splanchnic arterial vasoconstriction caused by IDN is the main mechanism of the decrease in $PpvO_2/PaO_2$. Our findings suggest that IDN reduces both afterload and preload during PHG. However, because the GBF change in this study correlated more closely with the change in $PpvO_2/PaO_2$ than with that in PVP, the improvement in GBF caused by IDN in rats with portal hypertension is caused mainly by suppression of blood inflow as a preload, as reflected by the reduction in $PpvO_2/PaO_2$. It is considered that suppression of hyper inflow by administration of IDN makes improvement of active congestion in gastric mucosa, consequently GBF will increase.

Decrease in $PpvO_2/PaO_2$ after IDN administration is attributable to reflex splanchnic vasoconstriction, which is secondary to the vasodilative effect of IDN. In the normal group, although PVP decreased after IDN administration, $PpvO_2/PaO_2$ did not decrease. Splanchnic blood flow is not increased without portal hypertension. Therefore, IDN might not function. The possibility of this mechanism is supported by the fact that splanchnic blood flow increases in portal hypertension⁴⁶⁾. Moreover, arterial baroreceptor control of splanchnic arteriolar resistance should be impaired in cirrhotic patients because they might have abnormal arterial baroreflexes^{47,38)}. The decrease in PVP after IDN administration in rats without portal hypertension is thought to be caused mainly by a decrease in intrahepatic vascular resistance⁴⁹⁾. Results of previous studies and our findings suggest that IDN

has a reflex vasoconstrictive effect on blood vessels, especially in a state of portal hypertension^{50,51}). In short, IDN partially corrects with the hyperdynamic state. Therefore, administration of IDN for the patient with portal hypertension will be useful for prevention of gastrointestinal bleeding from PHG and gastrointestinal varices.

In conclusion, we investigated the effect of isosorbide dinitrate (IDN) on pathological changes in the stomach accompanying portal hypertension in rats. The effect of IDN on changes in the stomach accompanying portal hypertension is attributable mainly to a decrease in preload, which suppresses inflow to the stomach, as reflected by a decrease in $PpvO_2/PaO_2$, rather than to a decrease in afterload on GBF, as reflected by a decrease in PVP.

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