The Effects of Intravenously Infused Catecholamines on Hepatic Blood Flow in Conscious Dogs with Experimental Obstructive Jaundice

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Running Head: Catecholamines and Hepatic Blood Flow

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実験的閉塞性黄疸を伴った意識下犬における静脈内投与カテコラミンの肝血流に及ぼす影響

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Abstract

This study was conducted to examine how the effects of dopamine and dobutamine on hepatic blood flow were influenced by obstructive jaundice in a conscious canine model. Prior to biliary obstruction, portal venous blood flow(PVF) increased in response to the infusion of either dopamine or dobutamine; at which time dopamine infused at 8μ g/kg/min produced an increase of 19±2% in PVF, while dobutamine infused at 16μg/kg/min produced an increase of 30±2%. Although hepatic arterial blood flow (HAF) decreased dose-dependently in response to the infusion of dopamine, no significant change was observed in HAF in response to any dose of dobutamine. Obstructive jaundice attenuated or completely abolished the PVF-increasing effect of dopamine, whereas it did not significantly alter the effect of dobutamine on hepatic blood flow. In dogs with obstructive jaundice, dopamine at 16μg/kg/min produced a decrease of 17±3% in PVF. These findings suggest that dobutamine is more effective than dopamine for increasing hepatic blood flow in patients with obstructive jaundice.

Key Words:hepatic blood flow, dopamine, dobutamine, obstructive jaundice

Introduction

Massive hepatectomy with combined portal vein resection and reconstruction has recently been performed as an aggressive treatment for hepatobiliary disease. Many patients have benefited from this operation whith has resulted in allowing them to maintain a good quality of life[1-3]; however, carcinoma of the biliary tract is often accompanied by obstructive jaundice and portal vein stenosis due to invasion of the carcinoma. Thus, despite continued advances in surgical techniques, massive hepatectomy and/or portal vein resection and reconstruction can result in postoperative hepatic failure and a fatal outcome in patients with obstructive jaundice[4,5]. In fact, portal hypertension, decreased portal venous blood flow (PVF), and low cardiac output (CO) have all been reported to occur following massive hepatectomy[6-10]. Furthermore, portal diversion has been reported to cause liver atrophy and impair regeneration following hepatectomy in animals[11,12],while portal venous insufficiency following hepatectomy limits hepatic regeneration, delays the recovery of liver function and finally causes hepatic failure[13-16]. Therefore, catecholamines such as dopamine or dobutamine are frequently administered, not only after the operation, but also during and before operations, such as massive hepatectomy, in an attempt to increase PVF and CO[17,18].

Dopamine(3,4-dihydroxyphenylethylamine) is a naturally occurring catecholamine that is the direct biochemical precursor of norepinephrine[19], while dobutamine(4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]- pyrocatechol hydrochloride)is a derivative of dopamine which was first synthesized by Tuttle and Mills[20]. Both of these sympathomimetic amines exert positive inotropic actions on the heart, and are the most potent agents available for the treatment of severe heart failure and shock[21,22], but the effects of these catecholamines on hepatic blood flow have been contradictory[23-28]. Moreover, despite attempts to characterize the hepatic hemodynamic response to biliary obstruction, the pattern of circulatory changes in the liver remains equivocal[29-31] , and few reports focusing specifically on the influence of obstructive jaundice on the effect these catecholamines have on hepatic blood flow

have been found. Moreover, most detailed studies on the hemodynamic changes after biliary obstruction have been conducted on subjects under anesthesia which can often alter the response of the cardiovascular system to a variety of physiological and pharmacological stimuli[32-34]. The aim of this study was to evaluate the influence of obstructive jaundice on the changes in hepatic blood flow induced by dopamine or dobutamine, examining conscious dogs with experimental obstructive jaundice.

Materials and Methods

Operation 1 : Surgical Implantation of Probes for Hepatic Blood Flow and CO

A total of ten beagle dogs of either sex weighing 8-12kg were fasted overnight, but allowed access to water. Anesthesia was induced by intravenous thiopental, 25mg/kg body weight and maintained with 1% enflurane delivered in a 2: 1 mixture of nitrous oxide and oxygen through a cuffed endotracheal tube using a ventilator. Laparotomy was performed through a midline incision and implantable transit time ultrasonic flow meter probes (Transonic Systems Inc.,Isaka,NY,USA) with a diameter of 3mm and of 6mm[35], were placed around the common hepatic artery and the portal vein, respectively, to measure hepatic arterial blood flow (HAF) and PVF. The gastroduodenal artery and right gastric artery were ligated to assure that only the arterial flow to the liver was measured. The abdomen was closed and the connecting wires from the probes were pulled out of the abdominal cavity through a subcutaneous tunnel and fixed in the neck (Fig1).

(Fig1)

A different group of seven beagle dogs of either sex weighing 8-12kg was used for the measurement of CO. Anesthesia was induced and maintained using the same maneuver as described above. Thoracotomy was carried out and an implantable transit time ultrasonic flow meter probe (Transonic Systems Inc.,Isaka,NY,USA) with a diameter of 16mm, was placed around the ascending aorta to measure CO. The thorax was closed after inflation of the lungs.

Operation2: Experimental Biliary Obstruction

A second operation was performed 2 weeks after the first operation in the same dogs, using the same anesthetic maneuver . Through a midline incision, the common bile duct was dissected just above the pancreas, after which a polyethylene catheter with a diameter of 3mm was inserted into the proximal end of the common bile duct, and its distal end was ligated. A cholecystectomy was also performed and the polyethylene catheter was connected to a metallic external biliary fistula on the anterior abdominal wall(Fig1), following which the abdomen was closed. The metallic external biliary fistula was closed with a lid 1week later to induce biliary obstruction in a conscious state.

Hemodynamic Measurements

HAF, PVF, CO and heart rate(HR) were measured in the conscious state 2 weeks after the animals had recovered from insertion of the ultrasonic flow meter probes to obtain control data before biliary obstruction (control period). After the stability of each measured variable had been confirmed for at least 30 min, basal values were obtained. Solutions of dopamine and dobutamine were prepared and infused intravenously using a Harvard infusion pump, and the order of drug infusion was altered. Dopamine and dobutamine were infused sequentially at rates of 2,4,8 and 16μg/kg/min. Each infusion rate was maintained for 15 min to allow for stabilization of the measured variables. After terminating one infusion, 30 min was allowed before another set of control measurements was taken, and the next infusion was commenced.

After the initial series of infusions, the α- or β-receptor blocking agents, phenoxybenzamine hydrochloride (Tokyo Kasei,Tokyo), and propranolol hydrochloride (Sigma), respectively, were infused at 1mg/kg to assess the α– or β-adrenergic effects of dopamine and dobutamine. After the actions of these blocking agents had been confirmed, dopamine and dobutamine were infused again and the same measurements were repeated. Measurement of the HAF, PVF, CO, and HR was

repeated 1 week after closing the external biliary fustula to obtain the values after biliary obstruction (biliary obstruction period). The infusion of dopamine or dobutamine was carried out using the same regimen as for the first set of measurements, and performed while the animals were conscious.

Data were recorded on a polygraph system (AT-600G, Nihon Koden, Tokyo, Japan) and a direct writing recorder (TI-2502, Tokai Irika, Tokyo, Japan). A tracing of (Fig2) experimental records is shown in Fig2.

Statistical Analysis

All recordings were analyzed at 1-min intervals. The basal value was taken as the mean for the 15 min period before the infusion of each agent, and the infusion value was taken as the mean for the 15 min infusion period. The response to each agent is expressed as the percent difference from the basal value in Figs 3-7.

All data are expressed as the means±SE. The statistical analysis of data was carried out by a one-way or two-way analysis of variance using Tukey's procedure for the multiple comparison of means, and the paired t-test for paired data. A P value below 0.05 was taken as the level of significance.

Results

Biochemical Data

The data obtained in both the control period and biliary obstruction period are (Table1) summarized in Table 1. There was a marked increase in serum total bilirubin, alkaline phosphatase, glutamate-pyruvate transaminase and glutamate-oxaloacetate transaminase after biliary obstruction.

The Effect of Dopamine in the Control Period

(Fig3) PVF was increased significantly by the dopamine infusion (Fig3). Dopamine produced an increase of 15±2% at 4μ g/kg/min, and of 19±2% at 8μ g/kg/min. However, at 16μ g/kg/min, no significant increase was observed. In contrast, HAF decreased progressively with the infusion of increasing concentrations of dopamine (Fig3). At 16μ g/kg/min, dopamine produced a decrease of 42±2% in HAF. CO increased dose-dependently in response to the dopamine infusion,with an increase of 33±4% in CO at 16μ g/kg/min(Fig3). HR was elevated by dopamine at 4 and 8μ g/kg/min, but was decreased significantly by dopamine at 16μ g/kg/min(Fig3).

Following the prior administration of phenoxybenzamine, the PVF-increasing (Fig4) effect of dopamine was remarkably enhanced at 8 and 16μ g/kg/min (Fig4). After phenoxybenzamine pretreatment, the dopamine infusion caused a dose-dependent augmentation of PVF, while its effect on HAF was unchanged. After the administration of propranolol, the increase in PVF with 4μ g/kg/min of dopamine was reduced to about 50% of that before propranolol treatment, and the PVF-increasing effect of dopamine at 8 and 16μ g/kg/min was completely abolished (Fig4). However, the effect of dopamine on HAF was essentially unchanged.

The Effect of Dopamine in the Biliary Obstruction Period

Biliary obstruction caused a decrease or reversal in the effect of dopamine on PVF (Fig3). The infusion at 4μ g/kg/min produced an increase of only 5±2% in PVF, while there was a decrease at 8μ g/kg/min, and a further decrease at 16μ g/kg/min of 17±3%. In contrast, the effects of dopamine on HAF, CO, and HR were similar to those observed in the control period(Fig3). The PVF-increasing effect of dopamine was restored dramatically after the prior administration of phenoxybenzamine at infusion rates of 4,8, and 16μ g/kg/min, and became similar to that observed in the control (Fig5) period when phenoxybenzamine was administered (Fig5).

The Effect of Dobutamine in the Control Period

PVF increased progressively in response to dobutamine at each infusion rate, with an increase of 19±3% and 30±2% at 8 and 16μ g/kg/min respectively (Fig6). (Fig6)

In contrast, no significant change was observed in HAF (Fig6). The dobutamine infusion increased CO in a dose-dependent manner, with an increase of 36±3% at 16μ g/kg/min (Fig6). HR remained unaltered up to 8μ g/kg/min, but was increased by about 20% at 16μ g/kg/min (Fig6). Following the prior administration of propranolol, there was no increase in PVF or CO, and HAF was decreased at all infusion rates (Fig7). (Fig7)

The Effect of Dobutamine in the Biliary Obstruction Period

PVF increased dose-dependently in response to the dobutamine infusion, with a similar effect to that observed in the control period (Fig6). The effects of dobutamine on HAF and HR were also similar to those observed in the control period (Fig6). The increase in CO was slightly attenuated after biliary obstruction, but the difference from the control period was not significant (Fig6).

Discussion

By conducting this study, we were able to examine the hepatic blood flow responses to infusions of dopamine and dobutamine, and the influence of obstructive jaundice on these responses in conscious dogs. Before biliary obstruction, PVF was increased by either dopamine or dobutamine; however, the highest dose of dopamine, being 16μ g/kg/min, resulted in much less of an increase than the lower doses. Examination of the effect of phenoxybenzamine administration suggested that this attenuated response was due to the α-adrenergic effect of dopamine, while the effect of propranolol administration suggested that the augmentation of PVF by all four doses of dobutamine and the higher doses of 8 and 16μ g/kg/min of dopamine was attributable to the β-adrenergic effect. However, dopamine at the dose of 4μ g/kg/min was thought

to increase PVF by both its β-adrenergic effect and its action on dopamine-specific receptors, which induce direct vasodilation of the mesenteric vascular bed[36,37].

After biliary obstruction, PVF continued to respond to the dobutamine infusion in a manner similar to that seen in the control period, whereas the PVF-increasing effect of dopamine was attenuated or completely abolished. This difference can possibly be explained in the following way: Even after biliary obstruction, the prior administration of phenoxybenzamine restored the PVF-increasing effect of dopamine to a similar magnitude as that seen in the control period after the administration of phenoxybenzamine. Furthermore, Hirsch et al.[23] reported that a direct infusion of dopamine into the portal vein caused no change in PVF in dogs, whereas infusion into the superior mesenteric artery(SMA) caused an increase in blood flow in this vessel by 206% and increased the PVF by 70%. They concluded that the augmentation of PVF by the infusion of dopamine was the result of an increment of mesenteric arterial blood flow. These data infer that the attenuation of the increasing effect of dopamine on PVF in the presence of obstructive jaundice might be due to enhancement of its α-adrenergic effect on the mesenteric vascular bed.

In a study on baboons with obstructive jaundice, Bloom et al.[38] reported that there was a significant decrease in the distribution of intrarenal blood flow to the cortex, and that the renal vessels showed enhanced sensitivity to infused noradrenaline. From their findings and our observations, we conclude that a similar enhanced sensitivity to the α-adrenergic effect of dopamine may occur in the mesenteric vascular bed after biliary obstruction.

In contrast to its influence on the effect of dopamine, biliary obstruction did not significantly alter the effect of dobutamine on PVF. Conversely, the increase in PVF following the infusion of dobutamine appeared to be due to the β-adrenergic effect of this agent. In fact, even in the biliary obstruction period, dobutamine infusions increased CO in a manner almost similar to that seen in the control period. Therefore it was concluded that PVF would continue to respond to the infusion of dobutamine through an unchanged β-adrenergic effect of dobutamine in obstructive jaundice.

HAF decreased progressively in response to the dopamine infusion, and this decrease was not blocked by the prior administration of either phenoxybenzamine or propranolol. These findings suggested that the reduction in HAF was probably attributable to the activation of dopamine-specific receptors, which induce vasoconstriction in the hepatic arterial vascular bed[39]. The fact that the infusion of dobutamine did not significantly change HAF was probably due to the balance between the promotor effect of augmented CO and the reverse effect of the buffer response, being the ability of the hepatic artery to decrease its flow in response to an increase in PVF, as proposed by Lautt et al[40].

In conclusion, the results of the present study showed that:

1.Obstructive jaundice reduced or completely abolished the increase in PVF induced by dopamine, but did not significantly alter the PVF-increasing effect of dobutamine.

2. HAF decreased in response to the infusion of dopamine dose-dependently, but no significant change was observed in HAF with the infusion of dobutamine.

3.Dobutamine may be more effective than dopamine for increasing PVF in patients with obstructive jaundice.

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Figure Legends

Fig.1. Schematic diagram of the experimental set up.

PV, portal vein; RGA, right gastric artery; GDA, gastroduodenal artery;

CHA, common hepatic artery; CBD, common bile duct.

Fig.2.Representative recording of the effects of intravenous dopamine given as 8 and 16μ g/kg/min, on PVF, HAF, and heart rate in the control period.

PVF, portal venous blood flow; HAF; hepatic arterial blood flow;

CO, cardiac output; HR, heart rate.

Fig.3. Response of hepatic blood flow(PVF, HAF), CO, and HR, to intravenous dopamine infusion in the control and biliary obstruction periods.

†$p<0.05$ vs basal value * $p<0.05$ ** $p<0.01$

N.S., not significant; PVF, portal venous blood flow; HAF, hepatic arterial blood flow; CO, cardiac output; HR, heart rate.

Each variable is expressed as the mean ±SD.

Fig.4. Effect of the prior administration of phenoxybenzamine or propranolol on hepatic blood flow responses to dopamine infusion in the control period.

†$p<0.05$ vs basal value * $p<0.05$ ** $p<0.01$

PVF, portal venous blood flow; HAF, hepatic arterial blood flow.

Each variable is expressed as the mean ±SD.

Fig.5. Effect of the prior administration of phenoxybenzamine on hepatic blood flow responses to dopamine infusion in the control and biliary obstruction periods.

† $p<0.05$ vs basal value N.S., not significant;

PVF, portal venous blood flow; HAF, hepatic arterial blood flow;

Each variable is expressed as the mean ±SD.

Fig.6. Response of hepatic blood flow(PVF, HAF), CO, and HR to intravenous dobutamine infusion in the control and biliary obstruction periods.

† $p<0.05$ vs basal value N.S., not significant;

PVF, portal venous blood flow; HAF, hepatic arterial blood flow;

CO, cardiac output; HR, heart rate.

Each variable is expressed as the mean ±SD.

Fig.7. Effect of the prior administration of propranolol on the responses of hepatic blood flow and CO to dobutamine infusion in the control period.

† $p<0.05$ vs basal value

PVF, portal venous blood flow; HAF, hepatic arterial blood flow;

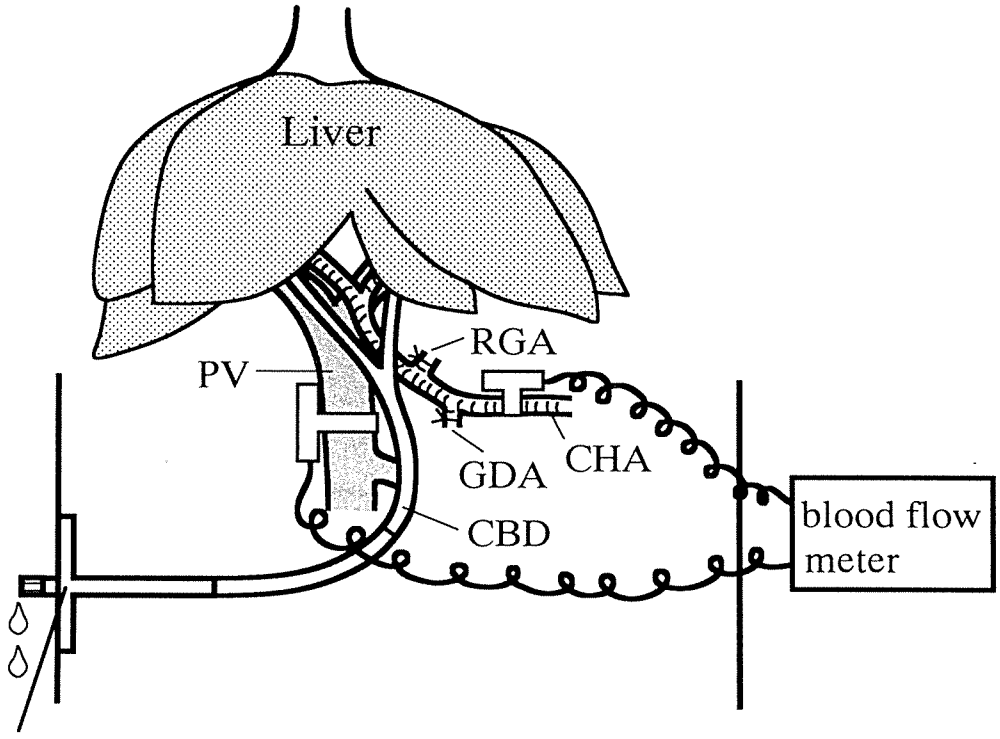
CO, cardiac output.

Each variable is expressed as the mean ±SD.

TABLE 1. Biochemical data for the control period and the biliary obstruction period

	control period (n=10)	biliary obstruction period (n=10)	probability level of difference
Serum total bilirubin (mg/dl)	0.2 ± 0.1	4.1 ± 0.4	< 0.01
Serum alkaline phosphatase (IU/l)	10.6 ± 1.5	396.4 ± 77.7	< 0.01
Serum glutamate-pyruvate transaminase (IU/l)	47.9 ± 5.6	886.2 ± 165.7	< 0.01
Serum glutamate-oxaloacetate transaminase (IU/l)	34.8 ± 4.6	153.1 ± 35.2	< 0.01
Blood urea nitrogen (mg/dl)	10.1 ± 1.1	9.7 ± 1.6	n. s.
Serum creatinine (mg/dl)	0.79 ± 0.11	0.66 ± 0.10	n. s.
Serum total protein (g/dl)	6.1 ± 0.3	6.5 ± 0.2	n. s.

Values are expressed as means ± SE n.s. = not significant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CBD
blood flow
meter
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(the second operation)

Fig. 1

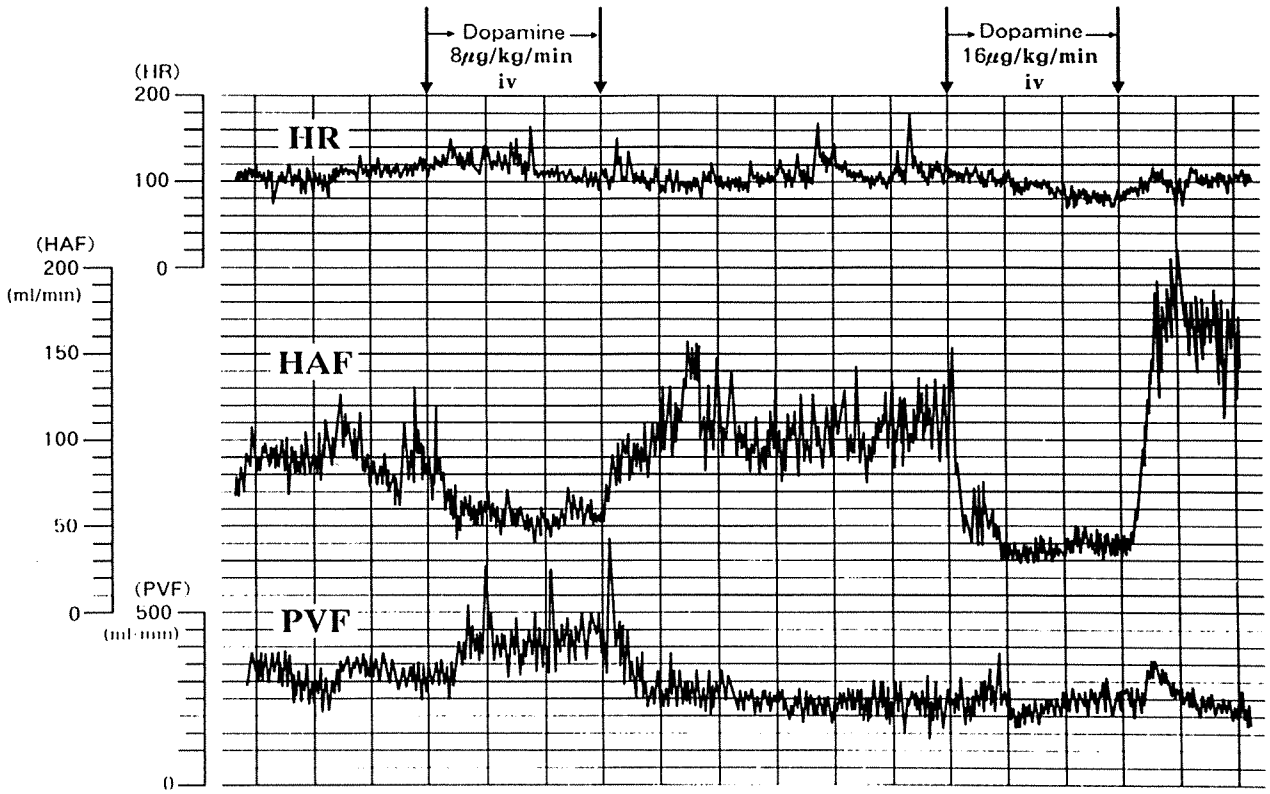
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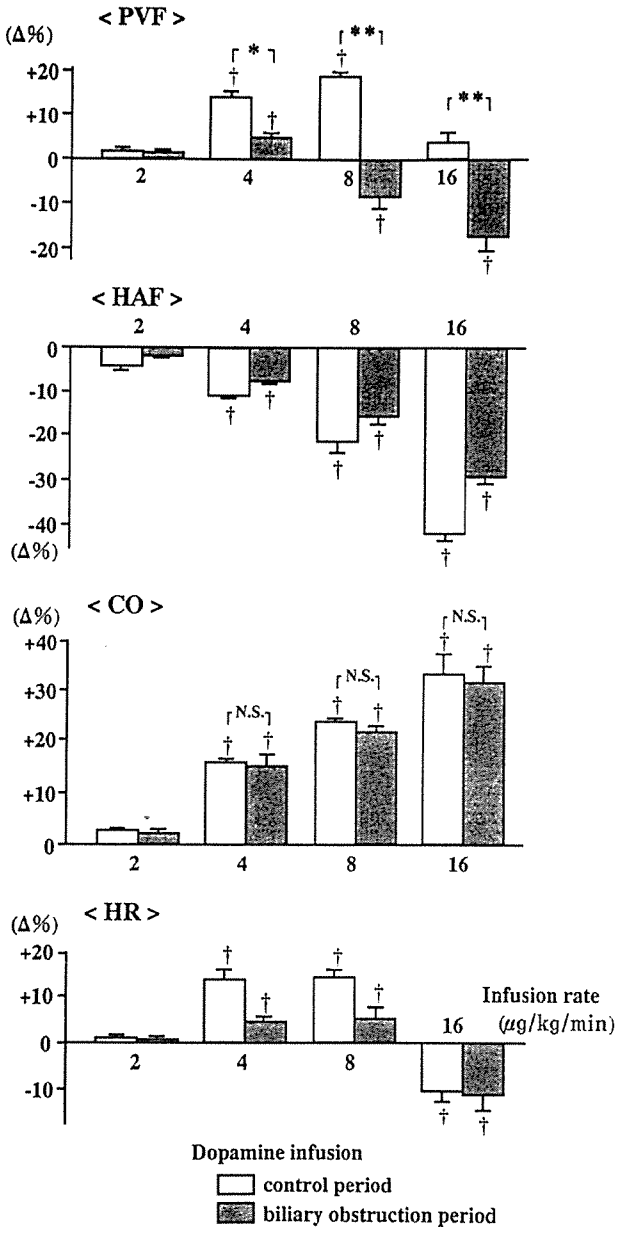
Fig. 2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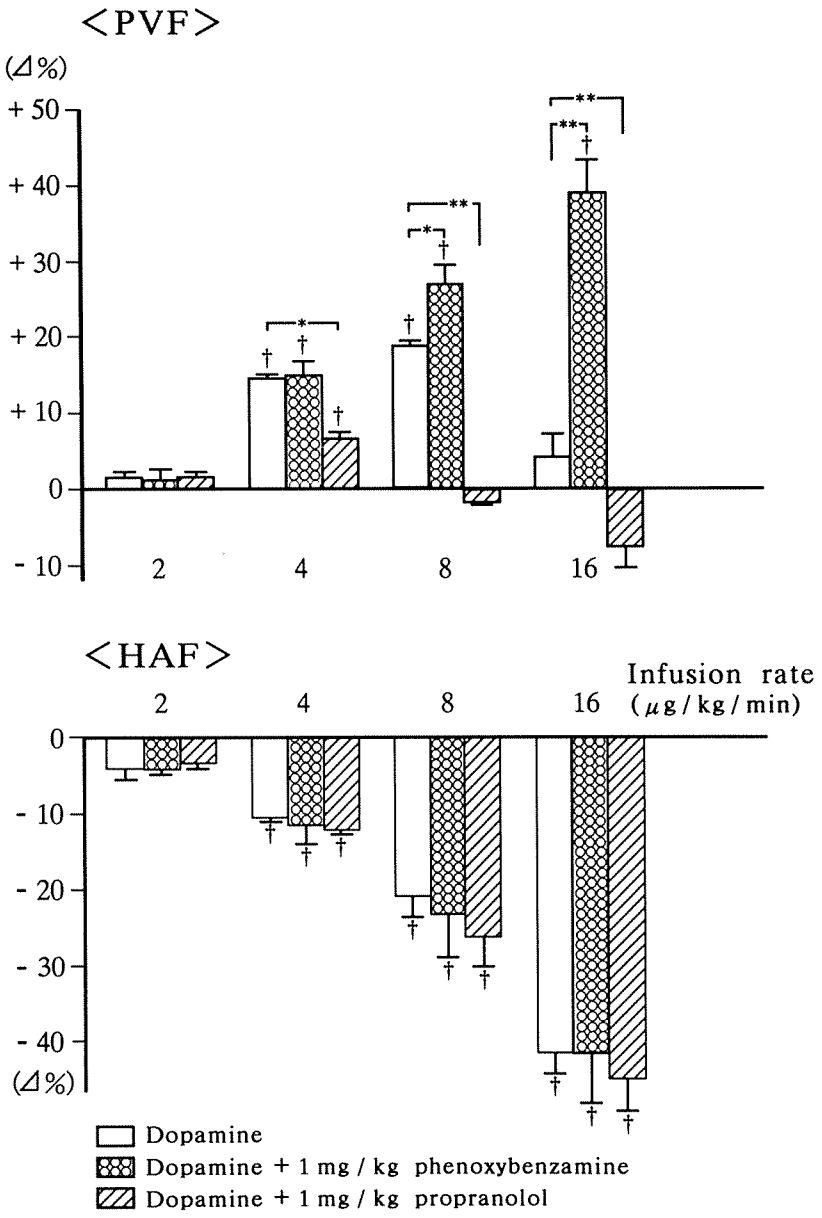
Infusion rate
(μg/kg/min)
Dopamine infusion
control period
biliary obstruction period

Fig. 3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Infusion rate
(μg / kg / min)
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(⊿%)
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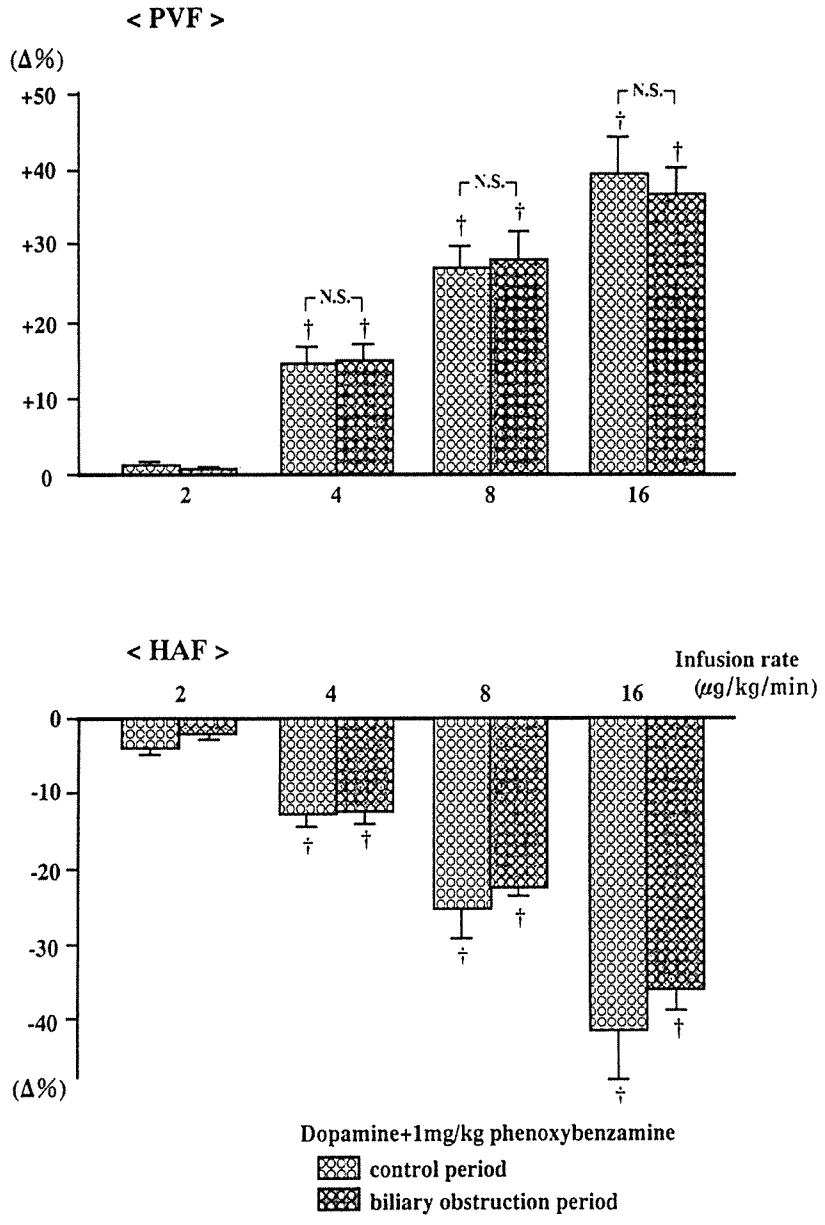
Dopamine + 1 mg / kg propranolol

Fig. 4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Infusion rate
(μg/kg/min)
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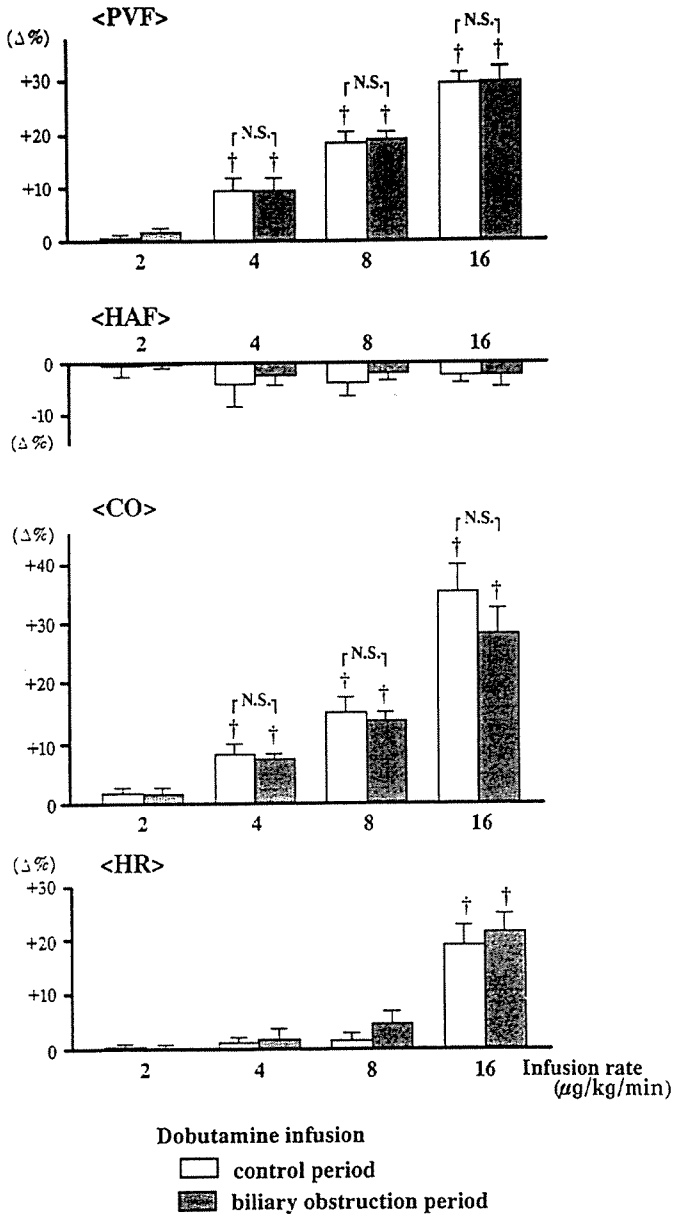
-10
-20
-30
-40
(Δ%)
Dopamine+1mg/kg phenoxybenzamine
control period
biliary obstruction period

Fig. 5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(Δ%)
+30
+20
+10
0
N.S.
2
4
8
16
<HAF>
0
-10
(Δ%)
<CO>
<HR>
Infusion rate
(μg/kg/min)
Dobutamine infusion
control period
biliary obstruction period

Fig. 6

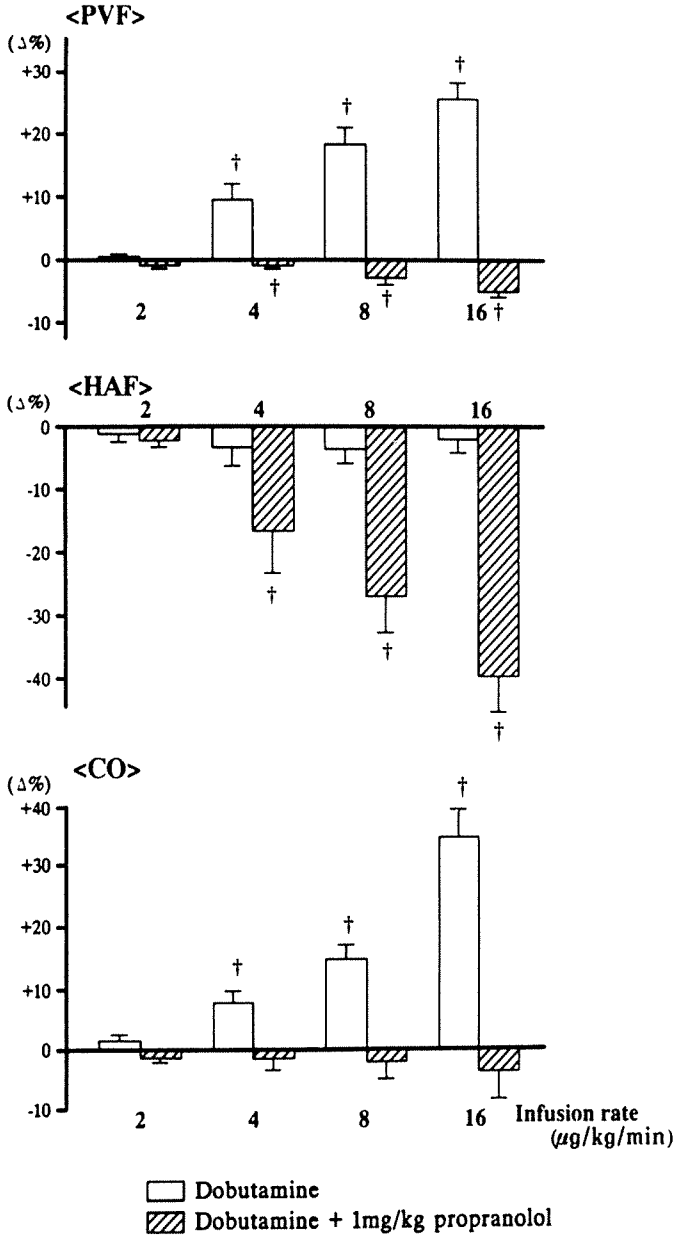
<PVF>
(Δ%)
+30
+20
+10
0
-10
2
4
8
16
†
<HAF>
(Δ%)
0
-10
-20
-30
-40
<CO>
(Δ%)
+40
Infusion rate
(μg/kg/min)
Dobutamine
Dobutamine + 1mg/kg propranolol

Fig. 7