The Selective Effects of Dopamine and Dobutamine on Liver Circulation in the Dog

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ABSTRACT. The selective effects of dopamine and dobutamine in various doses on liver circulation were studied in 12 mongrel dogs. Dopamine increased portal flow but decreased hepatic arterial flow markedly as infusion rate of dopamine increased. Dopamine 3 $\mu\text{g/kg/min}$ infusion rate produced vasodilation in mesenteric vascular bed and the portal flow ratio to cardiac output was significantly increased. Dobutamine increased both portal and hepatic arterial flows at the 5 and 10 $\mu\text{g/kg/min}$ dobutamine infusion rates, and decreased hepatic arterial flow at the 15 $\mu\text{g/kg/min}$ dobutamine infusion rate. Both dopamine and dobutamine increased total liver flows, however, total liver flow ratio to cardiac output was not increased. Pressure gradient of portal system was not changed during dopamine and dobutamine infusion, since both portal venous pressure and hepatic venous pressure were avariant from control values. These findings suggest that congestive hyperemia was not occurred in intrahepatic portal vascular system when portal flows were increased during dopamine and dobutamine infusion. The results of this study demonstrate that both dopamine and dobutamine did not produce selective increases in total liver blood flow. In addition, both agents should be safe to use to the normal liver patient; total liver blood flow did not decrease and intrahepatic congestive hyperemia was not occurred when portal flow was increased.—**KEY WORDS:** canine, dobutamine, dopamine, liver blood flow.

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Dopamine and dobutamine have been utilized for treatment of congestive heart failure and low cardiac output syndrome. Both agents exert positive inotropic actions with different effects on each vasculature. Dopamine produces vasoconstriction in high dose and vasodilatation of renal, coronary, cerebral, and mesenteric vascular beds by action on a specific dopamine receptor in low dose [1, 21]. Dobutamine produces a small vasodilatation of peripheral vascular beds by small action on a β -2 adrenergic receptor [21–23].

Liver blood flow is regulated by two separate circuits having different physiologic controls, the portal vein and hepatic artery. The hepatic artery, a branch of the abdominal aorta, functions as an autoregulator of liver blood flow. Blood from the abdominal viscera flows through the portal vein into the liver and is independent of hepatic function [8, 9]. Many kind of mechanisms have been reported to operate portal venous and hepatic arterial blood flows [8, 9, 14–16, 19, 20]. The effects of adrenergic receptors in both vessels have been thought as one of the important mechanisms to operate those flows [10, 20].

Few studies of liver circulation of dopamine and dobutamine have been conducted for cardiovascular and mesenteric actions of these agents and the mechanisms involved have not yet been clarified [4, 24]. The low dose of dopamine showed a large increase in portal flow with a decrease in mesenteric vascular resistance by action on a specific dopamine receptor. High dose of dopamine, however, produced a decrease in portal flow by action on a α -1 adrenergic receptor and that may produce a portal hypertension [12, 21]. Alternation in portal flow of dopamine and dobutamine may lead to the hepatic arterial

autoregulation. Systemic changes affecting dopamine and dobutamine infusion could make a great effect on both hepatic arterial and portal venous flows.

Currently, dopamine and dobutamine have gained wide clinical usage during surgery with acute or chronic congestive heart failure and emergency treatment. Veterinary surgery is performed to correct portal-systemic circulation shunts (congenital and acquired) as well as diseases leading to portal hypertension [2]. A thorough understanding of selective effects of dopamine and dobutamine on liver circulation and an appropriate choice of these drugs are essential in the treatment of these disorders and prevention of postoperative hepatic insufficiency. The purpose of this study was to examine the selective effects of dopamine and dobutamine on liver circulation with emphasis on both changes in hepatic arterial and portal venous flows.

MATERIALS AND METHODS

Animals and anesthesia: Twelve healthy adult mongrel dogs (18.7 ± 5.1 kg) with negative microfilaria tests were anesthetized with sodium thiopental and intubated for controlled ventilation with a volume respirator (KV-1+1, Kimura Medical Instruments). Blood gases and pH were maintained within physiologic normal range by controlling ventilation and administering sodium bicarbonate. Intravenous sodium pentobarbital (6 mg/kg/hr) was continuously administered with lactated Ringer's solution (10 ml/kg/hr) through a right cephalic vein.

Surgical procedure: A 6F catheter was inserted through the right femoral artery to the level of the celiac artery for determining arterial pressure (AP) and for blood collec-

tion. Another 6F catheter was inserted through the left femoral vein to the level of the caudal vena cava for administration of drugs. A 6F pig's tail catheter was inserted through the right femoral vein and passed into the hepatic vein for monitoring of hepatic venous pressure (HVP). A 7F Swan-Ganz thermistor-tipped catheter was inserted through the right jugular vein and passed into the pulmonary artery for determining cardiac output.

A midline celiotomy was performed from the xiphoid cartilage to approximately 5 cm caudal to the umbilicus. The hepatorenal ligament was incised and the proper hepatic artery and the portal vein were carefully isolated. A 2–3 mm electromagnetic flowmeter probe (FC-020T, FB-030T, Nihon Kohden Corp.) was placed around the hepatic artery for recording of hepatic arterial blood flow (HABF). The gastroduodenal artery was ligated to ensure that true hepatic arterial blood flow was measured. A purse string suture was made on the portal vein and a 4F catheter was inserted into it to measure portal venous pressure (PVP). Temporary splanchnic occlusion was accomplished with clamps placed on the celiac artery and the caudal vena cava cranial to the liver. A 3 cm longitudinal incision was made into the portal vein and a 6 mm in-line electromagnetic flowmeter probe (FP-060T, Nihon Kohden Corp.) was placed into it for recording of portal venous blood flow (PVBF). The portal venous incision was closed with a simple continuous suture pattern and clamps placed on the celiac artery and the caudal vena cava cranial to the liver were released. An average occlusion time was 10 min and maximum time was 13 min (Fig. 1).

Measurements and calculations: Heart rate was calculated from the electrocardiogram (ECG) using lead II, the standard limb lead. A thermal recorder (WS-682G, Nihon Kohden) was used via a polygraph (RMP-6018M, Nihon Kohden) to directly record electrocardiogram (ECG), arterial pressure (AP), portal venous pressure (PVP), hepatic venous pressure (HVP), hepatic arterial blood flow (HABF), portal venous blood flow (PVBF), and cardiac output (CO). Cardiac output was determined by the thermal dilution technic [6]. Mean arterial pressure

(MAP) was used as hepatic arterial pressure (HAP) since the hepatic artery is a branch of the abdominal aorta. Other parameters were calculated by the following equations:

$$\text{Total liver blood flow (TLBF)} = \text{PVBF} + \text{HABF}$$

$$\text{Pressure gradient of portal system (PGP)} = \text{PVP} - \text{HVP}$$

$$\text{Portal venous resistance (PVR)} = \text{PGP}/\text{PVBF}$$

$$\text{Mesenteric vascular resistance (MVR)} = (\text{MAP} - \text{PVP})/\text{PVBF}$$

$$\text{Hepatic arterial blood flow index (HABFI)} = (\text{HABF}/\text{CO}) \times 100$$

$$\text{Portal venous blood flow index (PVBFi)} = (\text{PVBF}/\text{CO}) \times 100$$

$$\text{Total liver blood flow index (TLBFI)} = (\text{TLBF}/\text{CO}) \times 100$$

Experimental protocol: Hemodynamic parameters were measured following a 30–60 min equilibration period. Dogs were randomly placed in two following groups: (a) dopamine infusion group (n=6); (b) dobutamine infusion group (n=6). After initial data acquisition, dopamine or dobutamine was infused with a infusion pump; the order of drug infusion rate was altered. Dopamine was infused at rates of 3, 7, and 15 $\mu\text{g}/\text{kg}/\text{min}$, and dobutamine was infused at rates of 5, 10 and 15 $\mu\text{g}/\text{kg}/\text{min}$. Each infusion rate was maintained for at least 15 min to allow for stabilization of all measured variables, at which time hemodynamic parameters were obtained.

Statistics: Data were represented by means $\pm$ standard deviation (SD). Paired Student's *t* tests were used to determine significant differences from the initial values. $P < 0.05$ was taken as the level of significance.

RESULTS

The cardiac index (CI) was significantly increased during dopamine and dobutamine infusion ($p < 0.05$). The heart rate was significantly increased ($P < 0.05$) at the 7 and 15 $\mu\text{g}/\text{kg}/\text{min}$ dopamine infusion rates ($P < 0.01$) and at the 5, 10 and 15 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine infusion rates ($P < 0.05$). The mean arterial pressure was significantly increased at the 15 $\mu\text{g}/\text{kg}/\text{min}$ dopamine infusion rate (Table 1).

Hepatic arterial blood flow was significantly decreased during dopamine infusion ($p < 0.01$) and significantly increased at the 5 and 10 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine infusion rates ($P < 0.05$). At the 15 $\mu\text{g}/\text{kg}/\text{min}$ dobutamine infusion rate, however, hepatic arterial blood flow was significantly decreased when compared to the control value ($p < 0.01$). Portal venous blood flow was significantly increased during dopamine and dobutamine infusion ($p < 0.05$).

Fig. 1. Schematic drawing of the experimental preparation. See text for detailed explanation.

Table 1. Changes in cardiac function during dopamine and dobutamine infusion

	Dopamine				Dobutamine			
	Control	3 $\mu\text{g/kg/min}$	7 $\mu\text{g/kg/min}$	15 $\mu\text{g/kg/min}$	Control	5 $\mu\text{g/kg/min}$	10 $\mu\text{g/kg/min}$	15 $\mu\text{g/kg/min}$
Heart rate (beats/min)	140 $\pm$ 14	144 $\pm$ 15	175 $\pm$ 19**	187 $\pm$ 23**	135 $\pm$ 15	158 $\pm$ 12*	152 $\pm$ 10*	146 $\pm$ 8*
Cardiac output index (l/min/m ²)	2.27 $\pm$ 0.18	2.29 $\pm$ 0.12*	2.52 $\pm$ 0.31*	2.96 $\pm$ 0.31**	2.01 $\pm$ 0.13	2.38 $\pm$ 0.20*	2.54 $\pm$ 0.27**	2.78 $\pm$ 0.41**
Mean arterial pressure (mmHg)	92 $\pm$ 14	89 $\pm$ 12	105 $\pm$ 18	144 $\pm$ 22**	88 $\pm$ 15	101 $\pm$ 16	84 $\pm$ 15	81 $\pm$ 15

Values are means $\pm$ SD. Significant changes from control: *P<0.05, **P<0.01.

Table 2. Hemodynamic changes in liver circulation during dopamine and dobutamine infusion

	Dopamine				Dobutamine			
	Control	3 $\mu\text{g/kg/min}$	7 $\mu\text{g/kg/min}$	15 $\mu\text{g/kg/min}$	Control	5 $\mu\text{g/kg/min}$	10 $\mu\text{g/kg/min}$	15 $\mu\text{g/kg/min}$
Hepatic arterial blood flow (ml/min/m ²)	177.3 $\pm$ 13.4	145.7 $\pm$ 16.9**	108.9 $\pm$ 17.5**	118.4 $\pm$ 18.4*	174.9 $\pm$ 15.7	191.7 $\pm$ 13.2*	197.6 $\pm$ 11.2*	150.6 $\pm$ 13.2**
Portal venous blood flow (ml/min/m ²)	318.0 $\pm$ 24.9	368.9 $\pm$ 28.6*	368.8 $\pm$ 29.2*	412.2 $\pm$ 31.4*	299.6 $\pm$ 39.9	328.8 $\pm$ 27.5*	376.4 $\pm$ 31.2**	402.3 $\pm$ 41.2**
Total liver blood flow (ml/min/m ²)	496.2 $\pm$ 24.2	514.7 $\pm$ 18.0	478.1 $\pm$ 27.6	530.7 $\pm$ 29.1*	474.5 $\pm$ 31.2	520.1 $\pm$ 21.2*	575.0 $\pm$ 24.8**	553.1 $\pm$ 33.2**
Portal venous resistance (mmHg/ml/min/m ²)	0.014 $\pm$ 0.003	0.012 $\pm$ 0.002	0.012 $\pm$ 0.003	0.010 $\pm$ 0.002*	0.013 $\pm$ 0.002	0.013 $\pm$ 0.003	0.012 $\pm$ 0.003	0.010 $\pm$ 0.003*
Mesenteric vascular resistance (mmHg/ml/min/m ²)	0.27 $\pm$ 0.05	0.22 $\pm$ 0.04*	0.24 $\pm$ 0.04	0.32 $\pm$ 0.08	0.27 $\pm$ 0.14	0.28 $\pm$ 0.11	0.21 $\pm$ 0.12	0.18 $\pm$ 0.15

Values are means $\pm$ SD. Significant changes from control: *P<0.05, **P<0.01.

Fig. 2. Hemodynamic changes in intrahepatic portal system during dopamine and dobutamine infusion. (mean $\pm$ SD). PVP: Portal venous pressure, PGP: Pressure gradient of portal system, HVP: Hepatic venous pressure.

Total liver blood flow was significantly increased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$) and all infusion rates of dobutamine ($P<0.05$). Portal venous resistance was significantly decreased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$) and at the 15 $\mu\text{g/kg/min}$ dobutamine infusion rate ($P<0.05$). Mesenteric vascular resistance was significantly decreased at the 3 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$) and did not differ from the control values at the other dopamine infusion rates and during dobutamine infusion (Table 2).

Portal venous pressure and hepatic venous pressure were avariant from the initial levels during dopamine and

Fig. 3. Changes in ratios of blood flow in the hepatic artery, portal vein, and total liver to cardiac output during dopamine and dobutamine infusion. The values are expressed as percentages of cardiac output. Values are means $\pm$ SD. Significant changes from control: *P<0.05 **P<0.01. TLBFI: total liver blood flow index, PVBFI: portal venous blood flow index, HABFI: hepatic arterial blood flow index.

dobutamine infusion. Pressure gradient of portal system that was calculated as the subtraction hepatic venous pressure from portal venous pressure was not significantly changed during dopamine and dobutamine infusion (Fig. 2).

Changes in ratios of blood flow in the hepatic artery (HABFI), and portal vein (PVBFI) and total liver

(TLBFI) to cardiac output during dopamine and dobutamine infusion are illustrated (Fig. 3). The control HABFI, PVBFI, and TLBFI of dopamine infusion group were 8, 14 and 22%, respectively. At the 3 $\mu\text{g/kg/min}$ dopamine infusion rate, PVBFI was significantly increased compared to the control value ($p < 0.05$). HABFI and TLBFI were significantly decreased from the control values at the 7 and 15 $\mu\text{g/kg/min}$ dopamine infusion rates ($p < 0.05$). The control HABFI, PVBFI, and TLBFI of dobutamine infusion group were 8, 15 and 23%, respectively. HVBFI, PVBFI, and TLBFI were avariant from the control values at the 5 and 10 $\mu\text{g/kg/min}$ dobutamine infusion rates. At the 15 $\mu\text{g/kg/min}$ dobutamine infusion rate, HABFI and TLBFI were significantly decreased from the control values ($p < 0.05$).

DISCUSSION

The use of electromagnetic flowmeters gives insight into the changes in the relationship between hepatic arterial and portal venous blood flow. However, the measurement of portal venous blood flow using electromagnetic owme outside the vessel has made difficult. The portal vascular wall has so low resilience that electromagnetic flowmeter is difficult to be placed around the portal vein with correct angle [3]. In the present study, therefore, electromagnetic flowmeter was placed into the portal vein using splanchnic occlusion technic and this manner enabled to take accurate and reliable measurement of portal venous blood flow [2].

Previous reports have demonstrated that both dopamine and dobutamine produce inotropic and chronotropic effects and dopamine produces vasoconstriction in high dose by action on β -1 adrenergic receptor [1, 21–23]. In this study, our results of cardiovascular effects of both agents were similar to those previously reported. Heart rate was increased to 8–17% above control value during dobutamine infusion. Dopamine produced a greater chronotropic response in proportion to the dosage of dopamine. Both dopamine and dobutamine produced greater increases in cardiac output. High dose of dopamine produced a greater increase in mean arterial pressure.

Previous studies have shown that portal flow depends upon cardiac output [5, 6, 9, 11, 15, 16]. In this study, both dopamine and dobutamine produced greater increase in protal venous blood flow by an elevation in cardiac output. However, at the 3 $\mu\text{g/kg/min}$ dopamine infusion rate, portal flow ratio to cardiac output was significantly increased and mesenteric vascular resistance was significantly decreased when compared with control values. Therefore, this increase in portal flow in low dose of dopamine was due to not only an elevation in cardiac output but also an increase in mesenteric blood flow by action on a specific dopamine receptor to mesenteric vascular bed. Both portal and hepatic venous pressures were avariant from control values when portal flows were increased during dopamine and dobutamine infusion.

Therefore, pressure gradient of portal system was not changed. These findings were supported by the results that intrahepatic portal vascular resistances were decreased when portal flow were increased. Furthermore, these findings suggest that congestive hyperemia was not occurred in intrahepatic portal vascular system when portal flows were increased during dopamine and dobutamine infusion. However, it is important to keep in mind that both dopamine and dobutamine may aggravate a portal hypertension to the patients such as congestive heart disease, cirrhosis, and chronic hepatitis.

There are three different opinions about the effect of dopamine on hepatic arterial flow. Oka *et al.* report that 1.5–1.0 $\mu\text{g/kg/min}$ of dopamine infusion produced an increase in hepatic arterial flow caused by a reduction in hepatic arterial resistance [18]. Hepatic arterial flow was decreased in proportion to the dosage of dopamine during halothane anesthesia by Matsumoto *et al.* [17]. Kageshima *et al.* report that hepatic arterial flow did not change during dopamine infusion in normal pig [12]. In this study, dopamine produced a great reduction in hepatic arterial flow. The mechanism of reciprocity of total hepatic flow (RTHF) may partially explain this observation [19]. The RTHF mechanism compensates for decreased (or increased) hepatic blood flow by a reduction (or increase) of either portal vein or hepatic artery flow. Lauth *et al.* referred to the RTHF mechanism as the hepatic arterial buffer response (HABR) based on the blood flow regulating effect of the hepatic artery [13–15]. By this mechanism, hepatic arterial flow adjusts the changes in total hepatic flow caused by variations in portal flow. Hirsch *et al.* reported that dopamine has a reduction effect in hepatic arterial flow [10]. In high dose of dopamine infusion, β -1 adrenergic response of dopamine may also explain this decrease in hepatic arterial flow. On the other hand, 5 and 10 $\mu\text{g/kg/min}$ of dobutamine infusions produced elevations in hepatic arterial flow. The previously reported findings that hepatic arterial flow was increased during dobutamine infusion and this result might be caused by parallel elevations between hepatic arterial flow and cardiac output [17, 21]. At the 15 $\mu\text{g/kg/min}$ dobutamine infusion rate, however, hepatic arterial flow was significantly decreased and the ratio of hepatic arterial flow to cardiac output was also decreased. One possibility is to assume that the RTHF mechanism was acted greater than the effecting by increasing in cardiac output in high dose of dobutamine.

Total liver blood flow was increased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate and all infusion rates of dobutamine. The ratio of total liver flow to cardiac output was decreased at the 7 and 15 $\mu\text{g/kg/min}$ dopamine infusion rates and 15 $\mu\text{g/kg/min}$ dobutamine infusion rate. These decreases were due to greater reductions in hepatic arterial flow.

The results of this study demonstrate that both of dopamine and dobutamine did not produce a selective increase in total liver blood flow. However, both agents might be safe to use to the normal liver patient; total liver

blood flow did not decrease and intrahepatic congestive hyperemia was not occurred when portal flow was increased.

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