The Effects of Dopamine and Dobutamine on Liver Oxygen Supply-Uptake Relationship in the Dog

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ABSTRACT. The effects of dopamine and dobutamine in various doses on liver oxygen supply-uptake relationship were studied in 12 mongrel dogs. Dopamine 3 and 7 $\mu\text{g/kg/min}$ infusion rates and dobutamine 5 $\mu\text{g/kg/min}$ infusion rate did not produce any changes in total liver oxygen delivery. On the contrary, total liver oxygen delivery was increased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate and dobutamine 10 and 15 $\mu\text{g/kg/min}$ infusion rates. The ratio of total liver oxygen delivery to the systemic oxygen delivery was increased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate. Liver oxygen extraction ratio was decreased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate and at the same rate of dobutamine. These decreases were due to the increases in oxygen delivery while both oxygen uptakes were avariant from control levels. The results of this study demonstrated that high dose of dopamine (15 $\mu\text{g/kg/min}$) and medium and high doses of dobutamine (10 and 15 $\mu\text{g/kg/min}$) should be useful to increase the liver oxygen delivery. However, these increases in liver oxygen delivery during dopamine and dobutamine infusion were not associated with an improvement in liver oxygen metabolism, since liver oxygen uptake was not changed.—**KEY WORDS:** dobutamine, dopamine, liver blood flow, liver oxygen extraction, liver oxygen supply-uptake relationship.

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Studies of dopamine and dobutamine on cardiovascular and/or peripheral vascular beds have been done extensively [1, 10, 18, 19, 22]. However, few studies of hepatic circulation and oxygenation on dopamine and dobutamine have been conducted and the mechanisms involved have not yet been clarified [5, 12, 13, 15, 20, 23].

Total liver oxygen delivery was determined both hepatic arterial and portal venous oxygen delivery. Furthermore, blood flow and oxygen content in those vessel are important factors of each oxygen delivery. 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, however, high dose of dopamine produced a decrease in portal flow by action on a α -1 adrenergic receptor and that may produce a portal hypertension [12, 18]. 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. Portal venous oxygen content is determined by the usage of mesenteric oxygen supply-uptake relationship that may be changed by the systemic and/or regional effects of dopamine and dobutamine [9].

The liver has many functions such as carbohydrate, protein, and fat metabolism, formation and excretion of bile, detoxification, phagocytosis, immunoreactions, and synthesis of blood coagulation factors. These functions are closely related to liver oxygenation. Decrease in liver oxygen supply results in centrilobular necrosis that contributes to the disruption of these liver functions [3, 14, 21].

Dopamine and dobutamine have gained wide clinical usage during surgery with acute or chronic heart failure

and emergency situation to maintain cardiac output and total body oxygen delivery. Currently, veterinary surgery is performed to correct portal-systemic circulation shunts (congenital and acquired) as well as diseases leading to portal hypertension [2]. Information regarding liver oxygen supply-uptake relationship during treatment affecting dopamine and dobutamine administration seems to be important when clinical decisions are being made. The purpose of this study was to examine the effects of dopamine and dobutamine on liver oxygen supply-uptake relationship with special emphasis on the effect of 1) changes in hepatic arterial and portal venous flows, 2) changes in arterial and portal venous oxygen content, and 3) changes in systemic oxygenation.

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 collection. Another 6F catheter was inserted through the left femoral vein to the level of the caudal vena cava for infusion of drugs. A 6F pig's tail catheter was inserted

through the right femoral vein and passed into the hepatic vein for determining hepatic venous pressure (HVP) and for blood collection. A 7F Swan-Ganz thermistor-tipped catheter was inserted through the right jugular vein and passed into the pulmonary artery for determining cardiac output and for blood collection.

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) and for blood collection. 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 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. Cardiac output was determined by the thermal dilution technique [6]. Mean arterial pressure (MAP) was used as hepatic arterial pressure (HAP) since the hepatic artery is a branch of the abdominal aorta.

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

Arterial, pulmonary arterial, portal and hepatic venous blood samples were obtained for measurements of pH/gas tensions and oxygen content and hemoglobin concentration (Hb) using a blood gas analyzer (GASTAT-1, Technomedica), and cytometer (MEK-5158, Nihon Kohden).

Total liver blood flow (TLBF) was calculated as the sum of portal venous blood flow and hepatic arterial blood flow (PVBF + HABF). Systemic oxygen delivery (D_{so_2}) was calculated as the product of cardiac output times arterial oxygen content ($CO \times Ca_{o_2}$). Liver oxygen delivery (D_{lo_2}) was calculated as the sum of hepatic arterial oxygen delivery ($D_{hao_2} = HABF \times Ca_{o_2}$) and the portal venous oxygen delivery ($D_{pvo_2} = PVBF \times C_{pvo_2}$). Liver oxygen delivery index ($D_{lo_2}I$) was ratio of oxygen delivery of the liver to systemic oxygen delivery ($D_{lo_2}/D_{so_2} \times 100$). Hepatic arterial oxygen delivery index ($D_{hao_2}I$) and portal venous oxygen delivery index ($D_{pvo_2}I$) were also calculated ($D_{hao_2}I = D_{hao_2}/D_{so_2} \times 100$, $D_{pvo_2}I = D_{pvo_2}/D_{so_2} \times 100$). Mesenteric oxygen delivery was calculated as the product of portal venous blood flow times arterial oxygen content ($PVBF \times Ca_{o_2}$). Systemic oxygen uptake (V_{so_2}) was calculated as the subtraction oxygen content of mixed venous blood from arterial oxygen content ($Ca_{o_2} - C_{vo_2}$) times cardiac output. Liver oxygen uptake (V_{lo_2}) was calculated as a difference between liver oxygen delivery and the product of hepatic venous blood flow times oxygen content of hepatic venous blood ($D_{lo_2} - HVBF \times C_{hvo_2}$). Mesenteric oxygen uptake (V_{mo_2}) was calculated as the difference between the hepatic venous and arterial oxygen content ($Ca_{o_2} - C_{hvo_2}$) times portal venous blood flow. Liver oxygen extraction ratio ($V_{lo_2}/D_{lo_2} \times 100$) was also calculated.

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 Telumo infusion pump; the order of drug infusion rate was altered. Dopamine was infused at rates of 3, 7 and 15 $\mu\text{g/kg/min}$, and dobutamine was infused at rates of 5, 10, and 15 $\mu\text{g/min}$. Each infusion rate was maintained for at least 15 min to allow for stabilization of all measured variables, at which time hemodynamic parameters and blood samples 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

Hepatic arterial blood flow was significantly decreased during dopamine infusion ($p < 0.01$) and significantly increased at the 5 and 10 $\mu\text{g/kg/min}$ dobutamine infusion rates ($P < 0.05$). At the 15 $\mu\text{g/kg/min}$ dobutamine infusion

Table 1. Changes in liver blood flow during dopamine and dobutamine administration

	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**

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

Fig. 2. Changes in oxygen content of arterial and portal blood during dopamine and dobutamine infusion. (mean $\pm$ SD). Cao₂: arterial oxygen content, Cpvo₂: oxygen content of portal blood.

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 ($p<0.05$). Total liver blood flow was significantly increased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$) and all infusion rate of dobutamine ($p<0.05$) (Table 1).

Arterial oxygen content was avariant from the control values during dopamine and dobutamine infusion. Oxygen content of portal blood was significantly increased at the 7 and 15 $\mu\text{g/kg/min}$ dopamine infusion rates ($P<0.05$) and 15 $\mu\text{g/kg/min}$ dobutamine infusion rate ($P<0.05$) (Fig. 2).

Systemic oxygen delivery and uptake were significantly increased at the 7 and 15 $\mu\text{g/kg/min}$ dopamine infusion rates ($P<0.05$) and 10 and 15 $\mu\text{g/kg/min}$ dobutamine infusion rates ($P<0.05$). Mesenteric oxygen delivery was significantly increased at the 7 and 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$) and 15 $\mu\text{g/kg/min}$ dobutamine infusion rate ($P<0.05$). Mesenteric oxygen uptake was avariant from the control values during dopamine and dobutamine infusion except for the 10 $\mu\text{g/kg/min}$ dobutamine infusion. Hepatic arterial oxygen delivery was significantly decreased during dopamine infusion ($P<0.05$) and was avariant from the control value during dobutamine infusion. Portal venous oxygen delivery was significantly increased during dopamine and dobutamine infusion ($P<0.05$). Total liver oxygen delivery was significantly increased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$). Liver oxygen uptake was avariant from the control values during dopamine and dobutamine infusion. Liver oxygen extraction ratio was significantly decreased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($P<0.05$) and 15 $\mu\text{g/kg/min}$ dobutamine infusion rate ($P<0.05$) (Table 2).

Changes in ratios of oxygen delivery of the hepatic artery (Dhao₂I), portal vein (Dpvo₂I), and total liver (Dlo₂I) to systemic oxygen delivery during dopamine and dobutamine infusion are illustrated (Fig. 3). The control Dhao₂I, Dpvo₂I, and Dlo₂I of dopamine infusion group were 7.7, 8.6 and 16.3%, respectively. Dhao₂I was significantly decreased compared to the control value

Table 2. Changes in oxygen supply-uptake relationship during dopamine and dobutamine administration

	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 $\mu\text{g/kg/min}$
Systemic oxygen delivery	100	109 $\pm$ 6	118 $\pm$ 10*	124 $\pm$ 15.3*	100	112 $\pm$ 12	121 $\pm$ 15*	135 $\pm$ 11*
Systemic oxygen uptake	100	119 $\pm$ 8	118 $\pm$ 14*	159 $\pm$ 21**	100	112 $\pm$ 24	124 $\pm$ 15*	135 $\pm$ 17*
Mesenteric oxygen delivery	100	107 $\pm$ 11	135 $\pm$ 15*	159 $\pm$ 24**	100	105 $\pm$ 14	120 $\pm$ 16	143 $\pm$ 22*
Mesenteric oxygen uptake	100	90 $\pm$ 26	114 $\pm$ 19	103 $\pm$ 17	100	101 $\pm$ 19	128 $\pm$ 16*	119 $\pm$ 11
Hepatic arterial oxygen delivery	100	76 $\pm$ 10*	59 $\pm$ 24**	49 $\pm$ 20**	100	119 $\pm$ 22	115 $\pm$ 18	95 $\pm$ 18
Portal venous oxygen delivery	100	121 $\pm$ 8*	126 $\pm$ 12*	208 $\pm$ 39**	100	111 $\pm$ 17	137 $\pm$ 15*	164 $\pm$ 32**
Total liver oxygen delivery	100	100 $\pm$ 4	101 $\pm$ 18	151 $\pm$ 27*	100	114 $\pm$ 16	127 $\pm$ 13*	131 $\pm$ 18*
Liver oxygen uptake	100	103 $\pm$ 13	99 $\pm$ 6	112 $\pm$ 18	100	101 $\pm$ 17	110 $\pm$ 26	103 $\pm$ 22
Liver oxygen extraction ratio	100	105 $\pm$ 8	97 $\pm$ 33	75 $\pm$ 20*	100	93 $\pm$ 17	89 $\pm$ 15	79 $\pm$ 19*

Values are expressed as percentages of control (control equals 100%).

Significant changes from control: *P<0.05, **P<0.01 (the analysis was performed on the absolute values obtained).

Fig. 3. Changes in ratios of oxygen delivery in the hepatic artery, portal vein, and total liver to systemic oxygen delivery during dopamine and dobutamine infusion. The values are expressed as percentages of systemic oxygen delivery. Values are means $\pm$ SD. Significant changes from control: * $P < 0.05$, ** $P < 0.01$. Dlo₂I: total liver oxygen delivery index, Dpvo₂I: portal venous oxygen delivery index, Dhao₂I: hepatic arterial oxygen delivery index.

($p < 0.01$). Dpvo₂I, and Dlo₂I were significantly increased from the control values at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate ($p < 0.05$). The control Dhao₂I, Dpvo₂I, and Dlo₂I of dobutamine infusion group were 7.8, 9.5, and 17.3%, respectively. Dpvo₂I, and Dlo₂I were avariant from the control values during dobutamine infusion. At the 15 $\mu\text{g/kg/min}$ dobutamine infusion rate, Dhao₂I was significantly decreased from the control values ($p < 0.05$).

DISCUSSION

Anesthesia with pentobarbital produces a stable cardiovascular condition in the dog [8] and no effect on liver blood flow [7]. The use of electromagnetic flowmeters gives insight into the changes in the relationship between hepatic arterial and portal venous blood flow. The experimental preparation that measures both hepatic arterial and portal venous flows using electromagnetic flowmeters has been studied previously and shown to be stable [11]. However, the measurement of portal venous blood flow using electromagnetic flowmeter 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 [4]. In the present study, therefore, electromagnetic flowmeter was placed into the portal vein using splanchnic occlusion technic and this manner had enabled accurate and reliable measurement of portal venous blood flow [2].

Total liver oxygen delivery was not changed at the 3 and 7 $\mu\text{g/kg/min}$ dopamine infusion rates. These findings were resulted from the reciprocal oxygen delivery to the liver; hepatic arterial oxygen delivery was decreased and portal venous oxygen delivery was increased. The decrease in hepatic arterial oxygen delivery was caused by a large decrease in hepatic arterial blood flow, since little changes were observed in arterial oxygen content. This decrease in hepatic arterial flow may represent at least three different possibilities. First, reciprocity of total hepatic flow

(RTHF) mechanism was functioned by the decrease in portal flow [16]. The RTHF mechanism compensates for decreased (or increased) hepatic blood flow by a reduction (or increase) of either portal vein or hepatic artery flow. Secondly, selective reduction effect in hepatic arterial flow of dopamine was functioned [10]. Thirdly, β -1 adrenergic response of dopamine produced a vasoconstriction in hepatic artery. First possibility seems unlikely for the following reason; hepatic arterial flow and total liver flow were increased while portal flow was increased during 5 and 10 $\mu\text{g/kg/min}$ dobutamine infusion. On the contrary, the increase in portal venous oxygen delivery was caused not only by the increase in portal venous blood flow, but also by the increased in oxygen content of portal blood. The observed increase in portal venous oxygen content could be due to the increase in mesenteric oxygen delivery while mesenteric oxygen uptake was not changed. Kageshima *et al.* reports that total liver oxygen delivery was significantly increased by the increase in portal venous oxygen delivery during 10 $\mu\text{g/kg/min}$ dopamine infusion in normal pig [12]. At the 15 $\mu\text{g/kg/min}$ dopamine infusion rate, our data showed a similar result as a previous report; total liver oxygen delivery showed a large increase mainly caused by the doubly increase in portal venous oxygen delivery when compared to the control value. Furthermore, the ratio of total liver oxygen delivery to systemic oxygen delivery was also increased at this dose of dopamine infusion, while other doses of dopamine infusion did not change. As well as the 15 $\mu\text{g/kg/min}$ dopamine infusion rate, total liver oxygen delivery showed a large increase at the 10 and 15 $\mu\text{g/kg/min}$ dobutamine infusion rates. However, the ratio of total liver oxygen delivery to systemic oxygen delivery was not increased at these doses of dobutamine.

Liver oxygen extraction ratio has been used for assessing liver oxygenation, since it reflects both changes in its parameters as oxygen delivery and uptake [17, 19]. In the present investigations, liver oxygen extraction ratio was decreased at the 15 $\mu\text{g/kg/min}$ dopamine infusion rate and at the same rate of dobutamine. The similar observations were obtained in our previous studies and we misunderstood that the 15 $\mu\text{g/kg/min}$ dopamine infusion rate improved liver oxygen metabolism [5, 23]. The decreases in liver oxygen extraction ratios were due to the increases in oxygen delivery while both oxygen uptakes were avariant from control levels. Whenever liver oxygen metabolism improves, liver oxygen uptake should increase. Therefore, the decrease in oxygen extraction ratio was not due to the decrease in liver oxygen metabolism but due to an over-supply of oxygen to the liver.

The results of this study demonstrated that high dose of dopamine (15 $\mu\text{g/kg/min}$) and medium and high doses of dobutamine (10 and 15 $\mu\text{g/kg/min}$) should be useful to increase the liver oxygen delivery. However, these increases in liver oxygen delivery during dopamine and dobutamine infusion were not associated with an improvement in liver oxygen metabolism, since liver oxygen uptake did not change. In addition, high dose of dopamine

and dobutamine may produce or aggravate the portal hypertension to the patients with congestive mesenteric circulation, since they produce a significant increase in portal venous blood flow.

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