The Effect of Indomethacin on Liver Blood Flow and Oxygen Supply-Uptake Relationship in the Dog

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ABSTRACT. The effects of indomethacin on liver blood flow and oxygen supply-uptake relationship were investigated using a right heart bypass technique. Portal venous blood flow was decreased by the mesenteric vascular effects of indomethacin, which produce intense mesenteric vasoconstriction. Hepatic arterial blood flow was increased and therefore, total liver blood flow was not significantly changed after indomethacin administration. Portal venous oxygen delivery was significantly decreased by reductions in both portal venous blood flow and portal venous oxygen content. Total liver oxygen delivery, however, was not changed after indomethacin administration. This response was caused by a large increase in hepatic arterial oxygen delivery. Liver oxygen uptake and liver oxygen extraction ratio were not changed after indomethacin administration. We conclude, therefore, that total liver blood flow and oxygen delivery were well maintained, even if the mesenteric vascular effects of indomethacin decreased portal venous blood flow and portal venous oxygen delivery.

KEY WORDS: canine, indomethacin, liver blood flow, liver oxygen supply-uptake relationship, right heart bypass.


Indomethacin has gained wide clinical and experimental usage as a prostaglandin synthetase inhibitor. Indomethacin has been shown to decrease perfusion in several vascular beds including the kidney, stomach, intestine, spleen and brain [2, 3, 5, 8, 14, 18, 26]. In the mesenteric vascular beds, indomethacin produces intense vasoconstriction and decreases mesenteric blood flow [3, 5, 11].

The liver is a key organ in body metabolism and defense mechanisms and those functions are closely related to liver circulation. The portal circulation accounts for about 75%–80% of the total liver flow and about 50% of the total liver oxygen supply, and is wholly dependent on mesenteric, gastric, and splenic circulations and is not controlled by the liver itself [9, 13, 20]. Therefore, a decrease in portal flow due to administration of indomethacin would be hypothesized to change liver flow and oxygen supply-uptake relationship.

In the last ten years, a considerable number of indomethacin studies have been made on mesenteric circulation, however, no studies on liver circulation and/or oxygenation have been performed. We investigated the effects of indomethacin on liver circulation using a modified right heart bypass surgery.

MATERIALS AND METHODS

Animals and anesthesia: Eight healthy adult mongrel dogs with negative microfilaria tests, weighing 21.0±8.1 kg, were fasted for 24 hr. Anesthesia induction was achieved with sodium thiopental, 8–25 mg/kg IV. Muscle relaxation was achieved with pancuronium bromide, 0.05 mg/kg IV. Anesthesia was maintained with sodium pentobarbital (6 mg/kg/hr) that was continuously administered with lactated Ringer’s solution (10 mg/kg/hr) through the right cephalic vein. Controlled ventilation to maintain a Paco2 of 35–40 mmHg was provided through an endotracheal tube using a quantitative respirator (KV-1+1, Kimura Medical Instruments). Base Excess was maintained within range of -5 to 0 by administering sodium bicarbonate.

Modified right heart bypass surgery: A 6F catheter was inserted through the 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 jugular vein to the level of the anterior thoracic cauda to measure central venous pressure (CVP).

Right heart bypass was then established. Laparotomy was performed and a 4F catheter was inserted into the splenic vein and passed proximally into the portal vein for measuring portal venous pressure (PVP) and for blood collection. A 2–3 mm electromagnetic flowmeter probe (FC-020TB-0030T, Nihon Kohden) 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.

Thoracotomy was performed by median stenotomy. The caudal thoracic vena cava was carefully isolated and encircled with umbilical tape and a 8F catheter was inserted through the caudal thoracic vena into the hepatic vein for determining of hepatic venous pressure (HVP) and for blood collection. The heart was exposed by incising the pericardium from the apex to the base. The pulmonary artery and the aortic root were isolated. The pulmonary artery was encircled with umbilical tape and a 6F catheter was inserted to collect mixed venous blood. Left atrial pressure (LAP) was recorded by another 6F catheter inserted through the left atrial appendage into the left atrium. Sodium heparin (200 IU/kg) was then administered intravenously and activated coagulation time (ACT) was maintained at 400 to 500 sec by additional heparin.
administration.

A 10–12F perfusion cannula was inserted through the right ventricular outflow tract into the pulmonary artery and a 16–18F venous drainage cannula through the right atrium into the right ventricle. With placement of the cardiac cannulas, the umbilical tape on the pulmonary artery was tightened to initiate extracorporeal circulation through the right heart bypass.

After stabilization of blood flow, a 12–14F venous drainage cannula was inserted into the left femoral vein and passed into the abdominal cava; this cannula tip was positioned just caudal to the junction of the left renal vein. A second cannula of the same size was inserted through the superior site of the vena cava and passed to the junction of the hepatic vein and vena cava. Umbilical tape with Rommel tourniquets were placed around the abdominal cava just proximal to the renal veins and thoracic cava completely isolating the hepatic circulation (Fig. 1).

To proceed with extracorporeal circulation, the rotational speed of roller pump and height of a reservoir were adjusted so that AP, CVP, and LAP were almost the same as those before the initiation of extracorporeal circulation. The extracorporeal circulatory systems consist of a roller pump (Tonokura Medical Industry), a heat exchanger (MHE-32P, Senko Medical Industry), a reservoir (11, Terumo), TYGON tube (Norton), and perfusion and venous drainage cannulas (BARD). The three drainage cannulas (i.e., right heart, liver, caudal tract) were connected to Stirling resistors composed of a penrose drain and TYGON tube.

The priming solution was prepared by mixing physiological saline and dextran 40 (Midori Juji) (4:1) and adding 4,000 IU/l of sodium heparin and 24 mEq/l of sodium bicarbonate. Total volume of the solution administered was determined by a dilution of the hematocrit to 20–25%.

Measurements and calculations: A thermal recorder (WS-682G, Nihon Kohden) was used via a polygraph (RMP-6018M, Nihon Kohden) to directly record electrocardiogram (ECG), arterial pressure (AP), central venous pressure (CVP), left atrial pressure (LAP), hepatic venous pressure (HVP), portal venous pressure (PVP), hepatic arterial blood flow (HABF), hepatic venous blood flow (HVBF), and cardiac output (CO). Mean arterial pressure (MAP) was used as hepatic arterial pressure (HAP) since the hepatic artery is a branch of the abdominal aorta. 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).

Portal venous blood flow (PVBF) was calculated as the subtraction of hepatic arterial blood flow from hepatic venous blood flow (HVBF-HABF). Hepatic arterial resistance (HAR) was calculated as the subtraction hepatic venous pressure from mean arterial pressure (MAP-HVP) divided hepatic arterial blood flow. Portal venous resistance (PVR) and mesenteric vascular resistance (MVR) were also calculated (PVR = (PVP-HVP)/PVBF, MVR = (MAP-PVP)/PVBF). Systemic oxygen delivery (Dso2) was calculated as the product of cardiac output times arterial oxygen content (CO × CaO2). Liver oxygen delivery (DL02) was calculated as the sum of hepatic arterial oxygen delivery (Dha02 = HABF times CaO2) and the portal venous oxygen delivery (Dpvo2 = PVBF times oxygen content of portal venous blood (Cpvo2)). Mesenteric oxygen delivery was calculated as the product of portal venous blood flow times arterial oxygen content (PVBF × CaO2). Systemic oxygen uptake (Vso2) was calculated as the subtraction oxygen content of mixed venous blood from arterial oxygen content (CaO2 - CvO2) times cardiac output. Liver oxygen uptake (VL02) was calculated as a difference between liver oxygen delivery and the product of hepatic venous blood flow times oxygen content of hepatic venous blood (Dl02 - HVBF × ChvO2). Mesenteric oxygen uptake (Vmo2) was calculated as the difference between the hepatic venous and the arterial oxygen content (CaO2 - CvO2) times portal venous blood flow. Systemic oxygen extraction ratio (Vso2/Dso2 × 100), liver oxygen extraction ratio (VL02/Dl02 × 100), and mesenteric oxygen extraction ratio (Vmo2/Dmo2 × 100) were also calculated.

Preparation of indomethacin: Indomethacin (10 mg/ml, 1-[p-Chlorobenzoyl]-5-methoxy-2methylindole-3-acetic acid) was dissolved in 1.32% (wt/vol) NaClO3 and diluted with physiologic saline. The solution was isotonic and the pH was 7.8.

Experimental protocol: After hemodynamics and acid-base equilibrium were stabilized for 30–60 min following the start of extracorporeal circulation, hemodynamic parameters and blood samples were obtained. After initial hemodynamic parameter determinations, indomethacin (10 mg/kg) was administered in the venous reservoir.

Fig. 1. Schematic drawing of modified right heart bypass preparation.
Thirty minutes following indomethacin administration, hemodynamic parameters and blood samples were obtained. During the experiment, the speed of the roller pump was fixed to maintain the initial cardiac output value.

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

**RESULTS**

Table 1 shows changes in hepatic hemodynamics before and after indomethacin administration.

After indomethacin administration, hepatic arterial blood flow was significantly increased (p<0.01) and portal venous blood flow was significantly decreased (p<0.01) when compared to the control values; hepatic venous blood flow was avariant from the control value. Portal venous pressure and hepatic venous pressure were avariant from the control values after indomethacin administration, and mean arterial pressure was significantly increased when compared to the control value (p<0.01). Hepatic arterial resistance was avariant from the control value after indomethacin administration, and portal venous resistance and mesenteric vascular resistance were significantly increased when compared to the control value (p<0.05, 0.01).

The arterial oxygen content and hepatic venous oxygen content were avariant from the control values after indomethacin administration; portal venous oxygen content was significantly decreased when compared to the control value (p<0.01) (Fig. 2).

Table 2 shows changes in oxygen supply-uptake relationship before and after indomethacin administration.

After indomethacin administration, systemic oxygen delivery, uptake, and extraction ratio were avariant from the control values. Mesenteric oxygen delivery was significantly decreased when compared to the control value (p<0.01), and mesenteric oxygen uptake was avariant from the control value after indomethacin administration; mesenteric oxygen extraction ratio was significantly decreased when compared to the control value (p<0.01). Hepatic arterial oxygen demand was significantly increased (p<0.05), and portal venous oxygen demand was significantly decreased (p<0.01) after indomethacin administration; total liver oxygen demand was avariant from the control value. Liver oxygen uptake and liver oxygen extraction ratio were avariant from the control values after indomethacin administration. In the control period, the ratios of oxygen demand in the hepatic arterial and portal venous to total liver oxygen demand were 40 and 60%, respectively, and changed 72 and 28% after

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Significant changes from control*: p<0.05, **: p<0.01.
MAP: Mean arterial pressure, PVP: Portal venous pressure, HVP: Hepatic venous pressure.

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The 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). Dso₂: Systemic oxygen delivery, Vso₂: Systemic oxygen uptake, Eso₂: Systemic oxygen extraction ratio, Dmo₂: Mesenteric oxygen delivery, Vmo₂: Mesenteric oxygen uptake, Emo₂: Mesenteric oxygen extraction ratio, Dhao₂: Hepatic arterial oxygen delivery, Dpvo₂: Portal venous oxygen delivery, Vlo₂: Liver oxygen delivery, Elo₂: Liver oxygen uptake, Vlo₂: Liver oxygen extraction ratio.
indomethacin administration (Fig. 3).

**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 flowmeter outside the vessel has made difficult. The portal vascular wall has so low resilience that electromagnetic flowmeter is difficult to placed around the portal vein with correct angle [1]. In the present study, therefore, portal venous flow was calculated as the subtraction hepatic arterial blood flow from total liver blood flow which took accurate and reliable measurement using a modified right heart bypass preparation.

It is well recognized that prostaglandins can by synthesized from either vascular endothelium or gastric mucosal cells [12, 22] and act as regulatory hormones influencing perfusion through individual vascular beds. Prostaglandins $E_1$, $E_2$, and $I_2$ have a primary vasodilating effect on the mesenteric circulation [7, 10]. As indomethacin has obvious vascular effects due to prostaglandin inhibition, it is reasonable to assume that mesenteric circulation is also affected. Indomethacin has been shown to produce intense vasoconstriction in the mesenteric vascular bed of the dog under basal flow conditions [4] and when flow is controlled with a pump [2]. However, another prostaglandin inhibitor did not produce similar mesenteric vasoconstriction and the mechanism of mesenteric vasoconstriction by indomethacin is unknown [3, 5]. In the present study, indomethacin produced intense mesenteric vasoconstriction and decreased mesenteric blood flow and these results were same as the previous reports [2, 3, 5]. In contrast to the effects of indomethacin on mesenteric blood flow (portal venous blood flow), hepatic arterial blood flow was increased. This increase in hepatic arterial blood flow was probably due to the mechanism of reciprocity of total hepatic flow (RTHF) [23]. The RTHF mechanism compensates for decreased (or increased) hepatic blood flow by a reduction (or increase) of either portal vein or hepatic artery flow. Lautt *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 [15–17]. By this mechanism, hepatic arterial flow adjusts the changes in total hepatic flow caused by variations in portal flow. In this study, total liver blood flow was not changed before and after indomethacin administration. This finding also supports that RTHF occurs after indomethacin administration.

As well as total liver blood flow, liver oxygen delivery is well maintained after indomethacin administration. Liver oxygen delivery is determined by portal venous oxygen delivery and hepatic arterial oxygen delivery. In normal liver, each oxygen delivery accounts for 50% of total liver oxygen delivery [9, 13]. Portal venous oxygen delivery showed a large decrease during indomethacin administration. This decrease in portal venous oxygen delivery resulted from not only the decrease in portal venous blood flow as we have mentioned before but also the decrease in oxygen content in the portal vein. Furthermore, the decrease in portal venous oxygen content was due to the increase in mesenteric oxygen extraction ratio after indomethacin administration. On the other hand, hepatic arterial oxygen delivery showed a large increase due to the effect of indomethacin. This increase in hepatic arterial oxygen delivery resulted from the increase in hepatic arterial blood flow that should be caused by RTHF mechanism. Therefore, the reason that total liver oxygen delivery was maintained well after indomethacin administration was due to reciprocal changes in portal venous and hepatic arterial oxygen delivery.

Liver oxygen extraction ratio has been used for assessing liver oxygenation, since it reflects both changes in its parameters as oxygen delivery and uptake [19, 21]. In the present investigations, total liver oxygen delivery and liver oxygen uptake were not significantly changed, thus, liver oxygen extraction ratio was not also changed after indomethacin administration.

Therefore, total liver blood flow and oxygen delivery were well maintained by various compensatory mechanisms; even though the mesenteric vascular effects of indomethacin decreased both portal venous blood flow and portal venous oxygen delivery.

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**REFERENCES**

THE EFFECT OF INDOMETHACIN ON LIVER CIRCULATION


