Effects of Hypovolemic Shock and Reperfusion on Liver Blood Flow in the Dog

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(Received 26 July 1994/Accepted 17 April 1995)

ABSTRACT. Liver blood flow was investigated in hypovolemic shock using a modified right heart bypass technique which can obtain accurate portal blood flow. Findings were similar to those previously reported: hepatic blood flow accounted for 34% of cardiac output in this study; 76% of hepatic blood flow was delivered from the portal vein and 24% from the hepatic artery. Hypovolemic shock markedly decreased total liver blood flow by a reduction in portal venous blood flow. The findings of this study provide evidence that mesenteric blood flow is a peripheral circulation circuit where blood flow is restricted during reduced circulatory volume. Development of a hepatic arterial buffer response during hypovolemic shock was confirmed by an increased ratio of hepatic arterial flow to cardiac output. Reduced total hepatic blood flow during hypovolemic shock returned to control flow by an increase in hepatic arterial flow after reperfusion. The results of this study demonstrate that compensated reactions for maintaining liver blood flow mainly due to the hepatic arterial buffer response were functioned both during hypovolemic shock and after elimination of shock.—KEY WORDS: canine, hepatic arterial buffer response, hypovolemic shock, liver blood flow, right heart bypass.


Hepatic blood flow is regulated by two separate circuits having different physiologic controls, the portal vein and hepatic artery. Hepatic arterial blood flow accounts for about 20 to 24% of the total hepatic blood flow with the remainder supplied by the portal vein. The hepatic artery, a branch of the abdominal aorta, functions as an autoregulator of liver blood flow. The hepatic arterial autoregulation is of lesser degree than the cerebral or coronary autoregulation mechanisms [6, 13, 18, 21-23]. Blood from the abdominal viscera flows through the portal vein into the liver and is independent of hepatic function [9, 12]. The mechanisms have been reported to operate between the portal venous and hepatic arterial flows in order to maintain total hepatic flow, but they remain unclear in cases of shock [6, 13, 14].

Hemorrhage, trauma and burns reduce circulating blood volume and cardiac output, resulting in hypovolemic shock. Systemic blood pressure is decreased by reduced cardiac output but is increased by sympathetic reflexes and catecholamine release via the aortic and carotid sinuses and subsequently increased peripheral vascular resistance [2, 29, 30]. Shock alters blood flow to organ circuits by enhanced vascular reflexes [5, 28, 30].

The liver, a key organ in bodily metabolism and defense mechanisms, plays an important role in the pathology and outcome of hypovolemic shock. Fewer studies of hepatic circulation during hypovolemic shock [7, 14, 25, 30] have been conducted than for cerebral, coronary and renal circulations and the mechanisms involved have not yet been clarified.

Currently, veterinary surgery is performed on dogs and cats to correct portal-systemic circulation shunts (congenital and acquired) as well as diseases leading to portal hypertension. A thorough understanding of the hepatic circulation is essential in the diagnosis and treatment of these disorders. Prevention of postoperative hepatic insufficiency also requires studies in anesthetic management and hepatic circulation. We investigated liver circulation and the effects of changes in the systemic circulation during and after hypovolemic shock using a modified right heart bypass surgery (3-vessel-bleeding right heart bypass surgery).

MATERIALS AND METHODS

Experimental procedure: Eight healthy adult mongrel dogs (19.1±6.1 kg) with negative microfilaria tests were anesthetized with sodium thiopental (25 mg/kg) 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 (7.35 < pH <7.45, 35 mmHg < Pco2 < 45 mmHg) 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.

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 cranial thoracic vena cava to measure central venous pressure (CVP).

Right heart bypass was then established. A midline celiotomy was performed from the xiphoid cartilage to approximately 5 cm caudal to the umbilicus. A 4F catheter was inserted into the splenic vein and passed proximally into the portal vein to measure portal venous pressure (PVP). The hepatorenal ligament was incised and the caudal prerenal vena cava and the proper hepatic artery
were carefully isolated. Umbilical tape was then applied to the prerenal vena cava and 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.

Thoracotomy was performed by median sternotomy. The caudal thoracic vena cava was carefully isolated and encircled with umbilical tape. The heart was exposed by incising the pericardium from the apex to the base. The pulmonary artery was isolated from aortic root. The pulmonary artery was encircled with umbilical tape and a 6F catheter was inserted to determine pulmonary arterial pressure (PAP). Left atrial pressure (LAP) was recorded by a 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 was positioned 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 extracorporeal blood flow, a 12–14F venous drainage cannula was inserted into the left femoral vein and passed into the caudal vena 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 previously isolated vena cava and passed to the junction of the hepatic vein and vena cava. A 6F catheter was inserted through the caudal thoracic vena cava into the hepatic vein for monitoring of hepatic venous pressure (HVP). Umbilical tape with Rommel tourniquets was placed around the abdominal vena cava just proximal to the renal veins and thoracic vena cava completely isolating the hepatic circulation (Fig. 1).

Roller pump output and reservoir height were adjusted so that AP, CVP, and LAP were similar as values prior to the initiation of extracorporeal circulation. The extracorporeal circuit consisted of a roller pump (Tonokura Medical Industry), a heat exchanger (MHE-32P, Senko Medical Industry), a reservoir (1 L, Thermo), TYGON tube (Norton), and perfusion and venous drainage cannulas (BARD). The three drainage cannulas (i.e. right heart, liver, caudal trunk) were connected to Starling 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 4000 IU of sodium heparin and 24 mEq of sodium bicarbonate per liter. Total volume of the solution administered was determined by a dilution of the hematocrit to 20–25%.

 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), pulmonary arterial pressure (PAP), central venous pressure (CVP), left atrial pressure (LAP), hepatic venous pressure (HVP), 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. Other parameters were calculated by the following equations:

\[
\text{Portal venous blood flow (PVBF)} = \frac{HVBF}{HABF}
\]

\[
\text{Hepatic arterial resistance (HAR)} = \frac{\text{MAP} - \text{HVP}}{\text{HABF}}
\]

\[
\text{Portal venous resistance (PVR)} = \frac{\text{PVP} - \text{HVP}}{\text{PVBF}}
\]

\[
\text{Hepatic arterial blood flow index (HABFI)} = \frac{\text{HABF}}{\text{CO}} \times 100
\]

\[
\text{Portal venous blood flow index (PVBF)} = \frac{\text{PVBF}}{\text{CO}} \times 100
\]

\[
\text{Hepatic venous blood flow index (HVBF)} = \frac{\text{HVBF}}{\text{CO}} \times 100
\]

Development of hypovolemic shock: Hemodynamic parameters were measured following a 30–60 min equilibration period following the start of extracorporeal circulation. After initial data acquisition, the roller pump speed was reduced over one min until mean arterial pressure decreased to 40 mmHg. Once developed systemic hypotension was maintained for 15 min. To eliminate
LIVER BLOOD FLOW DURING HYPOVOLEMIC SHOCK

The pump speed was increased until the cardiac output returned to the control level within one min. Hemodynamic parameters were obtained immediately after onset of shock, and immediately before and after reperfusion. Additional measurements were obtained at 10, 15 and 30 min after reperfusion.

Statistics: Data were represented by the mean ± standard deviation (SD). Multiple comparison one factor ANOVA was used to determine significant difference from the initial value. The correlation of hepatic arterial blood flow and portal venous blood flow to the cardiac output and systemic mean arterial pressure was analyzed using linear regression by least squares. P<0.05 was taken as the level of significance.

RESULTS

The cardiac index (CI) and stroke volume index (SI) were significantly decreased during hypovolemic shock (p<0.01). The stroke volume index was significantly increased 10 min after correction of the hypovolemia when compared to the initial control SI (p<0.05). When compared to the initial value, heart rate was significantly increased (P<0.05) during hypovolemia and significantly decreased (p<0.05) 10 min after it's elimination. During the hypovolemic period, mean arterial pressure was maintained at 40 mmHg; however it was significantly decreased immediately after shock when compared to the control mean arterial pressure (p<0.05). Left atrial pressure was significantly decreased during shock (p<0.01) (Table 1).

Hepatic arterial blood flow was significantly decreased to 57% of the control value during shock (p<0.01) and increased significantly after correction of hypovolemia when compared to the control hepatic arterial blood flow (p<0.01). Portal venous blood flow was significantly decreased to 39-52% of the control value during hypovolemic shock (p<0.01), but variant from the control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Shock</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>172±12</td>
<td>206±19*</td>
<td>202±21*</td>
</tr>
<tr>
<td>Cardiac output index (l/min/m²)</td>
<td>2.46±0.53</td>
<td>1.18±0.40**</td>
<td>1.16±0.36**</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat/m²)</td>
<td>14.29±4.40</td>
<td>5.73±2.65**</td>
<td>5.56±2.30**</td>
</tr>
<tr>
<td>Left atrial pressure (mmHg)</td>
<td>7.1±1.7</td>
<td>5.0±1.4**</td>
<td>5.2±1.7**</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>79±6</td>
<td>40±9**</td>
<td>40±0**</td>
</tr>
</tbody>
</table>

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

a) Fixed to control value by roller pump speed.
b) Fixed to 40 mmHg by roller pump speed.

Table 2. Changes in hepatic circulation during hypovolemic shock and after reperfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Shock</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic arterial blood flow (ml/min/kg)</td>
<td>7±1</td>
<td>44±2**</td>
<td>44±2**</td>
</tr>
<tr>
<td>Portal venous blood flow (ml/min/kg)</td>
<td>23±5</td>
<td>12±3**</td>
<td>9±2**</td>
</tr>
<tr>
<td>Hepatic venous blood flow (ml/min/kg)</td>
<td>30±6</td>
<td>16±3**</td>
<td>13±3**</td>
</tr>
<tr>
<td>Hepatic arterial resistance (mmHg/ml/min/kg)</td>
<td>14.56±1.70</td>
<td>10.75±3.76**</td>
<td>10.70±2.06**</td>
</tr>
<tr>
<td>Portal venous resistance (mmHg/ml/min/kg)</td>
<td>0.15±0.08</td>
<td>0.28±0.16**</td>
<td>0.50±0.15**</td>
</tr>
<tr>
<td>Hepatic arterial blood flow index (%)</td>
<td>8±1</td>
<td>9±4</td>
<td>10±1</td>
</tr>
<tr>
<td>Portal venous blood flow index (%)</td>
<td>26±3</td>
<td>25±4</td>
<td>22±2**</td>
</tr>
<tr>
<td>Hepatic venous blood flow index (%)</td>
<td>34±5</td>
<td>35±8</td>
<td>32±4</td>
</tr>
</tbody>
</table>

Values are means±SD. significant changes from control: *P<0.05, **P<0.01.
Fig. 2. Correlation between hepatic arterial blood flow (HABF) and cardiac output (CO). The line was obtained by linear regression analysis.

Fig. 3. Correlation between hepatic arterial blood flow (HABF) and mean arterial pressure (MAP). The line was obtained by linear regression analysis.

Fig. 4. Correlation between portal venous blood flow (PVBF) and cardiac output (CO). The line was obtained by linear regression analysis.

Fig. 5. Correlation between portal venous blood flow (PVBF) and mean arterial pressure (MAP). The line was obtained by linear regression analysis.

Fig. 6. Changes in ratios of blood flow in the hepatic artery, and portal and hepatic veins to cardiac output during hypovolemic shock and after reperfusion. The values are expressed as percentages of cardiac output. Values are the mean±SD. Significant changes from control: *P<0.05, **P<0.01. HVBF1: hepatic venous blood flow index, PVBF1: portal venous blood flow index, HABF1: hepatic arterial blood flow index.

value after correction of hypovolemia. Hepatic venous blood flow was significantly decreased to 44–54% of the control value during shock (p<0.01), but avariant from the initial level after elimination of shock. Hepatic arterial resistance was significantly decreased from the control value (p<0.01) during shock and following recovery from hypovolemia (p<0.01). Portal venous resistance was significantly increased during shock (p<0.01) and did not differ from the control value after correction of hypovolemia (Table 2).

The correlation of hepatic arterial blood flow and portal venous blood flow to the cardiac output and systemic mean arterial pressure revealed a significantly positive correlation (Figs. 2–5).

Changes in ratios of blood flow in the hepatic artery (HABF1), and portal (PVBF1) and hepatic veins (HVBF1) to cardiac output during and after hypovolemic shock are illustrated (Fig. 6). The control HABF1, PVBF1, and HVBF1 were 8, 26, and 34%, respectively. Fifteen min following hypovolemic shock, HABF1 was significantly increased compared to the control HABF1 (p<0.05) and PVBF1 was significantly decreased from the control PVBF1 (p<0.01). HVBF1 was avariant from the control value. After correction of the hypovolemic state, PVBF1 and HVBF1 were avariant from the control values; HABF1 was increased when compared to the control value (p<0.01).

**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 be placed around the portal vein with correct angle [3]. In this 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. In addition, a right heart bypass was employed to reduce cardiac output and maintain hypotension. This model overcomes the disadvantages of the Wiggers' shock model such as sympathetic response and unstable arterial pressure due to catecholamine release [2, 30].

In vivo autoregulation of arterial pressure occurs within ranges down to 20–30 mmHg in skeletal muscles, 30–40 mmHg in intestine, 50–60 mmHg in brain, and 60–70 mmHg in kidney [20]. In this study, mean arterial pressure was kept at 40 mmHg (50% decrease) during the hypotensive episode. Shock was maintained for 15 min in order to evaluate hepatic compensatory response during and after reversible shock. Previous studies reported that the kidney, the most susceptible organ to shock, functioned under blood pressure greater than 60 mmHg and that total hepatic flow was not reduced when blood pressure was 40% or less than normal [8, 20].

Blood flow is usually expressed per unit area or unit weight [6, 16, 19, 21–23]. Hepatic blood flow is often presented per hepatic tissue weight because radioactive microspheres are frequently employed to determine flow [4, 17, 31]. In this study, hepatic flow was expressed per body weight and compared with cardiac output to emphasize the relationship between systemic and hepatic circulation and also because the liver could not be weighed during extracorporeal circulation.

Hypovolemic shock reduced cardiac output by decreasing venous return, not by restraining cardiac contraction. When hypovolemic shock is reversible, compensatory responses are expected to occur to maintain the output during shock and if normal cardiac function is retained; both mean arterial and left atrial pressures should return to normal following elimination of the hypotensive state.

In this study, heart rate was increased while stroke volume was decreased during hypovolemic shock. These findings may be due in part to compensatory response worked to minimize reduction of cardiac output during shock. This response may be caused by a sympathetic reflex via pressure receptors in the aortic arch and carotid sinus. Hypovolemic shock did not appear to cause irreversible changes in the heart itself because left atrial and mean arterial pressure remained within physiological ranges after shock. In addition, no arrhythmia was found in any animal during or after shock.

The liver at rest is supplied with approximately 30% of the total cardiac output through the portal vein (80%) and hepatic artery (20%) [8–10, 14, 15, 24]. Hepatic blood flow accounted for 34% of cardiac output in this study; 76% of hepatic blood flow was delivered from the portal vein and 24% from the hepatic artery.

Previous studies have shown that portal blood flow depends upon cardiac output and hepatic arterial flow on mean arterial pressure [5, 6, 9, 10, 13, 18, 23, 24]. In this study and in contrast to previous studies, there was a positive correlation between hepatic arterial flow and cardiac output. This relationship was more obvious and more linear than the relationship between hepatic arterial flow and mean arterial pressure. Cardiopulmonary bypass and minimal pulse pressure may have attenuated the correlation of mean arterial pressure to hepatic arterial blood flow. Physiologic cardiovascular responses were rapidly modulated by the speed of the roller pump.

Liver blood flow was significantly reduced during hypovolemic shock because blood flow was decreased in both the portal vein and the hepatic artery. Liver blood flow appeared to be decreased mainly by a reduction in portal blood flow. Previous studies have reported this reduction in portal blood flow to be due to a decrease in splanchnic portal venous return [9, 12]. The present study supports the hypothesis that the mesenteric area is treated as a peripheral area when blood distribution is restricted during hypovolemic shock.

Hepatic arterial blood flow was significantly decreased during hypovolemic shock. Hepatic arterial blood flow ratio to cardiac output was significantly increased; the mechanism of reciprocity of total hepatic flow (RTHF) may partially explain this observation [11, 26]. 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. The HABR was functioning by adenosine washout in hepatic artery and occurs in cats, dogs, rats, and humans [21–23]. By this mechanism, hepatic arterial flow adjusts the changes in total hepatic flow caused by variations in portal blood flow. The hepatic artery was found to buffer 25–51% of portal blood flow in an acute phase [24] and it was suggested to exert a higher buffering action under physiological conditions with non-operative invasion with an enhanced sympathetic nervous system responds sensitively [21].

Liver blood flow returned to the control level by a slight reduction in portal flow and a significant increase in hepatic arterial blood flow after correction of the hypovolemia. The ratios of flow in the portal vein and hepatic artery to cardiac output gave similar results following hypovolemia, since cardiac output was fixed to the control value. In addition to the development of the HABR, vasodilating effects of endogenous agents, including prostaglandins, adenosine and glucagon [1, 27], may be involved in increasing hepatic arterial blood flow, since resistance in the hepatic artery was lowered when hepatic arterial flow was increased after elimination of shock.

The results of this study demonstrate that compensatory responses for maintaining liver blood flow mainly due to the HABR were functioning during both hypovolemic shock and after elimination of shock. This mechanism might also be partially functioning as the defence mechanism of liver oxygenation during and/or after shock.
ACKNOWLEDGEMENTS. The authors acknowledge the fine technical and nursing assistance provided by the staff in Nippon Veterinary and Animal Science University, Veterinary Medical Teaching Hospital.

REFERENCES