The Effect of Hypovolemic Shock and Reperfusion on the Hepatic Oxygen Supply-Uptake Relationship in the Dog

Gen KINOSHITA, Makoto WASHIZU, Shigekatsu MOTYOUSHI, and Eugene M. BREZNOCK

Veterinary Medical Teaching Hospital, Department of Internal Medicine, Nippon Veterinary and Animal Science University, 1-7-1 Kyomarucho, Musashino, Tokyo 180, Japan, and Department of Surgery, School of Veterinary Medicine, University of California, Davis, 212 Medical Science 1-A, Davis, CA 95616, U.S.A.

(Received 26 July 1994/Accepted 17 April 1995)

Abstract. The hepatic oxygen supply-uptake relationship was investigated during hypovolemic shock using a right heart bypass technique. The results were dissimilar to those previously reported in that the ratio of liver oxygen delivery to systemic oxygen delivery was significantly decreased during shock. The decreased ratio was due to a significant decrease in the portal venous oxygen delivery when compared to the decrease in the systemic oxygen delivery. The decrease in portal venous oxygen delivery was caused not only by the decrease in portal venous blood flow, but also by the decrease in oxygen content of portal blood. The ratio of hepatic arterial oxygen delivery, on the other hand, was significantly increased during shock. Hypovolemic shock increased the liver oxygen extraction ratio to nearly 100% of the pre-shock value. These findings suggest a hepatic protective mechanism for matching oxygen uptake to rising hepatic oxygen requirements. Liver oxygen delivery returned to pre-shock value after correction of hypovolemia primarily due to a significant increase in hepatic arterial oxygen delivery. A significant negative correlation between the liver oxygen extraction ratio and the oxygen content of hepatic venous blood was observed. The hepatic venous oxygen content appears to be a simple and appropriate index of liver oxygenation in clinical medicine because it is difficult to evaluate the liver oxygen extraction ratio directly. - Key words: hepatic oxygen supply-uptake relationship, hypovolemic shock, liver oxygen extraction ratio, mesenteric circulation, right heart bypass.


The complexity of hepatic function is closely related to liver oxygenation. Decrease in liver oxygen delivery results in centrilobular necrosis that contributes to the disruption and decrease of liver function [2, 21, 25].

The liver, a key organ in body metabolism and defense mechanisms, plays an important role in the pathology and outcome of shock. Few studies of liver oxygenation during hypovolemic shock [1, 17, 20] have been conducted when compared to cerebral, coronary and renal oxygenations.

In veterinary surgical practice, temporary interruption of hepatic blood flow and oxygen flow that can control blood loss is utilized in certain procedures involving the liver for control (i.e. hepatic trauma, lobectomy and repair of intrahepatic portal venous shunts) [23]. Prevention of intraoperative and postoperative hepatic insufficiency requires a thorough understanding in anesthetic management and liver oxygenation. In this study, the investigated liver oxygenation and the effects of changes in the systemic circulation on hepatic vascular dynamics during and after hypovolemic shock was investigated using a modified right heart bypass canine model surgery [8, 12].

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 the right cephalic vein. 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 right jugular vein to the level of the cranial thoracic vena cava to measure central venous pressure (CVP). Then, modified right heart bypass surgery was established (Fig. 1) [12]. A laparotomy was

Fig. 1. Schematic drawing of 3-vessel-bleeding right heart bypass preparation.
performed and a 4F catheter was inserted into the splenic vein and passed proximally into the portal vein for monitoring portal venous pressure (PVP) and for blood collection. A 2–3 mm electromagnetic flowmeter probe (FC-020T, FB-030T, 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. A thoracotomy was performed by median sternotomy. An 8F catheter was inserted through the caudal thoracic vena cava into the hepatic vein for determining 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 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.

To proceed with extracorporeal circulation, the rotational speed of roller pump and height of a venous reservoir were adjusted so that AP, CVP, and LAP were almost the same as those before the initiation of extracorporeal circulation.

The extracorporeal circuit was primed with a solution prepared by mixing physiological saline and dextran 40 (Midori Jujji) (4:1) and adding 4000 IU/ml 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 acquire by direct recording the 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 the mean hepatic arterial pressure (HAP). 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 cytofmetric (MEK-5158, Nihon Kohden).

Portal venous blood flow (PVBF) was calculated as the difference of hepatic arterial blood flow and hepatic venous blood flow (HVBF-HABF). Systemic oxygen delivery (Dso2) was calculated as the product of cardiac output and arterial oxygen content (CO x CaO2). The liver oxygen delivery (Dlo2) was calculated as the sum of hepatic arterial oxygen delivery (Dhao2 = HABF times CaO) and the portal venous oxygen delivery (Dpvo2 = PVBF times oxygen content of portal venous blood (Cpvo2)). The liver oxygen delivery index (Dlo2/I) was the ratio of the liver oxygen delivery to the systemic oxygen delivery (Dlo2/Dso2 x 100). The hepatic arterial oxygen delivery index (Dhao2/I) and the portal venous oxygen delivery index (Dpvo2/I) were also calculated (Dhao2/I = Dhao2/Dso2 x 100, Dpvo2/I = Dpvo2/Dso2 x 100).

Mesenteric oxygen delivery was calculated as the product of portal venous blood flow and arterial oxygen content (PVBF x CaO2). Systemic oxygen uptake (Vso2) was calculated as the difference between the arterial oxygen content and the mixed venous blood oxygen content (CaO2 - Cvo2) times cardiac output. The liver oxygen uptake (Vlo2) was calculated as a difference between liver oxygen delivery and the product of hepatic venous blood flow times oxygen content of hepatic venous blood (Dlo2 - HVBH times Chvo2). Mesenteric oxygen uptake (Vmo2) was calculated as the difference between the arterial oxygen content and the portal venous oxygen content (CaO2 - Cpv2) times portal venous blood flow. The liver oxygen extraction ratio (Ello2 = Vlo2/Dlo2 x 100), and the mesenteric oxygen extraction ratio (Emo2 = Vmo2/Dmo2 x 100) were also calculated.

Development of hypovolemic shock: Hemodynamic parameters and blood samples were obtained following a 30–60 min equilibration period following the initiation of the extracorporeal circulation. After initial data acquisition, the roller pump speed was reduced over one min until mean arterial pressure decreased to 40 mmHg. Hypovolemic hypotension was maintained for 15 min and the pump speed was increased until the cardiac output returned to the control level within one min. Hemodynamic parameters and blood samples were obtained immediately after the onset of hypotension, and immediately after reperfusion. Additional measurements were obtained at 10, 15 and 30 min following the hypotensive episode.

Statistics: Data were represented by means ± standard deviation (SD). Multiple comparison one factor ANOVA were used to determine significant differences from the control values. Linear regression by least squares was used to describe the relation between each parameters. P<0.05 and P<0.01 were used as the level of significance.

RESULTS

Hepatic arterial blood flow was significantly decreased during hypovolemic hypotension (p<0.01), and significantly increased after correction of the hypotension (p<0.01), when compared to the control level. Portal venous blood flow was significantly decreased during the hypotensive period (p<0.01). Arterial oxygen content was avariant from the control value throughout the study. Oxygen content of portal blood was significantly decreased during hypotension (p<0.01) (Table 1).

Systemic oxygen delivery and uptake were significantly decreased during hypotension (p<0.01), and avariant from the control value after correction of the hypotension. Mesenteric oxygen delivery and uptake were significantly decreased during hypotension (p<0.01), and avariant from the control value after correction of the hypotension.
Table 1. Changes in blood flow and oxygen content of the blood suppling the liver during hypotension and following reperfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Hypotension</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
<td>15 min</td>
<td>0 min</td>
</tr>
<tr>
<td>Hepatic arterial blood flow (ml/min/kg)</td>
<td>7±1</td>
<td>4±2**</td>
<td>4±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>Arterial oxygen content (ml/dl)</td>
<td>9.56±2.07</td>
<td>9.58±2.22</td>
<td>9.78±2.28</td>
</tr>
<tr>
<td>Portal venous oxygen content (ml/dl)</td>
<td>6.59±1.80</td>
<td>3.95±1.67**</td>
<td>4.19±1.78**</td>
</tr>
</tbody>
</table>

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

Table 2. Changes in oxygen supply-uptake relationship during hypovolemic hypotension and following reperfusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypotension</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
<td>15 min</td>
</tr>
<tr>
<td>Systemic oxygen delivery</td>
<td>52±8**</td>
<td>50±9**</td>
</tr>
<tr>
<td>Systemic oxygen uptake</td>
<td>72±15**</td>
<td>77±15*</td>
</tr>
<tr>
<td>Mesenteric oxygen delivery</td>
<td>56±12**</td>
<td>39±6**</td>
</tr>
<tr>
<td>Mesenteric oxygen uptake</td>
<td>98±29</td>
<td>73±12**</td>
</tr>
<tr>
<td>Mesenteric oxygen extraction ratio</td>
<td>192±56*</td>
<td>203±61*</td>
</tr>
<tr>
<td>Hepatic arterial oxygen delivery</td>
<td>64±18**</td>
<td>73±23*</td>
</tr>
<tr>
<td>Portal venous oxygen delivery</td>
<td>35±14*</td>
<td>25±10**</td>
</tr>
<tr>
<td>Liver oxygen delivery</td>
<td>42±11*</td>
<td>37±9**</td>
</tr>
<tr>
<td>Liver oxygen uptake</td>
<td>75±35</td>
<td>69±30*</td>
</tr>
<tr>
<td>Liver oxygen extraction ratio</td>
<td>205±44*</td>
<td>218±51*</td>
</tr>
</tbody>
</table>

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).

The mesenteric oxygen extraction ratio was significantly increased to 92–103% over the control value during hypotension (p<0.01), and significantly increased (p<0.05) 10 to 30 min after it was eliminated. Hepatic arterial and portal venous oxygen delivery were significantly decreased during hypotension (p<0.01). Following the hypotensive episode liver oxygen delivery was increased significantly (p<0.01) when compared to the control value. Ten minutes after hypotension, portal venous oxygen delivery was decreased significantly (p<0.05) when compared to the control value (Table 2).

A positive correlation existed between the hepatic arterial blood flow and hepatic arterial oxygen delivery (Fig. 2). No correlation existed between the arterial oxygen content and hepatic arterial oxygen delivery (Fig. 3). A positive correlation existed between the portal venous blood flow and oxygen content and portal venous oxygen delivery (Figs. 4–5). A negative correlation existed between the portal venous oxygen delivery and the mesenteric oxygen extraction ratio (Fig. 6).

Both liver oxygen delivery and uptake were significantly decreased during hypotension (p<0.05, 0.01), and avariant from the control value after correction of the hypotension. The liver oxygen extraction ratio was significantly increased during hypotension (p<0.01), and

![Fig. 2. Correlation between hepatic arterial oxygen delivery (Dhao2) and hepatic arterial blood flow (HABF). The line was obtained by linear regression analysis.](image-url)
Changes in ratios of oxygen delivery of the hepatic artery (Dhao₂), portal vein (Dpvo₂), and liver (Dlo₂) to systemic oxygen delivery during and after hypovolemic hypotension are illustrated (Fig. 8). The control Dhao₂, Dpvo₂, and Dlo₂ were 16, 18, and 34%, respectively. During hypotension, Dhao₂ was increased significantly (p<0.05), and Dpvo₂ was decreased significantly (p<0.05) when compared to the control values. Dlo₂ was significantly decreased when compared to the control Dlo₂ (p<0.01). After hypotension, Dhao₂ was significantly increased of the control Dhao₂ (p<0.05), and Dpvo₂ was significantly decreased of the control Dpvo₂ (p<0.05). Dlo₂ was avarient from the control value.

**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].

In vivo autoregulation of arterial pressure occurs in skeletal muscles, intestine, brain, and kidney. In this study, mean arterial pressure was kept at 40 mmHg (50% decrease) during the hypotensive episode. Hypotension was maintained for 15 min to evaluate hepatic compensatory response during and after reperfusion. Previous studies reported that the kidney, the most susceptible organ to hypotension, 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 value [6].

Liver oxygen delivery was significantly reduced during hypotension. This decrease in oxygen delivery resulted from the decrease in hepatic arterial oxygen delivery and portal venous oxygen delivery. The decrease in hepatic arterial oxygen delivery was caused by a large decrease in hepatic arterial blood flow, since little changes in arterial oxygen content was present. The decrease in portal venous oxygen delivery was caused not only by the decrease in portal venous blood flow, but also by the decrease in oxygen content of portal blood. During hypotension, oxygen delivery to the mesenteric viscera was significantly decreased primarily decreased portal venous blood flow, while oxygen uptake was reduced significantly creating an increased oxygen extraction ratio. The observed increase in the mesenteric oxygen extraction ratio could be due to an increase to oxygen removal from the blood because of an unaltered oxygen demand [26].

The assumption that the change in the ratio of liver oxygen delivery to systemic oxygen delivery during hypovolemic hypotension is well maintained and is similar to that of the cerebral and coronary circulation, is now widely accepted [5, 19, 20]. However, the liver oxygen delivery index was decreased under the conditions imposed during this investigation. This decrease in liver oxygen delivery index was due to the decrease in portal venous oxygen delivery index, even though an increase in hepatic arterial oxygen delivery index was observed. The decrease in portal venous oxygen delivery was caused by the unaltered oxygen requirements of the pre-portal tissues such as stomach, spleen, and intestines, which had to extract the same amount of oxygen from a decreased delivery. It may be assumed that the liver oxygen delivery index might be well maintained by an increase in hepatic arterial oxygen delivery during moderate hypovolemic hypotension.

Lutz et al. [17] reported that the increase in the liver oxygen extraction ratio was the main mechanism for matching oxygen uptake to rising hepatic oxygen requirements in the presence of marked reduced hepatic oxygen delivery. This hepatic oxygen extraction ratio has been used for assessing liver oxygenation, since it reflects both changes in its parameters as oxygen delivery and uptake. In this investigation, the liver oxygen extraction ratio was increased up to nearly 100% of the control value during hypotension. It appears that the liver was protected by a mechanism which matches oxygen uptake to rising hepatic requirements.

Liver oxygen delivery returned to the pre-hypotensive value during reperfusion. This response was due to an increase in hepatic arterial oxygen delivery in the presence of a continued decrease in the oxygen delivery to the liver via the portal vein. In fact, both changes in hepatic arterial and portal venous oxygen delivery were caused by changes in hepatic arterial and portal venous blood flows. The phenomenon of reciprocal blood flow in the liver has been reported [4, 7, 9-11, 13-16, 18, 24]. An intrinsic mechanism by which hepatic arterial blood flow increases in response to decrease in portal venous blood flow, and the resulting decrease in portal oxygen delivery, would offer
an excellent buffer system with which to maintain adequate oxygen of the liver during periods of stress. This study confirmed the report of Nagano et al. [20] which showed that the liver oxygen extraction ratio increased in response to a decrease in hepatic venous oxygen content. Because it is difficult to evaluate the liver oxygen extraction ratio directly, the hepatic venous oxygen content could be utilized as a simple and appropriate index of liver oxygen supply-uptake relationship in clinical veterinary medicine. Severe splanchnic ischemia and hypoxia produces myocardial depressant factor (MDF), a negative inotropic substance and endothelial system depressor [22]. Since the splanchnic viscera can induce such a vital role in the development of shock, it seems appropriate to investigate splanchnic circulation and oxygenation during shock and after shock, and to realizing the mechanism for maintaining adequate oxygenation of the liver.

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