Suppression of Liver Blood Flow by Carbon Dioxide Pneumoperitoneum can be Improved by Prostaglandin E_{1} in Pigs

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Summary. Portal venous blood flow (PVF), hepatic arterial blood flow (HAF), and systemic arterial pressure (SAP) were examined after prostaglandin E\textsubscript{1} (PGE) injection into the jugular vein under variably enhanced intraabdominal pressure (IAP) in pigs. The IAP was controlled by carbon dioxide pneumoperitoneum. When IAP was increased to 8 or 12 mmHg, PVF was reduced but HAF and SAP were unchanged. In this IAP condition the injection of PGE at 0.25 \mu g/kg/min for 2 min produced an increase in PVF without causing any change in HAF or SAP. The response in PVF was dose-dependent. When IAP was increased to 16 mmHg, PVF and HAF were reduced without any change in SAP. In such a case, no noticeable changes in PVF, HAF, or SAP were seen with the same dose of PGE. These results suggest that PGE is effective in increasing PVF in an enhanced IAP condition, but such circulatory improvement due to PGE appears limited to IAP at about less than 12 mmHg.

Key words— intraabdominal pressure, pneumoperitoneum, prostaglandin E, splanchnic circulation, pig.

INTRODUCTION

The development of laparoscopic surgery has revolutionized modern general surgical practice including cholecystectomy, appendectomy, bowel resection, and selective vagotomy.\textsuperscript{[1-5]} These procedures appear to reduce post-operative pain and shorten hospitalization, but cardiovascular collapse or the suppression of intraabdominal organ blood flow after carbon dioxide (CO\textsubscript{2}) pneumoperitoneum has also been documented\textsuperscript{[6-9]} Therefore the pneumoperitoneum should be maintained at a pressure of less than 12 mmHg, which has a minimal influence on systemic and hepatic hemodynamics, during laparoscopic operations.\textsuperscript{[10,11]} Recently, it has been found that dopamine is effective in increasing portal venous blood flow (PVF) under enhanced intraabdominal pressure (IAP) condition.\textsuperscript{[12]} On the other hand, prostaglandin E\textsubscript{1} (PGE), another agent that dilates the vascular wall of the superior mesenteric artery\textsuperscript{[13-15]} or the portal vein,\textsuperscript{[16-20]} has been shown to increase PVF.

This experiment was designed to investigate whether PGE influences systemic and hepatic circulation associated with CO\textsubscript{2} pneumoperitoneum.

MATERIALS AND METHODS

Six female Landrace-White-Duroc (WD) pigs weighing 25 to 28 kg were used. They were housed individually (12h: 12h, light-dark cycle) with lights on at 06:00 h. They were fed on a standard diet (Spurt G, Nihon Nosan, Yokohama) with free access to tap water.

The animals were intubated for general anesthesia with a mixture of 1.0% halothan and 1.0 l/min oxygen, and were allowed to breathe mechanically on a closed air circuit (AR-300, Acoma Medical Products, Tokyo, Japan). The anal temperature was kept at 35.0 ± 1.0°C with a heating pad (UH-CHW-II, Junkan, Saitama). Analysis of gas in the blood was necessary in order to maintain adequate ventilation with an analyzer (ABL-2, Radiometer, Copenhagen).
blood gas conditions during the experiment are summarized in Table 1.

The portal vein and the common hepatic artery were exposed after midline incision. The gastroduodenal artery was ligated at its origin from the common hepatic artery. PVF and HAF were measured with an ultrasonic volume flow meter (Transonic T201, Advance, NY). The probes for blood flow estimation were placed around the portal vein and the common hepatic artery at a position 1 to 2 cm caudal to their bifurcation. The data were recorded on a graph with a pen (Bio color Graph 2G82, Nihon Denki San Ei, Tokyo). Systemic arterial pressure (SAP) was obtained from the left common carotid artery and recorded with the same recorder.

Following the setting of the probes, a cannula was placed on the abdomen and the abdominal wall was closed in two layers. Pneumoperitoneum was performed through the cannula with a surgical CO₂ insufflator (Olympus Winter & Ibe, Hamburg), and the level of IAP increased step by step at 0, 8, 12, and 16 mmHg.

PGE (Ono Pharmaceutical Co., Ltd., Osaka) dissolved in saline was injected into the jugular vein (0.1, 0.25, or 0.5 μg/kg/min). The amount used in each test injection was 2.0 ml, and it was completed in 2 min with an infusion pump. Saline was used as the control. It was preliminarily observed that the same amount of saline produced no measurable effect on either flow or pressure; portal flow response due to PGE was saturated 2 min after injection, and the magnitude of the response remained almost the same even when the injection was continued for more than 2 min. Test injections were given at about 12-min intervals as in previous experiments.

The collected blood samples were cooled immediately on ice and centrifuged at 2,200 rpm for 20 min. The serum was stored at −20°C until autoanalyzer (Hitachi-736, Hitachi, Tokyo) measurement of the total protein (TP, Biuret method), albumin (Alb, Bromcresol green method), glucose (Glc, glucose oxidase method), total bilirubin (TB, azobilirubin method), glutamic pyruvic transaminase (GPT, Ultraviolet method), alkaline phosphatase (Alp, Bessey-Lowry method), blood urea nitrogen (BUN, urease ultraviolet method), and creatinine (Cre, Jaffe method).

The results were calculated as percentages of the value obtained immediately before drug administration. Samples were collected following the first and second responses by each animal to a specific solution. The significance of differences was evaluated by analysis of variance without repetition and Duncan’s multiple range test. P<0.05 was considered significant.

### RESULTS

The blood hemoglobin concentration, pH, and gas tension showed adequate ventilation of the animals (Table 1). It is possible that a considerable number of factors moderating PGE action on the vasculature could have been fixed. Basal levels of SAP, HAF, and PVF before and after enhancing IAP are shown in Table 2. Responses in these parameters were similar to those reported before.

PGE (0.25 μg/kg/min) injection into the jugular vein increased PVF when IAP was kept at 12 mmHg (Figs. 1 and 2). The increase in PVF reached its maximum 2 min after the injection, then returned to the preinjection level within the following 2 min (Fig. 2). ANOVA revealed that the differences among groups and among times were significant: F₁,₈₃ =
Table 2. Hepatic circulatory parameters 15 min after pneumoperitoneum

<table>
<thead>
<tr>
<th>Intraabdominal pressure (mmHg)</th>
<th>0</th>
<th>8</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mmHg)</td>
<td>91.8 ± 2.7</td>
<td>91.8 ± 2.7</td>
<td>91.2 ± 1.4</td>
<td>88.3 ± 1.0</td>
</tr>
<tr>
<td>HAF (ml/min)</td>
<td>97.3 ± 2.8</td>
<td>97.3 ± 2.8</td>
<td>95.1 ± 11.0</td>
<td>108.3 ± 11.2</td>
</tr>
<tr>
<td>PVF (ml/min)</td>
<td>176.2 ± 3.8</td>
<td>156.2 ± 3.8</td>
<td>143.3 ± 3.9a</td>
<td>120.3 ± 4.5b</td>
</tr>
<tr>
<td>THF (ml/min)</td>
<td>263.5 ± 4.0</td>
<td>243.5 ± 4.0</td>
<td>238.3 ± 11.5</td>
<td>230.7 ± 10.4b</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM (n=6). a)P < 0.05 vs 0. b)P < 0.01 vs 0. c)P < 0.05 vs 0.

Fig. 1. Effects of jugular injection of PGE on SAP, HAF, and PVF under intraabdominal pressure at 12 mmHg. PGE 0.25 μg/kg/min was given for 2 min. The open bar in the top indicates the time of PGE injection.

Fig. 2. Time courses for SAP, HAF, and PVF following PGE administration. Jugular injection of PGE (●, 0.25 μg/kg/min) or saline (○) was done with intraabdominal pressure at 12 mmHg. The open bar in the top indicates the time of PGE injection. Values are the mean ± SEM (n=6). a)P < 0.01 vs ○. b)P < 0.05 vs ○.

SAP was unchanged when PGE (0.25 μg/kg/min) was injected into the jugular vein after enhancing IAP at 12 mmHg (Figs. 1 and 2). The differences among groups and times were not reliable: F_{i,3}=1.335, P > 0.05 and F_{i,3}=1.335, P > 0.05, respectively. SAP fell significantly when PGE (0.5 μg/kg/min) was injected. However the SAP response to PGE was not dose-dependent.

PVF responses due to PGE (0.25 μg/kg/min) were compared under different levels of IAP, and the response was diminished when IAP was increased to 12 mmHg. Further diminution in PVF response was

43.072, P < 0.002 and F_{i,3}=16.272, P < 0.002, respectively. Based on this finding, the PVF response due to PGE was compared 2 min after PGE administration. It was found that the response due to PGE was dose-dependent (Fig. 3).

HAF was unaffected after PGE (0.25 μg/kg/min) injection into the jugular vein under IAP at 12 mmHg (Figs. 1 and 2). The differences among groups and times were not reliable: F_{i,3}=0.070, P > 0.05 and F_{i,3}=0.049, P > 0.05, respectively. No significant change in HAF was seen when 0.5 μg/kg/min PGE was injected (Figs. 2 and 3).
induced when IAP was increased to 16 mmHg (Fig. 4).

Blood chemical parameters, which indicate liver and kidney functions, are shown in Table 3. It was noted that GPT was increased after IAP was increased to 16 mmHg. No change was seen in kidney function parameters.

DISCUSSION

Although enhanced IAP has been shown to suppress the blood supply to the abdominal organs by reducing the effective perfusion pressure,\(^{\text{10-12}}\) it was found that PGE administration is capable of increasing PVF under an enhanced IAP condition (Figs. 1, 2, and 3). This is partially consistent with the view that the systemic administration of PGE enhances PVF in rats, dogs, and pigs.\(^{\text{18-21}}\) The action of PGE on the vascular wall seemed to be specific to PGE under enhanced IAP, because the PVF response due to PGE was dose-dependent (Fig. 3).

The PVF response to PGE occurred within 30 sec after injection (Fig. 1). PGE appeared to have immediate effects on the vascular structure even when the visceral vascular walls were compressed by enhanced IAP.

The action site of PGE has been considered to be localized in the superior mesenteric arterial vascular bed,\(^{\text{13-16}}\) but a vasodilative action by PGE has also been demonstrated in the portal venous vascular bed of animals.\(^{\text{18-20}}\) In the present PVF response, either the mesenteric artery or the portal vein or both would therefore be involved.

The mode of PGE action on the vascular wall has been presumed from the pressure response. Nakano and Cole noted a biphasic change in portal venous
pressure after PGE administration,\textsuperscript{40} and they interpreted this to mean that the initial rise may be caused by a reflex sympathetic stimulation, and that any subsequent decrease may be due to a direct vasodilator effect on the portal venous vasculature. In the present study, PGE induced PVF response without an inhibitory phasic pattern. This could prove that some sympathetic mechanisms, which provoke the initial stimulatory portal flow response to PGE, are exerted in the liver,\textsuperscript{19,20} and the IAP variation did not moderate the mode of PGE action on the vascular wall.

Effects on PVF following PGE injection were of short duration (Fig. 1), possibly owing to the rapid removal of PGE from circulation;\textsuperscript{25} it has been shown that the biological activity of PGE is reduced by 70-93% after a single circulation,\textsuperscript{24} PGE exogenously injected at 0.25 μg/kg/min caused an increase in PVF without a change in SAP (Fig. 2). This seems to support previous findings that PGE is substantially metabolized and inactivated by the lungs and the liver,\textsuperscript{23,27} and it also indicates that the physical components of IAP did not affect PGE metabolism.

Of particular interest is the response in HAF (Figs. 1 and 2). Although responses in PVF due to PGE were relatively great when the IAP was enhanced, the response in HAF was small (Figs. 1 and 2). The sympathetic nerve innervating the liver is a factor controlling HAF, and stimulation of this nerve has been shown to decrease the HAF.\textsuperscript{28} The finding mentioned above therefore implies that neural participation is not involved in the HAF response.

The pressure of CO\(_2\) in the blood is increased during CO\(_2\) pneumoperitoneum, this being a result of the combined effects of the absorption of CO\(_2\) across the peritoneum.\textsuperscript{29-32} However, with the mechanical ventilation used in this study, the change in arterial PCO\(_2\) was not so large (Table 2). It is likely that the cardiostimulatory effects of hypercapnia are minimal in the observed circulatory response.

Although the concentration of PGE which had an effect on PVF was unchanged during IAP application between 0 and 12 mmHg, the effective concentration of PGE acting on PVF was increased when IAP was increased to 16 mmHg (Fig. 4). Considering these results together with reports that the hepatic vascular bed is one of the major blood reservoirs\textsuperscript{33} and that enhanced IAP has been shown to compress vascular walls, which decrease the circulation to the viscera and cause stasis,\textsuperscript{34} the IAP can be considered a significant factor in determining the blood reservoir function of the liver during pneumoperitoneum.

The finding that PGE effectively increased PVF even when IAP was increased (Fig. 3) suggests that PGE could improve the hepatic circulation during laparoscopic surgery in clinical practice, where PGE is usually given continuously. This also implies that PGE administration is useful in cases where the hepatic circulation acutely deteriorates during an operation.

There is a mechanical interaction between the peritoneal cavity and the thoracic cavity through the diaphragm, and the heart function can be inhibited when the diaphragm is moved upward by increased IAP.\textsuperscript{34} However the increase in IAP below 12 mmHg had a minimal effect on the heart, because SAP response to PGE administration was small (Figs. 1, 2, and 3). It is believed that cardiac function in response to PGE can not be modulated by IAP when it is below 12 mmHg. On the other hand, the physical impact on the peritoneal cavity produced a liver parameter which may have indicated some dysfunction (Table 3). Further study on this aspect is necessary.

**Table 3. Blood chemical parameters after pneumoperitoneum**

<table>
<thead>
<tr>
<th>Intraabdominal pressure (mmHg)</th>
<th>0</th>
<th>12</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP (g/dl)</td>
<td>5.1 ± 0.2</td>
<td>5.1 ± 0.2</td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>2.1 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>Glc (mg/dl)</td>
<td>126 ± 5</td>
<td>129 ± 7</td>
<td>127 ± 5</td>
</tr>
<tr>
<td>TB (mg/dl)</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>GPT (U)</td>
<td>36 ± 3</td>
<td>48 ± 5</td>
<td>54 ± 4\textsuperscript{a}</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>123 ± 17</td>
<td>124 ± 15</td>
<td>122 ± 14</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>7.6 ± 0.4</td>
<td>7.8 ± 0.2</td>
<td>7.9 ± 0.4</td>
</tr>
<tr>
<td>Cre (mg/dl)</td>
<td>0.9 ± 0.0</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
</tbody>
</table>

Values are the mean ± SEN (n=6). \textsuperscript{a}P<0.05 vs 0.
The present observations lead us to conclude that the administration of PGE is useful in improving hepatic circulatory efficiency when laparoscopic surgery is done with CO₂ pneumoperitoneum.

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REFERENCES


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