Effect of two models of portal hypertension on splanchnic organ blood flow in the rat

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Summary

1. Splanchnic organ blood flow and cardiac output were measured by the microsphere method in fasted rats with prehepatic portal hypertension due to portal vein stenosis, in rats with intrahepatic portal hypertension due to bile duct ligation, and in unoperated normal rats.

2. Portal venous pressure was higher in both groups of portal hypertensive rats than in normal rats. Cardiac output was significantly higher in portal hypertensive rats than in normal rats.

3. In rats with portal vein stenosis, splanchnic blood flow was higher than in controls. This increase was caused by increased perfusion of all organs drained by the portal vein, and by increased hepatic arterial blood flow. In rats with bile duct ligation, splanchnic blood flow was not significantly higher than in normal rats: haemoperfusion of all organs contributing to the portal circulation decreased, whereas hepatic arterial blood flow increased. As cardiac output rose similarly, the differences observed between the two types of portal hypertension depend mainly on the difference in distribution of flow within the splanchnic bed.

Key words: blood flow, liver, portal hypertension.

Introduction

An increase in portal venous pressure is associated with changes in systemic haemodynamics [1-3]. In patients with portal hypertension, no method is currently available to measure blood flow in splanchnic organs individually. The purpose of this investigation was to study changes in splanchnic blood flow, by using the microsphere method, in rats with prehepatic portal hypertension due to portal vein stenosis and intrahepatic portal hypertension due to bile duct ligation.

Methods

Animals

Three groups of adult male rats (Charles River, Saint-Aubin-Lès-Elbeuf, France), initially weighing 200-250 g, were studied: ten with portal hypertension due to portal vein stenosis, ten with portal hypertension due to bile duct ligation and ten control animals.

Portal vein stenosis

To induce prehepatic portal hypertension, partial portal vein ligation was performed according to the method of Halvorsen & Myking [4]. Under ether anaesthesia, the portal vein was exposed by median laparotomy. A polyethylene catheter of 0.96 mm outside diameter (Biotrol Pharma, Paris, France) was placed beside the portal vein. A ligature between the bifurcation of the portal vein and the junction of splenic and mesenteric veins was tied around both the catheter and the portal vein; the catheter was immediately removed and the abdominal incision closed.

Bile duct ligation

To induce intrahepatic portal hypertension, ligation of the common bile duct was performed according to the method of Franco et al. [5]. Under ether anaesthesia, the common bile duct was exposed by median laparotomy and occluded by double ligature with a non-resorbable suture.
(7-0 silk). The first tie was below the junction of the hepatic ducts, and the second was above the entrance of the pancreatic ducts. The common bile duct was then resected between the two ligatures and the abdominal incision closed. Two to 4 weeks after bile duct ligation, marked jaundice and mild ascites developed. Secondary biliary cirrhosis due to chronic bile duct ligation [5] was histologically confirmed in these rats.

Haemodynamic measurements

Haemodynamic studies were performed 3 weeks after partial portal vein ligation and 4 weeks after bile duct ligation. All rats then weighed 300–350 g (after ligation of the bile duct, rats slightly decreased their weight and then return to normal). Rats were fasted 18 h before the haemodynamic study but were given water ad libitum. Haemodynamic studies were performed under pentobarbital anaesthesia (5 mg/100 g body wt. intra-peritoneally); rats were fixed in a supine position; rectal temperature was maintained at 38°C.

Splanchnic organ blood flow was measured by using the microsphere method previously described [6–9]. Under pentobarbital anaesthesia, the right common carotid artery was cannulated with a catheter of 0.70 mm outside diameter (William Cook Europe, ApS, Söborg, Denmark). The catheter was advanced into the left ventricle; its position was demonstrated by a left ventricular catheterization, by withdrawal of reference blood samples, or by microspheres (except for a transient fall during injection). Within 5 min after microsphere injection median laparotomy was performed to measure portal venous pressure. A polyethylene catheter (0.7 mm outside diameter; William Cook Europe, ApS, Söborg, Denmark) was inserted into the portal vein wall. Portal venous pressure was measured with the catheter and recorded on a square-wave electromagnetic manometer (Telco, Gentilly, France). The zero reference level was aligned with the right atrium. The adequacy of catheterization for pressure measurement was confirmed by rapid response of the tracing and easy aspiration of blood.

Statistical analysis

The values are expressed as means ± 1 SD. The Wilcoxon test for unpaired samples was used for statistical comparisons.

Results

The mean values for arterial pressure were not significantly different in the three groups [110 ± 8 mmHg (mean ± SD) in normal rats; 107 ± 14
mmHg and 98 ± 9 mmHg in rats with portal hypertension due to portal vein stenosis and bile duct ligation, respectively).

Mean values of blood flow to splanchnic organs are presented for all groups in Table 1. In rats with portal hypertension due to portal vein stenosis, the total arterial flow to organs drained by the portal vein ranged from 21.12 to 29.91 ml/min (26.14 ± 3.55 ml/min). Those with portal hypertension due to bile duct ligation ranged from 8.73 to 20.16 ml/min (14.65 ± 3.39 ml/min). In the former group, the mean value was significantly higher than that found in normal rats, whereas, in the latter group, the mean value was significantly lower than normal (Table 1). Splanchnic blood flow in the two groups ranged from 23.65 to 36.33 ml/min (29.82 ± 3.91 ml/min) in rats with portal vein stenosis, and from 13.52 to 27.19 ml/min (20.73 ± 4.06 ml/min) in rats with bile duct ligation; the mean value in the first group was significantly higher than that measured in normal rats, whereas, in the second group, the mean value was not significantly different from normal (Table 1).

Distribution of cardiac output to various splanchnic organs in rats with portal hypertension due to portal vein stenosis or bile duct ligation, compared with normal rats, is shown in Table 2. In rats with portal hypertension due to portal vein stenosis, the percentage of cardiac output supplying organs drained by the portal vein (stomach, intestine, colon, spleen and mesentery-pancreas) ranged from 18.87 to 32.49%, with a mean value (25.24%) significantly higher than that found in normal rats (20.77%). In those with portal hypertension due to bile duct ligation the distribution of cardiac output to the portal bed ranged from 9.22 to 22.84% with a mean value (15.10%) significantly lower than normal (Table 1).

Distribution of cardiac output to splanchnic bed (portal venous bed and liver) in the two groups ranged from 22.51 to 35.53% in rats with portal vein stenosis, and from 14.38 to 27.21% in rats with bile duct ligation. In the former group, the mean value was significantly higher than in normal rats, whereas, in the latter group, the mean value was not significantly different (Table 1).

Splanchnic organ blood flow expressed per g tissue wt. in rats with portal hypertension due to portal vein stenosis or to bile duct ligation, and in normal rats, is summarized in Table 3. In rats with portal vein stenosis the differences with the control group of splanchnic organ blood flow expressed per g tissue wt. were similar to those expressed per ml/min except for mesenteric-pancreatic and hepatic blood flows (Table 3). In rats with bile duct ligation, blood flows expressed per g tissue wt. were different from those expressed per ml/min except for gastric, splenic and hepatic blood flows (Table 3).

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**Table 1. Splanchnic organ blood flow, portal venous tributary blood flow and splanchnic blood flow in rats with portal hypertension due to portal vein stenosis or to bile duct ligation, and in normal rats**

<table>
<thead>
<tr>
<th>Blood flow (ml/min)</th>
<th>Normal (n = 10)</th>
<th>Portal vein stenosis (n = 10)</th>
<th>Bile duct ligation (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>0.59 ± 0.06</td>
<td>0.84 ± 0.36†</td>
<td>0.66 ± 0.24*</td>
</tr>
<tr>
<td>Intestinal</td>
<td>11.67 ± 1.68</td>
<td>17.64 ± 4.03‡</td>
<td>7.96 ± 2.44‡</td>
</tr>
<tr>
<td>Colonic</td>
<td>1.81 ± 0.49</td>
<td>2.12 ± 0.43‡</td>
<td>1.34 ± 0.55‡</td>
</tr>
<tr>
<td>Splenic</td>
<td>1.77 ± 0.62</td>
<td>1.99 ± 0.43‡</td>
<td>1.12 ± 0.53§</td>
</tr>
<tr>
<td>Mesenteric-pancreatic</td>
<td>2.05 ± 0.49</td>
<td>3.55 ± 1.38‡</td>
<td>3.57 ± 1.18§</td>
</tr>
<tr>
<td>Portal venous tributary</td>
<td>17.89 ± 1.70</td>
<td>26.14 ± 3.55†</td>
<td>14.65 ± 3.39§</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1.99 ± 0.52</td>
<td>3.68 ± 1.78‡</td>
<td>6.08 ± 2.09†</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>19.88 ± 2.02</td>
<td>29.82 ± 3.91‡</td>
<td>20.73 ± 4.06*</td>
</tr>
</tbody>
</table>

*Not significantly different from normal; † not significantly different from bile duct ligation; ‡ significantly different from normal (P < 0.01); § significantly different from bile duct ligation (P < 0.001); ¶ significantly different from bile duct ligation (P < 0.01); ‡‡ significantly different from normal (P < 0.05); ‡‡‡ significantly different from normal (P < 0.02); ‡‡‡‡ significantly different from bile duct ligation (P < 0.02).
TABLE 2. Percentage of distribution of cardiac output to splanchnic organs, portal venous tributary, and splanchnic tributary in rats with portal hypertension due to portal vein stenosis or to bile duct ligation, and in normal rats

Results are mean values ± SD. Portal venous tributary is equal to the sum of percentages of cardiac output of the stomach, intestine, colon, spleen and mesentery-pancreas. Liver is equal to the percentage of cardiac output of the hepatic artery. Splanchnic tributary is equal to the sum of percentages of cardiac output of the portal venous tributary and the liver.

<table>
<thead>
<tr>
<th>Percentage of cardiac output</th>
<th>Normal (n = 10)</th>
<th>Portal vein stenosis (n = 10)</th>
<th>Bile duct ligation (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.69 ± 0.09</td>
<td>0.78 ± 0.25*†</td>
<td>0.71 ± 0.27*</td>
</tr>
<tr>
<td>Intestine</td>
<td>13.53 ± 2.14</td>
<td>17.17 ± 4.60*‡</td>
<td>8.25 ± 2.80 $</td>
</tr>
<tr>
<td>Colon</td>
<td>2.09 ± 0.56</td>
<td>2.03 ± 0.35*†</td>
<td>1.36 ± 0.50 $</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.09 ± 0.66</td>
<td>1.90 ± 0.30*∥</td>
<td>1.13 ± 0.48 $</td>
</tr>
<tr>
<td>Mesentery–pancreas</td>
<td>2.37 ± 0.57</td>
<td>3.36 ± 1.23 ¶</td>
<td>3.65 ± 1.12 ¶</td>
</tr>
<tr>
<td>Portal venous tributary</td>
<td>20.77 ± 1.94</td>
<td>25.24 ± 4.36 **‡</td>
<td>15.10 ± 3.60 §</td>
</tr>
<tr>
<td>Liver</td>
<td>2.31 ± 0.55</td>
<td>3.63 ± 1.46*∥</td>
<td>6.17 ± 1.87 ††</td>
</tr>
<tr>
<td>Splanchnic tributary</td>
<td>23.08 ± 1.90</td>
<td>28.87 ± 3.79 ††</td>
<td>21.27 ± 3.82*</td>
</tr>
</tbody>
</table>

* Not significantly different from normal; † not significantly different from bile duct ligation; ‡ significantly different from bile duct ligation (P < 0.001); ¶ significantly different from normal (P < 0.01); § significantly different from bile duct ligation (P < 0.01); ¶¶ significantly different from normal (P < 0.02); ** significantly different from normal (P < 0.05); †† significantly different from normal (P < 0.001).

TABLE 3. Splanchnic organ blood flow in rats with portal hypertension due to portal vein stenosis or to bile duct ligation, and in normal rats

Results are mean values ± SD. Hepatic is equal to hepatic arterial blood flow.

<table>
<thead>
<tr>
<th>Blood flow (ml min⁻¹ g⁻¹ tissue wt.)</th>
<th>Normal (n = 10)</th>
<th>Portal vein stenosis (n = 10)</th>
<th>Bile duct ligation (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>0.41 ± 0.08</td>
<td>0.66 ± 0.23*†</td>
<td>0.47 ± 0.14‡</td>
</tr>
<tr>
<td>Intestinal</td>
<td>3.23 ± 0.47</td>
<td>3.65 ± 1.04*§</td>
<td>1.88 ± 0.78‡</td>
</tr>
<tr>
<td>Colon</td>
<td>1.67 ± 0.54</td>
<td>2.54 ± 0.78*∥</td>
<td>1.12 ± 0.40¶</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.63 ± 0.94</td>
<td>1.72 ± 0.30††</td>
<td>0.49 ± 0.32*§</td>
</tr>
<tr>
<td>Mesenteric–pancreatic</td>
<td>0.62 ± 0.24</td>
<td>0.97 ± 0.42††</td>
<td>0.67 ± 0.26‡</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0.21 ± 0.27</td>
<td>0.52 ± 0.41*†</td>
<td>0.38 ± 0.13‡</td>
</tr>
</tbody>
</table>

* Significantly different from normal (P < 0.01); † not significantly different from bile duct ligation; ‡ not significantly different from normal; § significantly different from bile duct ligation (P < 0.01); ¶ significantly different from bile duct ligation (P < 0.001); §§ significantly different from normal (P < 0.05).

Mean values for cardiac output in rats with portal hypertension due to portal vein stenosis and in rats with portal hypertension due to bile duct ligation were: 104.95 ± 16.80 ml/min and 97.50 ± 6.78 ml/min, respectively. No significant difference in cardiac output was found between these two groups of rats, whereas the mean values for cardiac output in these rats were significantly higher than in normal rats (86.75 ± 6.71 ml/min) (P < 0.02 and P < 0.01, respectively).

In rats with portal hypertension due to portal vein stenosis and in those with portal hypertension due to bile duct ligation the mean values for portal venous pressure were 13.8 ± 2.0 mmHg and 13.1 ± 1.8 mmHg, respectively, and were significantly higher than those measured in normal rats (7.2 ± 0.7 mmHg) (P < 0.001 in both).

Discussion

Methods used in the present study to induce portal hypertension in the rat were previously described [4–6, 8]. The degree of portal hypertension was similar in all cases, but mechanisms and haemo-
dynamic effects differed between the two groups. In rats with portal vein stenosis, portal hypertension is of so-called 'prehepatic' type: the liver is normal, neither liver failure nor liver fibrosis occurs, and, as shown by others, portosystemic collateral circulation is extensive [8, 11]. In rats with bile duct ligation, portal hypertension is of the so-called 'intrahepatic' type: secondary biliary cirrhosis develops [5] associated with manifestations of liver failure (jaundice and ascites). The liver lesions are similar to those observed in rats with cirrhosis induced by repeated injections of CCl₄ [8]. In both types of portal hypertensive rats, it has already been demonstrated that by 3-4 weeks of the haemodynamic study, induced portal hypertension is constant, permanent and stable [4, 5, 8]. In the present study, haemodynamic studies were performed in fasted rats and consequently splanchic organ weights, mainly the intestine, as well as splanchic organ blood flows markedly differ from fed animals [12].

The two types of portal hypertension have opposite effects on both distribution of cardiac output to splanchic organs and organ blood flow. In rats with portal hypertension due to portal vein stenosis, portal venous tributary blood flow increased, whereas in those with portal hypertension due to bile duct ligation, this tributary blood flow decreased. Such a discrepancy in results was marked with intestinal, colonic and splenic perfusion, but was minimal with gastric and mesenteric-pancreatic flow. Changes in splanchic organ blood flow did not directly depend on changes in cardiac output, which increased in both groups, but mainly on the distribution of cardiac output. The increase in portal venous bed perfusion in rats with portal vein stenosis was the sum of an increase in both the percentage of cardiac output and the cardiac output itself. Such effects of portal hypertension on perfusion of splanchic organs are not clearly understood; induced splanchic resistance may differ between the two types of portal hypertension, thereby inducing various modifications in portal venous drainage.

A sustained increase in hepatic arterial blood flow was observed in both types of portal hypertensive rats. This effect disappeared when hepatic arterial blood flow was expressed per g of liver tissue, and depended mainly on an increase in the fraction of cardiac output, rather than on a rise in cardiac output. Changes in hepatic arterial blood flow are related to changes in portal venous blood flow [13]. However, the correlation between hepatic arterial and portal venous blood flows probably does not directly depend upon portal venous tributary blood flow, but rather upon portal liver perfusion. This perfusion is reduced in the two types of portal hypertensive rat, since a large amount of blood from the portal venous tributary directly reaches the systemic tributary through spontaneous portosystemic shunts [8, 11]. The marked increase in hepatic arterial blood flow measured in rats with portal hypertension due to bile duct ligation has been previously reported in the dog [14-16]. This increase is nearly twice that measured in rats with portal hypertension due to portal vein stenosis. The difference in the hepatic arterial blood flow in the two types of portal hypertensive rats is unclear. In those with bile duct ligation, total splanchic blood flow increased slightly, because the increase in hepatic arterial blood flow compensated for the decrease in portal venous tributary blood flow. However, changes in splanchic blood flow in these rats were less marked than those observed in rats with portal vein stenosis. The difference between the two types might be related to the degree of development of portosystemic collateral venous circulation.

The haemodynamic changes common to both types of portal hypertension were a sustained elevation in portal venous pressure and an increase in cardiac output. The increase in cardiac output seems to be at least partially the consequence of the rise in portal venous pressure. This effect was recently demonstrated in rats [6, 17], and is a common response to portal hypertension in man [3, 18-20]. The mechanism for increased cardiac output is unknown, but this study suggests two possibilities. In rats with portal vein stenosis and wide portosystemic collateral venous circulation, the increase in cardiac output may be due to the opened splanchic shunt, as in rats with arteriovenous fistulae [21]. This relationship between the increase in cardiac output and the presence of portosystemic shunts may be compared with that observed in patients with portal hypertension due to portal vein obstruction; in these patients the liver is normal [20]. In rats with bile duct ligation, the increase seems to be due mainly to liver failure, a known effect in man with or without cirrhosis [22, 23].

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References


