Changes in Blood Flow and Function of the Liver After Right Portal Vein Embolization

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Hypothesis: Abrupt occlusion of hemihepatic portal vein induced by preoperative portal vein embolization (PVE) may result in drastic alterations in blood flow and functional mass of the liver.

Design: Prospective study investigating the outcome of an intervention (PVE).

Setting: University tertiary-care referral center.

Patients: Thirteen patients who underwent PVE before extended right hepatectomy.

Main Outcome Measures: The functional plasma flow and functional mass of the liver as well as the volumes of the left and right lobes were assessed before and after PVE. The functional plasma flow and functional mass of the liver were estimated by measuring the hepatic clearances of sorbitol (a high-extraction drug) and antipyrine (a low-extraction drug), respectively. The liver lobar volumes were measured by computed tomography.

Results: Hepatic plasma clearance of sorbitol (mean±SD; before PVE, 632.9±142.9 mL/min; day 14, 620.2±138.3 mL/min; not significant by 1-way repeated analysis of variance) and that of antipyrine (before PVE, 27.3±12.0 mL/min; day 14, 27.9±13.6 mL/min; P=.85, by paired t test) were stable after PVE. Fourteen days after PVE, the non–PVE-treated lobe was enlarged (mean±SD, 137%±30%) and the PVE-treated lobe was atrophic (mean±SD, 87%±15%); however, the total liver volume did not change significantly.

Conclusions: The functional mass and plasma flow of the entire liver were stable after PVE despite the drastic change in the lobar distribution of the portal blood flow, whereas the non–PVE-treated lobe increased significantly in size. Our findings suggest that PVE leads to an increase in both the volume and the functional capacity of the non–PVE-treated lobe.

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RADICAL EXCISION for patients with hilar cholangiocarcinoma and metastatic or primary liver tumors sometimes requires extensive hepatic resection, which is associated with significant postoperative risk of liver failure.

Preoperative portal vein embolization (PVE), which was first reported by Makuuchi et al., is now being performed widely to prevent liver failure, with the aim of inducing atrophy of the PVE lobe and compensatory hypertrophy of the lobe that remains intact after hepatectomy. Although the remaining lobe increases in volume for 2 to 3 weeks after PVE, as shown by serial computed tomography (CT), little is known about the effect of PVE on the blood flow and function of the liver.

In the present study, changes in these two measures were estimated through pharmacologic methods. In brief, functional plasma flow and functional mass of the liver were assessed after PVE in 13 patients by measuring the hepatic clearance of high- and low-liver extraction drugs, ie, sorbitol and antipyrine, respectively. Lobar volume changes after PVE were determined by serial CT and compared with the clearance data.

METHODS

PATIENTS

The study population comprised 13 patients who underwent right PVE 2 to 3 weeks before extended right lobectomy of the liver. They were 10 men and 3 women, with a mean age of 63.5 years (range, 48-77 years). The protocol was approved by the ethical committee of our institution. Each patient gave his or her written fully informed consent before the study. Of these 13 patients, 9 had bile duct carcinomas, 2 had gallbladder carcinomas, and 2 had...
tumors metastatic to the liver. Nine patients had obstructive jaundice that required biliary drainage; 2 were treated by the percutaneous transhepatic puncture method and 7 were treated by the endoscopic retrograde method. The PVE was performed after jaundice was relieved (serum total bilirubin level, <3.0 mg/dL [<53.5 μmol/L]). Absence of fibrosis or cirrhosis was confirmed in all patients at the time of scheduled surgery both macroscopically and histologically.

The PVE was performed as described previously.6 A transileocolic venous approach was adopted in 11 patients and percutaneous transhepatic approach in 2. The embolization material was a mixture of 0.5 to 1.0 g of gelatin powder (Upjohn Co, Kalamazoo, Mich), 2500 to 5000 U of thrombin (Green Cross Corp, Osaka, Japan), 10 to 20 mL of diatrizoate sodium meglumine (60% Urografin; Schering AG, Berlin, Germany), and 40 mg of gentamicin sulfate. Cessation of blood flow in the right portal branches was confirmed in each patient by portography immediately after PVE (Figure 1).

**STUDY DESIGN**

Hepatic plasma flow was estimated by measuring the hepatic plasma clearance of sorbitol (CLss,h) 1 day before PVE, approximately 4 hours after PVE, 7 days after PVE, and 14 days after PVE. The functional liver mass was estimated by measuring the hepatic plasma clearance of antipyrine (CLAP) before PVE and 14 days after PVE. Drugs such as ascorbic acid, which would interfere with the measurement of plasma concentration of sorbitol, were not given during the study period. The volumes of the left and right lobes were estimated by serial transverse CT before PVE and 14 days after PVE. The standard biochemical measures, including total bilirubin, serum aspartate aminotransferase, and serum alanine aminotransferase levels, were performed 1 day before and 7 and 14 days after PVE.

**TECHNIQUES**

Functional liver plasma flow was estimated by measuring CLss,h with the patient at rest after fasting overnight.10 After an initial loading dose of 2 g of sorbitol, additional sorbitol was given by peripheral intravenous infusion at a rate of 50 mg/min. Blood samples (4 mL) were collected from the other arm 60, 90, and 120 minutes after the infusion began. A steady-state plasma concentration (Css) of sorbitol was seen at 60 minutes. Urine samples were collected between 60 and 120 minutes. Plasma and urine concentrations of sorbitol were measured according to the enzymatic method of Bergmeyer et al.11 The steady-state total (CLss,t), renal (CLss,r), and CLss values were calculated from the infusion rate (I), the mean urinary output (U), and Css, according to standard equations:

\[
(1) \quad \text{CLss,t} = \frac{I}{C_{ss}}
\]

\[
(2) \quad \text{CLss,r} = \frac{U}{C_{ss}}
\]

\[
(3) \quad \text{CLss} = \text{CLss,t} - \text{CLss,r}
\]

The functional liver mass was evaluated by measuring the CLAP by a previously reported method.12 Blood was collected into heparinized polyethylene centrifuge tubes via the indwelling needle at 2, 4, 8, 12, 24, and 48 hours after an oral dose of 400 mg of antipyrine. Antipyrine was administered immediately after the sorbitol clearance test was terminated. After centrifugation, the plasma samples were stored at −80°C until analysis. The plasma concentration of antipyrine was measured by high-performance liquid chromatography.13 The plasma concentration of antipyrine (C) from 2 to 48 hours after oral administration followed one exponential equation, \( C = C_0 \times e^{-kt} \), where C is the initial plasma concentration extrapolated to time zero, k is the plasma elimination rate constant, t is the time from administration of antipyrine until blood sampling, and \( e^{-kt} \) is the exponential of −kt. Therefore, CLAP was calculated by means of the equation \( \text{CLAP} = \frac{k \times \text{dose}}{C_0} \). Both variables were calculated by nonlinear regression analysis.

To evaluate liver cell damage and function, we measured total bilirubin (in milligrams per deciliter), aspartate aminotransferase (in units per liter), alanine aminotransferase (in units per liter), serum lactate dehydrogenase (in units per liter), serum cholinesterase (in units per liter), percentage prothrombin activity, and activated partial thromboplastin time (in seconds) by standard methods.

The volumes of the hepatic lobes 2 weeks after PVE were calculated from the serial transverse CT images according to the method of Heymsfield et al.14 The total liver volume was calculated by adding together the volumes of the left and right lobes.

Figure 1. Portograms taken before (A) and after (B) embolization of the right portal branches. Portal vein embolization was performed through a percutaneous transhepatic approach in this patient. The right anterior and posterior branches were completely occluded with gelatin powder.
STATISTICAL ANALYSIS

All data are expressed as the mean±SD and were compared by the paired t test or 1-way repeated-measures analysis of variance. Differences were considered to be significant at \( P < .05 \).

RESULTS

The PVE was carried out safely in each patient and no operative complications were noted. Recanalization of the embolized portal vein had not developed in any patient at the time of the second antipyrine and sorbitol test, as evaluated by color Doppler ultrasonography and CT scan. The scheduled extended right hepatectomy was performed 2 to 3 weeks after PVE in 10 patients. In the other 3 cases, the decision not to resect the liver was made on the basis of intraoperative findings such as tumor invasion of the hepatoduodenal ligament and peritoneal dissemination.

The functional plasma flow of the liver, represented by \( CL_{ss,h} \), did not change significantly throughout the observation period (1-way repeated-measures analysis of variance); it was 632.9±142.9 mL/min (range, 438.4-933.2 mL/min) 1 day before PVE, 647.9±134.8 mL/min (range, 431.7-876.5 mL/min) 4 hours after PVE, 638.9±151.6 mL/min (range, 357.0-814.0 mL/min) 7 days after PVE, and 620.2±138.3 mL/min (range, 467.2-871.0 mL/min) 14 days after PVE (Figure 2).

The functional mass of the entire liver, represented by \( CL_{AP} \), was similar before PVE, 27.3±12.0 mL/min (range, 10.7-48.9 mL/min), and 14 days after PVE, 27.9±13.6 mL/min (range, 8.8-53.6 mL/min) (\( P = .85 \) by paired t test) (Figure 3).

The volume of the right lobe (with PVE) decreased from 769±166 cm\(^3\) (range, 413-1080 cm\(^3\)) before PVE to 661±154 cm\(^3\) (range, 380-937 cm\(^3\)) 14 days after PVE (\( P = .01 \), Figure 4A), whereas the volume of the left lobe increased from 344±60 cm\(^3\) (range, 243-450 cm\(^3\)) to 472±130 cm\(^3\) (range, 295-784 cm\(^3\)) (\( P < .001 \), Figure 4B). The total liver volume did not change significantly (\( P = .61 \)); it was 1113±213 cm\(^3\) (range, 656-1530 cm\(^3\)) before PVE and 1133±235 cm\(^3\) (range, 675-1502 cm\(^3\)) 14 days after PVE (Figure 4C).

The biochemical data for each patient are summarized in the Table. The mean total bilirubin level was significantly lower 14 days after PVE than before PVE (\( P < .001 \)). The other biochemical measures did not show significant change.

COMMENT

Portal vein embolization creates a unique clinical situation in that the distribution of lobar blood flow changes drastically without an immediate change in the functional hepatic mass. This situation differs greatly from cases of tumor invasion of the portal vein, in which occlusion of a
whether the arterial flow in the non-treated lobe increased to compensate, at least partly, for the addition of PVE. Many investigators have demonstrated an increase in portal blood flow after reduction of the hemihepatic portal vein by PVE does not change significantly after PVE, except for the total bilirubin value, which was decreased after PVE probably because of the biliary drainage. The finding that PVE did not have a deleterious effect on the liver as a whole is of major clinical concern because not all of the patients who undergo PVE subsequently undergo the planned extensive hepatic resection. Although the functioning of the left and right lobes cannot be assessed directly, 2 pieces of indirect evidence indicate that there is a net gain in the functional mass of the non–PVE-treated lobe after PVE. First, in the present study the total liver volume was unchanged because the volume increase in the non–PVE-treated lobe balanced the decrease in the PVE lobe (Figure 4C). Second, in a previous study, both the non–PVE-treated and the PVE-treated lobe were similar histologically to the left and in healthy subjects, so its hepatic clearance is thought to be a reliable measure of functional liver plasma flow.

In the present study, we assessed change in the blood flow and functional mass of the entire liver after PVE by measuring the hepatic clearance of high- and low-extraction drugs. Sorbitol is almost completely removed from the blood on the first pass through the liver in healthy subjects, so its hepatic clearance is thought to be a reliable measure of functional liver plasma flow. On the other hand, antipyrine, a model low-extraction drug that has a low intrinsic clearance, is fully absorbed after oral administration and is metabolized slowly by hepatic microsomal enzymes. Therefore, its hepatic clearance reflects exclusively the activity of drug-metabolizing enzymes, and it has been used as an indicator of the functional liver mass in various liver diseases.

Hepatic clearance of sorbitol did not change significantly during the post-PVE observation period. Although the method we used did not distinguish between portal and arterial blood flow, or between blood flow in the left and right lobes, it is well known that the portal blood flow is simply the sum of outflow of the extrahepatic splanchnic organs, and that it remains unchanged even after major hepatectomy in which the liver vascular bed is considerably reduced. Therefore, we think that the portal blood flow of the non–PVE-treated lobe after PVE was similar to the portal blood flow of the entire liver before PVE. Many investigators have demonstrated an increase in hepatic arterial blood flow after reduction of the portal blood flow. This phenomenon is teleologically interpreted as the hepatic arterial buffer response, the total hepatic blood flow is kept relatively constant so that the hepatic clearance rates of various hormones will be stable, resulting in hormonal homeostasis. In cases of segmental reduction of portal blood flow due to portal vein thrombi or obstruction by a tumor, CT images have suggested, albeit indirectly, that the arterial blood flow in the resected or obstructed lobe increases. On the basis of these observations, we think that the arterial blood flow in the PVE-treated lobe increased to compensate, at least partly, for the cessation of portal blood flow. However, it is not clear whether the arterial flow in the non–PVE-treated lobe decreases to compensate for the increase in the portal blood flow, because increased portal flow is uncommon in a clinical setting. In the present study, the functional plasma flow of the entire liver did not change after PVE, which is compatible with the above theory and which suggests that the arterial flow in the non–PVE-treated lobe does decrease. This notion is supported by the findings of the rat model of left portal vein ligation in which the increase of the right portal flow resulted in the selective decrease in the right hepatic artery flow. Furthermore, the observation of an isolated perfused human cirrhotic liver indicated that the hepatic arterial resistance was increased when the portal flow was increased mechanically.

The PVE did not affect the hepatic clearance of antipyrine, which we evaluated on the 14th postoperative day. Consequently, we conclude that abrupt occlusion of the hemihepatic portal vein by PVE does not change the total functional mass of the liver. To support this consideration, the biochemical data did not change significantly after PVE, except for the total bilirubin value, which was decreased after PVE probably because of the biliary drainage. The finding that PVE did not have a deleterious effect on the liver as a whole is of major clinical concern because not all of the patients who undergo PVE subsequently undergo the planned extensive hepatic resection. Although the functioning of the left and right lobes cannot be assessed directly, 2 pieces of indirect evidence indicate that there is a net gain in the functional mass of the non–PVE-treated lobe after PVE. First, in the present study the total liver volume was unchanged because the volume increase in the non–PVE-treated lobe balanced the decrease in the PVE lobe (Figure 4C). Second, in a previous study, both the non–PVE-treated and the PVE-treated lobe were similar histologically to normal liver, except for an increase in sinusoidal areas with low hepatocyte density in the PVE-treated lobe. This finding suggests that there is no difference in the functional efficiency of each hepatocyte in either lobe. Therefore, it is highly likely that the functioning of each lobe is proportional to its volumetric ratio both before and after PVE. Therefore, on the basis of unchanged total functional hepatic mass and total liver volume, we think that there was a net gain in the functional capacity of the non–PVE-treated lobe. These findings also suggest that the PVE lobe still functioned to a certain degree in the absence of portal flow at the time of right lobectomy. Of the present 10 patients who underwent scheduled extensive hepatic resection, postoperative CT examination was conducted in 2 patients to search for the focus of possible infection responsible for postoperative fever. In one patient, left lobar volume

<table>
<thead>
<tr>
<th>Postoperative Changes in Biochemical and Coagulation Assay*</th>
<th>Before PVE</th>
<th>After PVE</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin, mg/dL†</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>0.9 ± 0.1‡</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>55 ± 9</td>
<td>57 ± 6</td>
<td>51 ± 11</td>
<td>47 ± 6</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>95 ± 22</td>
<td>83 ± 18</td>
<td>72 ± 11</td>
<td>74 ± 10</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>278 ± 83</td>
<td>268 ± 63</td>
<td>275 ± 81</td>
<td>276 ± 7</td>
</tr>
<tr>
<td>ChE, U/L</td>
<td>108 ± 9</td>
<td>...</td>
<td>...</td>
<td>102 ± 7</td>
</tr>
<tr>
<td>Prothrombin activity, %</td>
<td>86.4 ± 3.9</td>
<td>...</td>
<td>...</td>
<td>80.7 ± 3.7</td>
</tr>
</tbody>
</table>

*PVE indicates portal vein embolization; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ChE, serum cholinesterase; and ellipses, not measured.
†To convert to micromoles per liter, multiply by 17.1.
‡P < .001 vs preoperative result by 1-way repeated-measures analysis of variance.
increased from 407 mL to 1088 mL in 30 days after hepatic resection; in the other patient, an increase from 548 mL to 674 mL occurred 17 days after right lobectomy. These results support the above notion, i.e., that the volume of the patient's left lobe was increased further to compensate for the loss of the partially functioning right lobe after PVE.

In conclusion, the present findings suggest that PVE increases the volume and functional capacity of the non-PVE-treated lobe without altering the blood flow of the entire liver and without having a deleterious effect on the liver as a whole.

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