Experimental Model of Extended Repeated Partial Hepatectomy in the Dog

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Abstract. The model of extended repeated partial hepatectomy without vascular shunt in dogs is presented. It consisted of 65% initial hepatectomy and after liver regeneration (6–10 weeks) repeated hepatectomy. Finally, only the papillary process of the caudate lobe (PPC), which constitutes 5% of the initial hepatic mass, was left intact. The most important finding was an ability of PPC to reconstitute the liver mass which enabled survival without the vascular shunt. After repeated hepatectomy the need for artificial hepatic assistance (parenteral nutritional support with frozen plasma) was imperative to offset the effects of acute hepatic failure and to support PPC regeneration.

Several experimental models of extended hepatectomy aimed at studying the possibilities of liver regeneration have been tried out [1, 2, 6, 7, 9, 13]. However, in the literature there are little data concerning repeated hepatectomy (RH). The concept of RH has been studied in the rat and shows that repeated resections do not diminish the regenerative response [1, 5, 8].

Now, following experimental studies, major hepatectomies in humans with acceptable postoperative mortality can be considered as a possible treatment for liver metastases or primary cancer. Unfortunately, the extent of liver resection must not exceed 80% of functional parenchyma if regeneration is to occur [14]. In the rat, when 90% hepatectomy is performed, no regeneration is observed in the 10% remaining liver. The major finding is an overwhelming steatosis with a survival of less than 40 h posthepatectomy [12]. However, complete regeneration of the liver has been described in one-stage 90% hepatectomized rats only if they were treated with testosterone [15].

In experimental studies on dogs, when liver resection is extended to 95% (subtotal hepatectomy), the survival usually does not exceed 4 h [2]. This can be prolonged up to 100 h using portocaval or mesenterico-caval shunt associated with artificial nutritional support [2, 11].

The purpose of this paper was to present the original model of extended repeated partial hepatectomy without vascular shunt in dogs. Only the papillary process of the cau-
date lobe (PPC) was left intact (left segment I according to Couinaud [4]), which is the smallest hepatic lobe and constitutes 5% of the initial hepatic mass.

Material and Methods

Eight healthy adult mongrel dogs weighing 14–27 kg and having fasted 1 day before surgery were used in this study. All the procedures were performed according to the principles of atraumatic and aseptic techniques with dogs under general anesthesia induced by intravenous injection of Nedonal (Thiopental) – 20 mg/kg – followed by tracheal intubation. The ventilation was maintained by respirator which delivered a 50% mixture of oxygen and nitrous oxide. During the operation dogs were perfused with Ringer lactate solution (approximately 1,000 ml).

Initial Hepatectomy (65%)

In the first step a 65% hepatectomy was performed by the techniques described previously [2, 3, 13] (fig. 1). The abdomen was entered through a vertical midline incision and self-retaining retractors were inserted. The following hepatic lobes were exposed: left lateral (segment II), left central (segment III), quadrate (segment IV) and right central (segment V). Their afferent vascular pedicles were divided, separately ligated (Flexidene 2-0) and sectioned. The liver was then retracted downwards and the left triangular and gastrohepatic ligaments were incised, taking care to avoid damaging the left phrenic vein which indirectly drains the PPC. The corresponding suprahepatic veins were dissected, ligated (Flexidene 2-0) and sectioned. The lobes were removed, including the gallbladder, with amputation of liver tissue distal to the ligature. The abdomen was closed without drainage and the animal placed in a metabolic cage for recovery. The average time for the procedure was about 60 min. No perfusion was needed in the postoperative period and oral alimentation could start from the 1st postoperative day.

Repeated Hepatectomy

Dogs were reoperated after a period of liver regeneration, which varied from 6 to 10 weeks (fig. 2). In the first step, two silicone catheters (Vygon) were introduced into jugular vein: one for parenteral nutritional support (PNS) and the second for plasma infusion. Urinary catheter was used to monitor diuresis during surgery and in the early postoperative period. Abdomen was reentered through the same vertical midline incision used for initial hepatectomy. The adhesions were dissected carefully with electrocoagulation to avoid bleeding and the remnant liver was exposed. Special attention was paid to dissection of adhesions between the right lateral and caudate lobe was gently dissected and the afferent vascular pedicles exposed. They were divided, separately ligated (Flexidene 2-0), and sectioned. Initially, the caudate lobe was removed. The plane of transection passed through the isthmus situated between the caudate lobe proper (right segment I) and PPC (left segment I). This is quite a narrow passage, measuring 2–3 cm in diameter. In the next step, the right lateral lobe was removed after downwards traction on the lobe which exposed the right suprahepatic vein. This vein was then ligated (Flexidene 2-0) and sectioned. The liver tissue was removed downwards following the vena cava, leaving its surface completely denuded. During this procedure the small hepatic veins entering the vena cava were gradually ligated. It is usually the most difficult phase of the operation, which may provoke excessive blood loss and possible postoperative death. When the resection was completed, only the PPC was left intact. It has its own vascular supply and should, therefore, remain well vascularized in the absence of technical error. Abdominal viscera were carefully examined and no signs of portal hypertension were found (e.g. splanchic stasis), which obviated the need for a vascular shunt. At the end of surgery, one peritoneal drain was inserted through the right lower quadrant of the abdomen and fixed to the parietal peritoneum. The abdomen is closed in two layers and the animal placed in a metabolic cage during recovery and follow-up. The average time of surgery was about 120 min.

Follow-Up

PNS was undertaken immediately after surgery and consisted of (per kilogram body weight, per 24 hours): 50 ml of water, 7.2 g of glucose, 0.2 g of nitrogen, electrolytes and trace elements in a nutritive
Repeated Partial Hepatectomy

Fig. 1. Initial hepatectomy (65%), including the lobes. LL = Left lateral; LC = left central; Q = quadrate; RC = right central and gallbladder; VC = vena cava; = remaining liver.

Fig. 2. RH, including the lobes. RL = Right lateral; CP = caudate proper; VC = vena cava; = remaining liver.

mixture supplemented by vitamins. PNS was continued up to 10–12 postoperative days, after which it was gradually supplanted by oral feedings. At the same time, in order to equilibrate the deficit of coagulation factors due to postoperative hepatic failure, fresh-frozen plasma was infused at gradually decreasing doses (per kilogram body weight, per 24 hours): 50 ml (including 300 ml at the end of operation) from day 0 to day 3, 30 ml from day 4 to day 6 and 16.6 ml from day 7 to day 10. Plasma was previously prepared from mongrel dogs and stored at -80°C. Ampicillin (2 g/day i.m.) was routinely administered up to the 8th postoperative day.

Results

The recovery from anesthesia after 65% hepatectomy was relatively rapid, whereas after RH it was prolonged to 3–5 postoperative h; at that time the dogs were usually standing in their cages. No postoperative mortality after 65% hepatectomy was observed. However, there were 3 postoperative deaths (37.5%) within 48 h following RH: 1 dog (No. 1) as a result of intraoperative blood loss (about 300 ml), and 2 dogs (No. 4 and 6) because of increasing posthepatectomy intraperitoneal bleeding. Bloody drainage during the first 4 postoperative days was observed in all cases. In the dogs who survived, this bleeding progressively decreased allowing removal of the intraperitoneal drain on day 4.

In order to follow remnant PPC regeneration, the dogs were sacrificed by bolus intravenous injection (20 mg) of potassium chloride at different time intervals (day 8, 16, 30,
Table I. Repeated partial hepatectomy in the dog: weight of hepatic resection and growth evolution of PPC

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight of the dog (kg)</th>
<th>Initial hepatectomy (65%)</th>
<th>RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>weight of hepatic resection</td>
<td>calculated weight of PPC</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>493</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>333</td>
<td>26</td>
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<tr>
<td>3</td>
<td>16</td>
<td>238</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>302</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>222</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>306</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>208</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>23.</td>
<td>412</td>
<td>32</td>
</tr>
</tbody>
</table>

a The weight of the gallbladder is excluded.
b Approximate mathematical calculation of 5% liver mass according to resection weight at 65% hepatectomy:

$$PPC = \frac{W \times 5}{65}$$, where W = weight of hepatic resection.
c Postoperative death.

45) chosen arbitrarily. The PPC was removed at necropsy and weighed to assess the degree of regeneration. All data concerning the weight of hepatic resection and growth evolution of PPC are summarized in table I. The different degrees of regeneration observed were characterized by rapid growth during the first 2 weeks. In one case (No. 8) PPC nearly regained the theoretical initial liver mass, i.e., approximately 640 g.

Two dogs (No. 1 and 4) who had died within 24 h after hepatectomy and for whom different degrees of PPC regeneration were observed, were used to calculate the approximate percentage of RH which varied between 75-80%:

$$RH, \% = \frac{W \times 100\%}{(PPC + W)}$$

where W = weight of hepatic resection at RH.

Discussion

The phenomenon of liver regeneration remains of major interest to surgeons, including both fundamental research and practical aspects related to hepatectomy in man. Hepatectomy in dog is an excellent model to study these problems because, as in man, the operative technique is based on anatomical dissection and individual ligation of blood vessels and bile ducts, supplying the portion of the liver to be resected, while preserving these structures in the remnant part. Moreover, anatomy of the dog liver readily permits isolation of the smallest hepatic anatomical lobe – PPC (left segment I) which in man corresponds to Spiegel's lobe [4] – in order to study the possibilities of regeneration. One-stage subtotal hepatectomy (95%) does not lend itself to such a study because
survival is limited to 100 h after hepatectomy. For this reason we adopted an experimental model based on RH which could be employed in man.

Dogs were reoperated after a period of 6–10 weeks of liver regeneration because, as Mallet-Guy et al. [9, 10] point out, the major part of hepatic parenchyma is reconstituted during this time.

The second operation (RH) on dog liver was a relatively difficult and time-consuming procedure necessitating gentle dissection of anatomical structures and perfect hemostasis. In the postoperative period the need for artificial hepatic assistance (PNS + frozen plasma) was imperative to offset the effects of acute hepatic failure and to support PPC regeneration. The length of artificial hepatic assistance was adapted to the postoperative course.

The postoperative mortality (37.5%) was not only due to technical error (intraoperative bleeding) but also to insufficient regeneration of the PPC after 65% hepatectomy (56 and 72 g, respectively), thereby resulting in acute hepatic failure following RH with a rapidly declining course (dogs No. 4 and 6).

This paper constitutes a preliminary report concerning the problems of RH in the dog. It showed, however, that the smallest hepatic anatomical lobe (5% of initial hepatic mass) – PPC (left segment I) – due to the phenomenon of liver regeneration enabled survival without vascular shunt. All these aspects present both practical and theoretical problems and warrant further studies.

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Key Word: multiplication into the liver

Hepatocytes were injected into the liver of rats [18]. The prolifera-
tion of hepatocytes injected into liver (group A) increased signifi-
cantly after transplantation. The prolifera-
tion of hepatocytes injected into the liver of rats 

The transplanted animals survived over 15, 17]. To ap-