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One liver for two: an experimental study in primates

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Abstract. The need for liver grafts is critical in countries where brain death is not accepted as a legal criterion for organ retrieval. This experimental study was conducted with nonhuman primates in order to evaluate the feasibility of liver transplantation using a living donor. An original technique was employed to remove the left part of the liver from the donor: transection of the parenchyma was done while the blood flow was kept to the left part of the liver. In the recipients, the graft was placed heterotopically. No blood transfusions were administered to donors or recipients. In spite of a few failures, due to consequences of intraoperative bleeding, several donor operations using this original technique were successful, in the immediate postoperative period as well as several months later. Among the recipients, the large number of early failures suggests that the heterotopic position is probably not the appropriate one and that orthotopic transplantation should be preferred.

Key words: Experimental liver transplantation - Living donor - Heterotopic graft - Primates.

Liver transplantation is rapidly expanding as the treatment for numerous patients with acute or chronic liver diseases. As a consequence, the shortage of organs from heart-beating human cadavers becomes critical, particularly for children and for emergency cases. There are other potential sources of organs, such as non-heart-beating human cadavers or nonhuman donors, and these are presently under investigation around the world. Theoretically, another source of liver grafts could result from the anatomical characteristics of the liver: though a unique organ, the liver is composed of two half-livers which can be surgically divided. Initially, we have shown that it was possible to perform orthotopic liver transplantation in children using an adult liver reduced in size by half [1]. However, this technique, which has markedly improved the feasibility of liver transplantation in children [3], does not increase per se the number of liver grafts available for transplantation.

Each half-liver has its own portal vein, hepatic vein, hepatic artery, and bile duct. Therefore, we decided to conduct an experimental study with primates in order to assess the feasibility of removing the left part of the liver from a living donor and grafting it in a smaller recipient.

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Animals and methods

Unrelated *Macaca crabiae* weighing 2-10 kg were obtained from the Centre d'Elevage des Saints Pères (Paris, France) and were used as donors and recipients.

After 12 h of fasting, anesthesia was induced using ketamine. Following tracheal intubation, anesthesia was continued using halothane. Monitoring included measurement of expirated carbon dioxide and direct measurement of arterial blood pressure. Central body temperature was maintained using a heating blanket. Intravenous administration of high-molecular-weight molecules, saline, or glucose was adapted to hemodynamic data. Sequential dosages of arterial blood gases, serum electrolytes and glucose were done during operation. No blood transfusion was administered. Neither an immunosuppressive regimen nor antibiotics were administered postoperatively. Donor and recipient operations were conducted simultaneously, and ten experiments were done.

The donor operation was performed through a midline incision. The round ligament, falciform ligament, and left triangular ligaments were divided. Using an operative microscope, the terminal 2 cm of the left hepatic vein were dissected from the surrounding parenchyma and encircled. Then the upper left portion of the hepatic pedicle was extensively dissected until complete mobilization of the left branches of the hepatic artery, hepatic duct, and portal vein was achieved. According to the particular animal, two to three glissonian pedicles going from the horizontal portion of the left glissonian pedicle to the quadrate lobe were ligated and divided, as well as one or two short pedicles going to the spigelian lobe. Then, without clamping the vascular structures going to the left part of the liver, the liver capsule was incised along a line between the right side of the round ligament and the right side of the end of the left hepatic vein. The transection was done step by step using a Kelly clamp with ligature or coagulation of each pedicle; it was conducted posteriorly and slightly to the left, ending in front

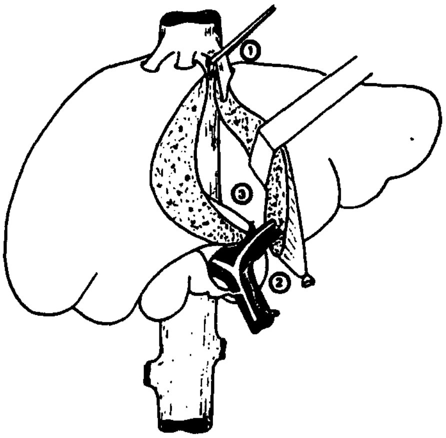

Fig. 1. Removal of the left part of the liver from a living primate donor: *1* dissection of the left hepatic vein, *2* dissection of the left glissonian pedicle, *3* complete transection of the liver parenchyma between the left glissonian pedicle and the left hepatic vein while the blood inflow and outflow are kept to the left part of the liver

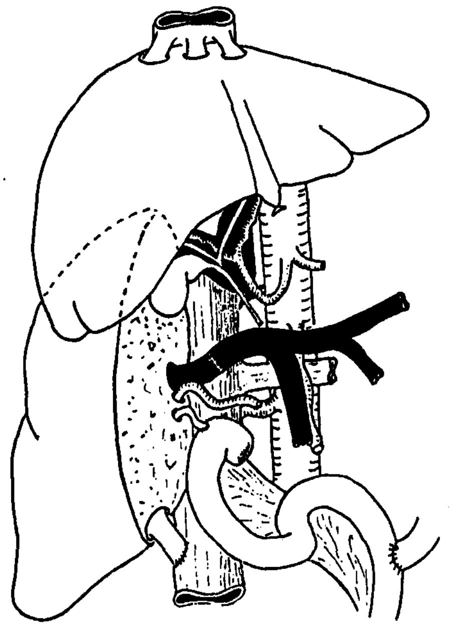

Fig. 2. Heterotopic auxiliary transplantation using the left part of the liver from a living primate donor

of the right border of the caudate portion of the spigelian lobe. This technique allowed us to maintain normal blood flow to the left part of the liver during transection of the parenchyma (Fig. 1). Finally, the left branches of the hepatic artery and portal vein and the left hepatic vein were clamped and divided. After a warm-ischemia time of less than 2 min, the graft was flushed and cooled via the left portal branch and the left hepatic artery using 200 ml of 4 °C Ringer's lactate solution and then immediately transplanted. In the donor, the stumps of the left portal branch, left hepatic artery, left hepatic vein, and left hepatic duct were either ligated or sutured. Before the abdomen was closed without drainage, inspection of the remaining liver revealed in all cases a small area of congestion on its left and anterior part, close to the transection plane.

The recipient operation was conducted through a midline incision. Since blood transfusion was not available, the technique requiring the least dissection was chosen: the graft was implanted in the recipient heterotopically as an auxiliary graft. The portal vein was mobilized in the hepatic pedicle and the duodenum and head of the pancreas were then reclined to the left to permit a large exposure of the vena cava above and below the renal veins. Various vessels were approached for further reconstitution of the arterial flow to the graft: hepatic artery (experiments 3, 4, and 6), right gastric artery (experiments 1 and 7), right external iliac artery (experiments 8 and 10), and right renal artery (experiments 2, 5, and 9). Generally, the graft was placed as follows: starting from the anatomical situation of a left liver lobe, the graft was translated to the right part of the abdomen, then distally a few centimeters along the inferior vena cava. It was then rotated 180° in the frontal plane so that the end of the hepatic vein of the graft was in a distal position and the inferior part of the left lobe and left glissonian pedicle were in a proximal position (Fig. 2).

The graft was then implanted by anastomosing the hepatic vein of the graft end-to-side to the right and anterior part of the vena cava, the portal branch of the graft end-to-end to the portal vein of the recipient, and the hepatic artery of the graft end-to-end to the right gastric artery or right external iliac artery, or end-to-side to the right renal artery or to the hepatic artery. The hepatic duct of the graft was implanted end-to-side on a Roux-en-Y jejunal loop.

Postoperatively, as soon as they awoke, donors and recipients were extubated and intravenous and arterial lines were removed. Use of the heating blanket was maintained as long as the animal remained in a supine position.

Results

Results are given in Table 1. Most donor operations were successful (6/10). In three cases the animal died at the end of operation (two cases) or the day after (one case) due to acute anemia resulting from repeated hemorrhagic episodes during transection of the liver parenchyma. One animal died 20 days after operation from the consequences of an acute ischemia of the left inferior limb due to thrombosis of the left femoral artery. Six animals were alive 3 months after operation. Three of these six animals were systematically killed. No intra-abdominal complications were noted. The right part of the liver was slightly enlarged as compared with the time of surgery. Surface, color, and consistency of the livers were normal and liver histology was normal. Three animals are alive and well 1 year after operation.

Recipient operations were far from being always successful. In three cases, death occurred at the end of surgery as a consequence of hemorrhage from the area of liver transection. This hemorrhage resulted from a marked congestion of the graft due to an inadequate position of the hepatic vein to vena cava anastomosis. In two cases where there was moderate intraoperative hemorrhage, the animals nevertheless had significant anemia at the end of surgery, failed to wake up, and died in the following hours.

One animal died 3 days after operation. Postoperatively it remained prostrate, with no inclination to climb at the bars of the cage, and became more and more jaundiced. Reoperation 3 days after the

Table 1. Heterotopic auxiliary liver transplantation in primates using part of the liver from a living donor

Experiment number	Donor			Recipient		
	Body weight (in kg)	Outcome	Cause of death	Body weight (in kg)	Outcome	Cause of death
1	7.5	Alive	-	2.5	Died (day 0)	Intraoperative hemorrhage
2	7.5	Alive[a]	-	2	Died (day 8)	Acute rejection
3	8	Alive[a]	-	4	Died (day 0)	Intraoperative hemorrhage
4	9	Died (day 0)	Intraoperative hemorrhage	4.1	Died (day 6)	Hepatic artery thrombosis
5	8.2	Alive	-	3.5	Killed (day 30)	Acute rejection
6	8	Died (day 20)	Ischemia of the inferior limb	4	Died (day 0)	Unknown
7	7	Alive[a]	-	3	Died (day 3)	Hepatic artery thrombosis
8	6.5	Died (day 0)	Intraoperative hemorrhage	3.5	Died (day 0)	Brain death
9	7.5	Died (day 1)	Anemia	2.5	Killed (day 20)	Acute rejection
10	8	Alive	-	3	Died (day 0)	Intraoperative hemorrhage

[a] Systematically killed three months after operation

initial surgery revealed complete necrosis of the graft secondary to thrombosis of the anastomosis between the hepatic artery of the graft and a very small right gastric artery of the recipient. Two animals died 6 and 8 days after surgery, the first because of necrosis of the graft due to thrombosis of the anastomosis between the hepatic artery of the graft and the hepatic artery of the recipient's liver, the second because of necrosis of the graft due to acute rejection.

Two animals were killed 20 and 30 days after grafting. Both animals had an uneventful postoperative recovery. Three days before being killed they became asthenic, anorectic, and jaundiced. At reoperation, the grafts were markedly enlarged with some degree of atrophy of the recipients' liver. No biliary or vascular anastomotic complications were observed. Histological examination of the grafts revealed signs of severe acute rejection.

Discussion

Theoretically, the use of one liver to support the life of two human beings can be envisaged in two situations: either using the liver from a cadaver donor for two recipients, or taking a part of the liver from a parent for transplantation in a young child. In the first situation, which is the simplest one, partition of the graft can be done as a bench procedure after the graft has been cooled. In the second situation, the graft is taken from a living donor in a way which, on the one hand, must be harmless for the donor and for his or her remaining liver and, on the other hand, makes it possible to obtain vascular and biliary segments suitable for anastomosis while avoiding any warm-ischemic damage to the graft's parenchyma.

This experimental study was conducted with a view to the second situation. Primates were chosen primarily because their liver does not differ much from a human liver, suggesting that information obtained from the experiments could be more easily transferred to clinical practice. Furthermore, in primates, which are erect animals, the wall of the hepatic vein is sufficiently thick and can easily be individualized from the surrounding parenchyma. With the help of an operative microscope it can be dissected free in its terminal portion inside the parenchyma. In fact, in our initial experiments conducted in rats and pigs (unpublished data), we observed that the hepatic veins had a thin wall and could not be separated easily from the surrounding parenchyma. A surgical approach to the left hepatic duct in its horizontal portion was described for treatment of human beings with postoperative biliary stenoses located at the confluence between the right and left hepatic ducts [4]. In this study, the approach was not limited to the left hepatic duct. The entire left glissonian pedicle had to be skeletonized in its horizontal portion. In order to obtain a sufficient length of portal vein, hepatic artery, and biliary duct, dissection of the left glissonian pedicle had to be extended as close as possible to the hilum. Thus, some degree of devascularization was inflicted on the left part of the quadrate lobe and on the caudate process of the spigelian lobe due to the necessary division of corresponding glissonian pedicles.

The original aspect of this study is that, in the donor, transection of the liver was conducted without clamping of any vascular structure in order to avoid warm-ischemic damage to the future graft. In all cases, at the end of transection there was an area of congestion on the left part of the quadrate lobe of the remaining liver. However, in three animals, when they were killed 3 months later, the liver appeared entirely normal. Except for one case in which we had to deal with an important hemorrhage which was directly lethal, bleeding in the donor was usually moderate. It was nevertheless excessive in three animals because of the absence of blood for transfusion.

In the recipients we hesitated between orthotopic and heterotopic transplantation. Orthotopic transplantation, which would have required the recipient to undergo a total hepatectomy without resection of the vena cava or a partial hepatectomy, was not chosen in order to reduce the risk of bleeding or hemodynamic disturbances and to shorten the portal vein clamping time. However, it is probable that the recently reported [6, 7] new technique for transplantation in children using a reduced-sized (segments 2 and 3) liver graft from an adult cadaver donor and keeping in place the vena cava of the recipient would be the best technique for the implantation of a liver graft obtained from a living donor. In this case, the shortness of the portal branch and hepatic artery of the graft would render a direct anastomosis with the recipient's portal vein and proper hepatic artery difficult or unfeasible because of the necessary rotation of the graft to the right. This difficulty could be surmounted by the use of an interposed vascular graft, particularly for the hepatic artery, or by lengthening the portal vein and hepatic artery of the recipient by using their left branches.

In this study, we attempted to place the graft heterotopically without removing the recipient's liver. The principles usually considered necessary for the success of a heterotopic auxiliary liver graft were adopted [2, 5, 9]: implantation on the inferior vena cava, as close as possible to the heart; portal venous inflow to the graft; suppression of the portal venous inflow to the recipient's liver when it is noncirrhotic.

The main difficulty with the recipient was the control of bleeding from the transected area of the graft. It was clearly related in some cases to the poor quality of the venous drainage of the graft, the graft causing torsion or compression of the anastomosis between the hepatic vein and the vena cava. The second difficulty lay in the hepatic artery anastomosis: implantation of the hepatic artery of the graft into the hepatic artery of the recipient was not always feasible because of the distance between the two vessels, and the right gastric artery of the recipient was usually too small. Implantation of the hepatic artery of the graft into the recipient's right renal artery seemed the most satisfactory technique.

In conclusion, our study presents a technique for obtaining a liver graft from a living donor in an animal species which bears a large similarity to human beings from the anatomical point of view. Our attempts to transplant these grafts heterotopically met with the difficulty of finding an adequate position for the graft. According to recent publications concerning transplantation of a reduced-sized liver from a cadaver donor in children, the orthotopic position with conservation of the vena cava of the recipient would probably be preferable.

If liver transplantation in children using a living donor now seems to be feasible, it nevertheless raises a major ethical problem due to the risk taken by the donor. In countries accepting brain death for organ retrieval, liver transplantation using a living related donor is justifiably considered with much reluctance: as a matter of fact, in children with fulminant hepatitis, the existence of a superurgent section with full priority on liver transplant waiting lists and the possibility of using the liver from any kind of adult cadaver donor has markedly shortened the waiting time for a graft. In contrast, in countries not presently accepting brain death for organ retrieval, it is clear that pressure for liver transplantation in children may soon lead to the use of liver grafts from living related donors [8, 10].

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