Review article

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New aspects of heterotopic liver transplantation

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Abstract. In this report the history and clinical results of heterotopic liver transplantation (HLT) are reviewed and some special aspects of current research on HLT are highlighted. The first laboratory experiments on liver transplantation were performed with auxiliary heterotopic grafts. The initial clinical results of HLT, however, were disappointing and orthotopic liver transplantation (OLT) evolved to be the procedure of choice. Of all the patients who received a heterotopic graft before 1980, only two survived. Since 1980, 50 HLTs are known to have been performed on 48 patients. Results of HLTs after 1986 are clearly better than earlier ones, and survival rates come within the range of those reported for OLT. Intraoperative fibrinolysis is found in the anhepatic phase of OLT, something which is absent in HLT. Tissue-type plasminogen activator (t-PA) is said to be responsible for this phenomenon, as well as for the postreperfusion hyperfibrinolysis. Parallel to the hemostatic changes, the intraoperative hemodynamic stability may be impaired by deleterious substances that arise during liver transplantation. Furthermore, the interaction between the two livers, the effect of HLT on portal pressure and hypersplenism, and the possible role of HLT in inborn errors of hepatic metabolism are described. Special attention is given to the treatment of acute hepatic failure. OLT, in an early phase of the disease, negates the possibility of spontaneous recovery, while delay of the decision to transplant may lead to further deterioration of the patient's clinical condition. As the procedure of HLT is reversible, the decision to transplant can be made more quickly. The clinical experience with HLT for acute liver failure is reported in detail.

Key words: Liver transplantation, auxiliary – HLT versus OLT – Fibrinolysis, HLT versus OLT – Acute hepatic failure, HLT

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Orthotopic liver transplantation (OLT) is a therapeutic option for patients with end-stage acute or chronic liver disease. In patients with advanced liver disease, however, the combination of portal hypertension, abundant venous collaterals, and severe clotting disturbances makes dissection and removal of the cirrhotic liver a demanding procedure. In the following anhepatic phase, the hemodynamic condition of the patient is further compromised by decreased venous return, unless a veno-venous bypass is used [51].

Heterotopic auxiliary liver transplantation (HLT) avoids the surgical trauma of removal of the recipient liver and the need for a veno-venous bypass system [22]. Furthermore, the host liver can provide synthetic and clearing liver function during the transplantation and in case of graft rejection or failure. Removal of the native liver also negates its potential recovery in patients with acute liver failure. Finally, with HLT, one does not have the feeling that an organ that looks normal and functions virtually normally (except for a single enzyme system) must be wasted, as occurs in OLT for patients with an inborn error of metabolism, where the organ is disposed of. Consequently, for some patients, HLT offers advantages over OLT.

In this report the history and clinical results of HLT are reviewed and some special aspects of current research on HLT are highlighted.

History

The first laboratory experiments on liver transplantation were performed with auxiliary heterotopic grafts and were carried out in 1955 [20, 65]. The first auxiliary liver transplantation in humans was performed in 1964 [1]. From that moment until 1980, 47 patients underwent heterotopic liver grafting, but only 2 patients survived longer *than* 1 year [59]. While OLT evolved to be the procedure of choice, the potential advantages of leaving the diseased liver in place continued to inspire researchers to study various experimental auxiliary models [33, 34, 38, 52, 54].

In the Laboratory for Experimental Surgery, in Rotterdam, the problems associated with the auxiliary proce-

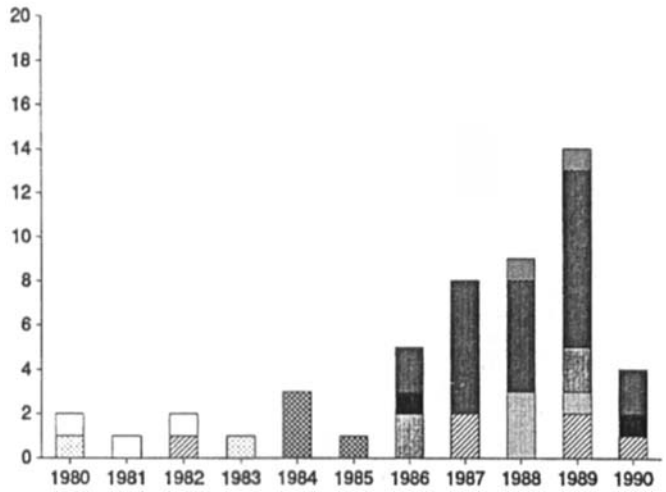

Fig. 1. Annual number of heterotopic liver transplantations from 1980 to 1990 by transplantation center. ▨ Brussels (Belgium); ▩ Tübingen (FRG); □ Nice (France); ▨ Paris (France); ▩ Toulouse (France); ■ Grenoble (France); ■ Rotterdam (The Netherlands); ▩ Philadelphia (USA); □ Others: Innsbruck (Austria), Hannover (FRG), and Capetown (South Africa)

dure were reviewed. With the definition of theoretical requirements for successful auxiliary heterotopic transplantation, a new concept of auxiliary partial liver transplantation was developed: a reduced-size liver, with both arterial and portal inflow and venous drainage through the suprahepatic vena cava of the graft into the recipient's infrahepatic vena cava, as close as possible to the diaphragm [44–47, 59, 60].

The results of these experimental studies led to the initiation of a clinical program in October 1986. In 1988, the favorable outcome in the first six patients in this program was reported [61]. All patients had end-stage liver disease and were considered by another transplant center to be at high risk for not surviving an OLT. Following auxiliary partial liver transplantation, they were alive and well, with good graft function, after a mean follow-up period of 14 months.

By now it has become evident that either method, HLT or OLT, can give good results. In an open comparative study between OLT and HLT, it was demonstrated that HLT could give long-term metabolic support and adequate decompression of the portal system and that it was associated with a morbidity and mortality comparable to that of OLT in medium-risk patients with end-stage chronic liver disease [40].

In the present survey, all HLTs that were performed from January 1980 through December 1990 are included. Data were collected from the European Liver Transplant Registry (ELTR), recent publications [8, 19, 24, 36, 39, 41, 56, 61], and personal communications.

In the decade under study, 50 HLTs in 48 patients were performed in 11 centers (Fig. 1). There were 27 men and 21 women with a median age (range) of 40.5 years (20–69 years) and 47 years (1–60 years), respectively. Three patients were 15 years or younger. Twenty-one patients underwent emergency transplantation. Details on indications are given in Table 1. In seven patients HLT was performed for acute or subacute liver disease (Table 2). The outcome of these transplantations is described below.

The main cause of death was sepsis, responsible for 12 of 32 deaths (Table 3). This is in accordance with the OLT experience. Four deaths were attributed to vascular complications. In contrast with OLT, where vascular complications are mainly arterial problems, in HLT the patency of the portal vein is most crucial. Two cases of hepatocellular carcinoma in the recipient liver were found after HLT. The low incidence of rejection as a cause of graft failure is remarkable.

Survival was assessed using the life-table analysis according to Kaplan and Meier [29], and survival times were compared with the log-rank test. Only primary HLTs were included in the life-table analysis. Cumulative survival was compared for emergency versus elective surgery (Fig. 2) and year of transplantation (before versus after January 1987; Fig. 3).

When comparing HLT survival in the present study with the results of OLT, it should be noted that the majority of these HLTs were performed only occasionally at various centers, and for exceptional indications, or they were attempted in high-risk patients. Furthermore, as in HLT, results of OLT before and after 1986 are significantly different. In the first report of the ELTR, 1-year survival – calculated in the cumulative series from 1968 through 1986 – was 44% for emergency and 46% for elective transplantation [9]. To date, various centers have reported 1-year survival rates ranging from around 70% to around 90% for elective transplantations [7, 13, 26, 27].

After January 1987, 14 emergency HLTs were performed with a 1-year survival rate of 71%. In Rotterdam, 16 primary HLTs were performed for cirrhosis and sclerosing cholangitis with a 1-year patient survival rate of 75%. It is expected that results of HLT will further improve when stringent indications are used and when patients other than extreme high-risk patients become candidates for heterotopic liver grafting.

Table 1. Indications for heterotopic liver transplantation 1980–1990

Chronic liver disease		No.
Cirrhosis:		
– posthepatic		11
– primary biliary		8
– alcoholic		4
– autoimmune		2
– metabolic		1
– unknown		6
Primary sclerosing cholangitis		2
Biliary atresia		1
Retransplantation		1
Tumor:		
– hepatocellular carcinoma		3
– secondary liver tumor		1
– benign liver tumor		1
Acute liver disease (within)		
Fulminant hepatic failure	(0–2 weeks)	2
Acute hepatic failure	(2–8 weeks)	4
Subacute hepatic failure	(8–26 weeks)	1
Total		48

Table 2. Heterotopic liver transplantation (HLT) for acute or subacute liver disease. PNF, Primary graft nonfunction; OLT, orthotopic liver transplantation

Center[a], year	Sex	Age	Etiology	Outcome
Paris, 1980	♀	17	Valproate	Sepsis, died day 24
Grenoble, 1986	♀	24	Unknown (viral?)	Alive 55 months
Rotterdam, 1986	♂	31	Unknown	PNF, died day 18
Rotterdam, 1987	♀	18	Unknown	PNF, re-HLT[b], died day 15
Rotterdam, 1989	♀	35	Autoimmune (?)	Alive 31 months
Philadelphia, 1988	♀	19	Unknown (viral?)	Alive 33 months, no medication
Philadelphia, 1989	♀	15	Wilson's disease	Rejection, OLT day 27

[a] Centers: Faculty of Medicine Paris-Sud, Hôpital Paul Brousse, Villejuif, France; Centre Hospitalier Regional et Universitaire de Grenoble, France; University Hospital Dijkzigt, Erasmus University, Rotterdam, The Netherlands; Jefferson Medical College, Philadelphia, Pennsylvania, USA

[b] Retransplantation with heterotopic liver graft

Table 3. Causes of deaths after heterotopic liver transplantation 1980–1990

Cause of death	No.
Bleeding in surgical field	4
Primary graft nonfunction	5
Vascular complication	4
Infection	12
Multiple organ failure	2
Rejection	2
Tumor (hepatocellular carcinoma in host liver)	2
Other	1
Total no. of deaths	32

New aspects

The concept of HLT continues to be the subject of various clinical and experimental studies in many countries, including Argentina [48], France [19, 25], Germany [50], Japan [32], Yugoslavia [53], and the United States [15, 62]. In the following section, some fascinating aspects of HLT will be described. These include: the absence of intraoperative fibrinolysis, the stability of hemodynamic parameters during the HLT procedure, the effect of HLT on portal pressure and hypersplenism, the interaction between the two livers in situ, the role of portal blood flow in HLT, the temporary support given by the heterotopic graft in acute liver failure, and the possible role of HLT in inborn errors of hepatic metabolism. Finally, two important modifications of HLT will be discussed.

Intraoperative fibrinolysis

The earliest reports on OLT already described increased fibrinolytic activity [57]. After comparing fibrinolytic activities, as measured by euglobulin clot lysis time and the formation of fibrin degradation products, during both OLT and HLT in the pig, we found more pronounced fibrinolytic activity during OLT [43].

The origin of this hyperfibrinolysis is still controversial, but there is strong evidence that increased levels of tissue-type plasminogen activator (t-PA) is the key issue. Normally, t-PA is produced by endothelial cells and removed from the circulation by the liver. In OLT, t-PA can accumulate in the anhepatic phase, while additional release is also likely. Levels of t-PA have been found by some to increase in the anhepatic phase or after reperfusion [5, 16, 42], while other investigators believe that t-PA release from the graft is not a major determinant of hemostatic disorders in liver transplantation [3, 58].

In an experiment comparing hemostatic changes in OLT and HLT in the pig, we showed not only increased t-PA levels in the anhepatic phase of OLT but also increased systemic t-PA levels after reperfusion in both OLT and HLT [6]. We demonstrated that this early rise in t-PA levels was most likely caused by its release from the endothelium of the graft and that this could be seen as a manifestation of preservation or reperfusion injury. In OLT, we also found continuously increasing t-PA levels in the postreperfusion period. This effect was particularly evident after long-term preservation, despite the fact that t-PA levels measured in the first hepatic outflow of the long-term preserved grafts were not increased [6]. We hypothesized that this late escalation of t-PA in OLT was caused by cytokines, produced in the damaged graft, that subsequently activated the intact recipient systemic endothelium to release, among other substances, t-PA. The same process probably occurred in HLT, but this effect was masked, as t-PA – or the activating cytokines – was cleared from the blood by the native liver.

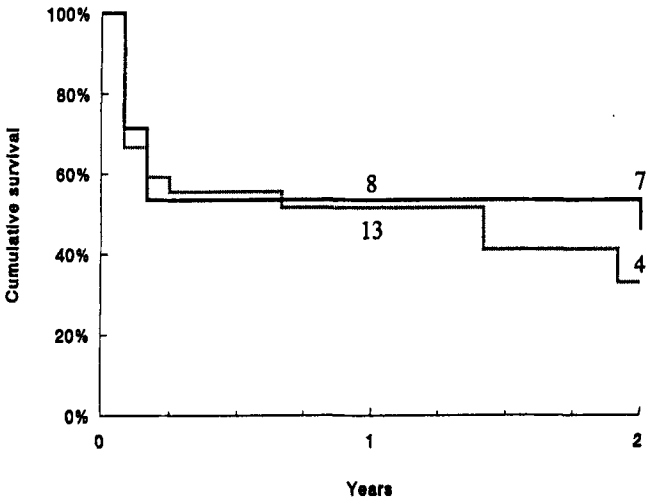

Fig. 2. Cumulative survival of patients after primary heterotopic liver transplantation from 1980 to 1990, according to the circumstances of the operation. —— Emergency surgery ($n = 21$); ---- elective surgery ($n = 27$)

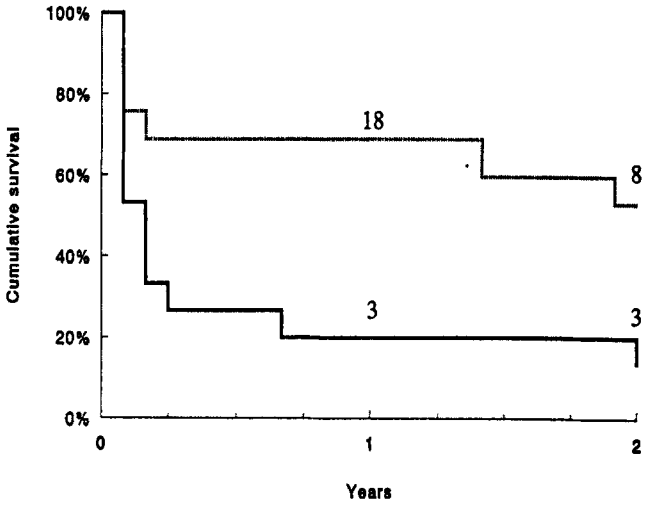

Fig. 3. Cumulative survival of patients after primary heterotopic liver transplantation, according to when operation was performed: —— 1980–1986 ($n = 15$); ----- 1987–1990 ($n = 33$); $P < 0.005$

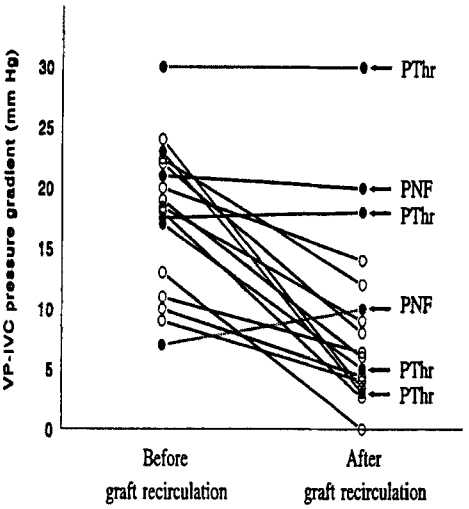

Fig. 4. Portal-caval pressure gradient (mm Hg) before and after recirculation of the graft in human heterotopic liver transplantation in Rotterdam (including one re-HLT). *PThr* Portal vein thrombosis; *PNF* primary graft nonfunction. ●—● Graft failure ($n = 6$); ○—○ no graft failure ($n = 11$); —— chronic liver disease ($n = 15$); ----- subacute liver disease ($n = 2$)

Intraoperative hemodynamics

Crossclamping the portal vein and the abdominal portion of the inferior vena cava causes a major loss of venous return and congestion of the obstructed portal and systemic venous beds. These problems can be prevented by the use of a veno-venous bypass system [51]. In clinical HLT for liver cirrhosis, portacaval collaterals can shunt the mesenteric blood flow. In addition, the caval and portal anastomoses are performed with partially clamped recipient vessels. Indeed, our clinical experience with HLT is that cardiac output seldom responds to partial clamping of the portal vein. It was demonstrated that in HLT, a veno-venous shunt, with its concomitant hazards, is expendable [22].

It is likely that deleterious substances accumulate in the stagnant blood of the congested venous beds. When suddenly returned into the systemic circulation at revascularization, these factors may cause depression of cardiovascular function, in spite of the restoration of venous return. This effect has been attributed to many substances, including potassium, hydrogen ions, ionized calcium, and unidentified vasoactive hormones [2, 14, 28, 31]. As long as the exact origin of this myocardial depression is unknown, these substances can be designated myocardial depressant factors (MDF).

To study the role of the host liver in clearing MDF at reperfusion of a heterotopic graft, we compared intraoperative hemodynamics in the pig during HLT and OLT [10]. After reperfusion of the graft, there was a marked increase in pulmonary vascular resistance in both HLT and OLT, but a decrease in systemic vascular resistance. The pulmonary vascular bed appeared to be the primary target of factors related to the reperfusion itself and not particularly related to the extent of preservation damage, i.e., air emboli, cellular debris, or temperature. The heart and the systemic vascular bed seemed to be primarily compromised by MDF. Extension of the graft preservation period resulted in poor cardiac performance, more often in OLT than in HLT. The native liver in HLT was postulated to metabolize the presumed MDF that had accumulated in the congested venous beds or were released by the graft upon reperfusion.

Correction of portal hypertension

An auxiliary heterotopic liver graft may be considered a functional side-to-side portacaval shunt. In this respect, HLT could alleviate portal hypertension. In 11 successful HLTs in chronic liver disease, the intraoperative pressure gradients between the portal vein and inferior vena cava decreased from a median value of 18 mm Hg (mean 17.0, 95% confidence limits 13.8–20.2) to 6 mm Hg (mean 6.4, 95% confidence limits 3.9–8.9; Fig. 4). Graft failure occurred in all of the 4 patients without a decrease in this portal-caval pressure gradient, while only 2 of the remaining 13 patients developed portal vein thrombosis ($P < 0.01$, Fischer's exact test). Hypersplenism is not only attributed to splenic congestion but also to gut-derived humoral factors that cause splenic stimulation [63, 64]. This theory explains why OLT can reverse hypersplenism [67] while this effect is controversial for portasystemic shunt procedures [17, 55]. In HLT, most collaterals are left intact and, therefore, theoretically, hypersplenism might persist after HLT, corresponding to the effect of a portasystemic shunt. Contrary to this speculation, heterotopic auxiliary liver transplantation was demonstrated to reverse hypersplenism [11]. A hypothesis that supports the reversal of hypersplenism by both OLT and HLT but not by a portasystemic shunt is that following successful liver transplantation, the above-mentioned splenotropic factors are cleared from the blood.

Interactions between the two livers

Theoretically, the presence of two livers may give rise to a "functional competition", as described between two liver lobes, one of which is handicapped by bile duct ligation

[49]. Hepatotropic factors could be responsible for the fact that portal blood flow is essential for the survival of an auxiliary graft in the presence of a healthy host liver [60]. With portal hypertension, the portal blood will be directed through the graft because of its lower vascular resistance compared to that of the cirrhotic liver. Therefore, it is unlikely that atrophy of the graft by means of functional competition will occur.

Indeed, in patients undergoing auxiliary heterotopic partial liver transplantation, compensatory hyperplasia of the graft and atrophy of the native liver was observed [66]. Regeneration after partial liver resection is thought to be directed towards restoring the original liver cell mass. However, despite the apparently increased total liver cell mass after auxiliary transplantation, regeneration of the graft was demonstrated. Graft regeneration was, therefore, considered to have been controlled by the amount of total functional liver cell mass. The graft, which had been reduced in size during the transplantation to approximately 80%, regained its original volume within 3 weeks after surgery. This is not different from the course after resection of the same liver volume for tumors. In contrast, the native liver decreased to ±30% of its immediate postoperative size within 3–6 months.

The presence of an additional, allogenic reticuloendothelial organ also implies immunological interactions between the two livers. Icard et al. [25] reported on an interesting study on class II major histocompatibility complex antigens on rat hepatocytes following transplantation. They suggested that the rejection response might be more severe and the pattern of class II expression different in HLT compared to OLT. It was postulated that in case of graft rejection after OLT, the inevitable liver failure would cause immunosuppression because of decreased lymphokine production, essential to hepatocyte class II induction. In addition, hepatic phagocyte function – also related to graft rejection – was suggested to be decreased with rejection in progress after orthotopic grafting but well maintained by the healthy host liver of the rat following auxiliary transplantation.

In contrast, in clinical HLT, rejection problems were not encountered to a larger extent than in OLT [40]. This inconsistency with the experiments of Icard et al. could be explained by the already decreased function of the reticuloendothelial system in cirrhotic livers. Although the number of patients is small, we have the impression that heterotopic grafts are even less vulnerable to immune attack than grafts in the orthotopic position (Table 3). In OLT, rejection occurs 40%–60% of the time [21, 30], while at present only 4 out of 22 HLTs in Rotterdam have been rejected. This is also in agreement with the observation in a rat model that an auxiliary liver graft yielded immunosuppression [4].

The role of portal blood flow in HLT

When auxiliary transplantation is performed in the presence of normal hemodynamic conditions of the recipient liver, the distribution of the portal flow is a major concern [62]. In an animal study on correcting inborn errors of metabolism, the best results were obtained with constriction or ligation of the recipient's own portal vein [37]. Clinical results of HLT in patients without portal hypertension were also affected by interruption of the portal blood flow to the recipient liver. With constriction or ligation of the host portal vein, good results were obtained, while otherwise primary graft nonfunction (PNF) or graft failure developed.

Constriction is theoretically attractive because the native liver still receives some portal blood. The preservation of portal flow to the host liver, however, increases the risk of thrombosis of the graft portal vein. Elevation of the vascular resistance of the graft by preservation injury or rejection will cause preferential flow to the native liver. Moreover, the innervated recipient liver is capable of regulating blood flow, while the denervated graft is dependent on passive flow distribution. On the other hand, complete ligation of the host portal vein assures graft portal flow but may interfere with the potential recovery of the recipient liver.

Temporary support in acute liver failure

In acute hepatic failure caused by drug intoxication, hepatitis, or allergic drug reactions, the liver might be expected to regenerate, provided the patient survives the critical phase. In those cases, there is a need for a reliable means of temporary support. An auxiliary graft implanted during that phase could provide uninterrupted support until the host's own liver recovers or until there is at least minimally effective function. Later the graft may be removed or left to atrophy. After recovery of the host liver, there is no need for lifelong immunosuppression with its concomitant sequelae. Successful canine [33] and porcine [46] HLT for fulminant hepatic failure has been described.

Clinical experience with HLT for acute hepatic failure is limited (Table 2). The first HLT for acute liver failure was performed by Bismuth in 1980 [8, 35]. A 17-year-old female developed acute hepatic failure related to valproate sodium. A reduced-size liver graft was placed in the right hypochondrium. The portal vein, hepatic artery, and infrahepatic vena cava were anastomosed end-to-side to the recipient vessels as initially described by Fortner et al. [18]. The portal vein to the host liver was not interrupted. After 10 days, septicemia, renal insufficiency, and possibly rejection occurred, and she died on the 22nd postoperative day. At necropsy, the graft was hypertrophic and the recipient liver had further atrophied. Histologically, marked centrilobular parenchymal cell necrosis was noticed in the graft.

In Grenoble in 1986, a HLT was performed on a 24-year-old female with acute hepatic failure resembling non-A/non-B hepatitis [36]. The same technique was used as in the former patient, although no resection was performed. A reintervention for hemostasis was necessary after 24 h, and a rejection crisis on day 10 was suppressed with methylprednisolone. Because of intractable ascites, the hepatic artery of the native liver was embolized on day 32, which successfully alleviated ascites in 5 days. After another rejection crisis and a revision of the biliary anastomosis, the patient was alive and well after 55 months. An angiography confirmed occlusion of the native hepatic

artery and portal vein: the patient's own liver had become cirrhotic.

In the Rotterdam program, three patients were heterotopically transplanted for acute or subacute liver failure. The technique differed from that used in the previous two HLTs in that the suprahepatic inferior vena cava was used for the caval anastomosis [61]. An 18-year-old man developed acute hepatic failure of unknown origin. A reduced-size HLT was performed without interruption of the host portal vein. Primary graft nonfunction (PNF) occurred, and when the necrotic graft was removed, the hepatic artery appeared to be occluded while the graft portal vein was patent. This patient died on day 18. The second patient, a 31-year-old woman, also presented with acute liver failure of unknown origin. Due to lack of space, a right hemihepatectomy of the graft was performed. She died on day 15 from PNF, despite re-HLT with ligation of the host portal vein.

The third patient was the most striking case in the Rotterdam experience and the one that definitely proved the point that HLT is capable of giving temporary support until the host liver recovers. A 35-year-old female was transplanted for subacute autoimmune hepatitis [39]. On day 1, portal vein thrombosis necessitated thrombectomy of the graft portal vein and ligation of the portal vein to the native liver. On day 25, a second revision of the portal vein anastomosis was required. On day 45, scintigraphy showed good uptake and excretion of the radioisotope almost exclusively in the graft. Unexpectedly, at 6 months, the scintigraphic picture had become completely reversed: the graft had diminished in size and function and uptake and excretion of the radioisotope was mainly found in the patient's own liver. Angiography showed preferential flow of portal blood to the recipient liver through venous collaterals. Immunosuppression was reduced and further atrophy awaited.

Two patients with fulminant hepatic failure were heterotopically transplanted in Philadelphia. The first, a 19-year-old female, was treated for liver failure of possible viral origin [41]. As suprahepatic exposure increased the intracranial pressure, an HLT was performed. Because of minimal flow to the graft, the portal vein to the native liver needed to be constricted about 80%. At 6 months, the graft was histologically normal and the native liver showed signs of severe resolving hepatitis. At about 2 years, the native liver had regained normal size and histological appearance. The heterograft had shrunken significantly and biopsy showed no hepatocytes. Immunosuppression was stopped. The second patient, a 15-year-old girl, presented with fulminant Wilson's disease. An HLT with an ABO-incompatible graft was performed because she could only be operated in a half-seated position, due to severe intracranial hypertension. Again, the host portal vein was constricted about 80%. She recovered neurologically from coma to full alertness within 10 days. Severe rejection necessitated retransplantation on the 27th postoperative day and an OLT was performed.

One of the most difficult problems in the management of patients with acute liver failure is the assessment of the need for, and the timing of, liver grafting. OLT in an early phase of the disease negates the possibility of spontaneous recovery; delay of the decision to transplant may lead to further deterioration of the patient's clinical condition. As the procedure of HLT is reversible, the decision to transplant can be made more quickly.

Taken together, of seven HLTs for acute liver failure, three patients died and one patient survived on graft function (after embolization of the native hepatic artery). The remaining three patients received temporary support from the heterotopic graft until the native liver recovered in two patients and until an OLT was possible in one.

Metabolic diseases of the liver

Alpha-1-antitrypsin deficiency, glycogen storage disease, tyrosinemia, Wilson's disease, and many other inborn errors of metabolism are gratifying indications for liver transplantation. Most of the characteristic metabolic perturbations of these disorders are corrected after liver transplantation. Since liver cirrhosis develops in the course of many of these diseases, adult liver transplantation is a frequent consequence.

The timing of OLT for metabolic disturbances in children is a dilemma. On the one hand, the recipient in question might not have deteriorated sufficiently to demand transplant at the time one of the scarce, pediatric donors becomes available. On the other hand, postponement of transplantation will almost inevitably lead to a further decline in the general condition of the recipient. Much of this reluctance can be overcome by leaving the recipient liver in situ. In this respect, the most attractive treatment for metabolic disease of the liver is hepatocyte transplantation [12], but as long as this treatment modality is not clinically successful, auxiliary transplantation appears to be the procedure of choice.

There is no clinical experience with HLT in children with inborn errors of hepatic metabolism. Data from experimental research suggest that portal inflow to the graft is essential, and when this is achieved, long-term substitution of the enzyme lacking occurs [37].

Modifications of HLT

Fourtanier et al. [19] reported a new technique of HLT in a patient with a portal vein thrombosis. OLT and the standard subhepatic HLT were, therefore, technically impossible. The graft was positioned in the left subphrenic space after splenectomy, with a cavorenal anastomosis, splenoportal venous anastomosis, and splenohepatic arterial anastomosis. The presence of a large splenic vein, splenomegaly, and a distended abdominal cavity in the recipient made this type of heterotopic transplantation particularly suited for this patient. This case report showed that modified heterotopic transplantation may be an alternative in patients who are otherwise unsuited for liver transplantation.

Another modification of HLT is the auxiliary transplantation of liver segments in the orthotopic position after resection of the left liver lobe of the recipient, as originally described by Bismuth and Houssin in 1985 [8]. In this way the preferable localization under the diaphragm is combined with leaving the recipient liver partially in situ. This may provide temporary support in case of acute

liver failure, allowing the recipient liver to regenerate [62]. One patient treated with orthotopic auxiliary liver transplantation was reported on by the Hannover group. Her own liver recovered and she was taken off immunosuppressive therapy [23].

Conclusions

For the majority of patients with chronic liver disease and for patients with malignant liver disease, OLT is the method of choice. For patients who have very advanced disease with severely disturbed hemostasis, for patients with pre-existing cardiovascular or pulmonary impediment, and for patients with acute hepatic failure and critical intracranial hypertension, HLT might be a better solution. The remaining synthetic and clearing function of the recipient liver during the transplantation provides greater hemostatic and hemodynamic stability.

It is argued that oncogenic tissue (and maybe an occult carcinoma) is left in situ when an auxiliary procedure is performed. This is especially true for patients with hepatitis B, and they should, therefore, not be considered candidates for HLT. Whether the risk of carcinoma in the recipient liver is a contraindication for transplantation in other patients with cirrhotic livers is a matter of discussion.

The most exciting application of HLT is in patients with acute hepatic failure. Because HLT is a reversible procedure, it can provide temporary support until recovery of the host liver. However, difficulties concerning portal blood flow distribution should be addressed. This also holds for HLT in treating patients with metabolic liver disease. Nevertheless, as long as hepatocyte transplantation is not clinically practical, HLT should be considered a potential treatment modality for these indications.

HLT is a valuable alternative to the gold standard, OLT. After more than 25 years, the time has come for comparative experimental and clinical studies between OLT and HLT.

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