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INVITED COMMENT

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Is it right to develop living related liver transplantation? Do reduced and split livers not suffice to cover the needs?

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The paper by Slooff [16], published in this issue of *Transplant International,* places the innovative techniques of liver transplantation in a very appropriate perspective regarding the currently nonreducible shortage of size-matched donors in pediatric liver transplantation. We have updated our own results obtained with reduced size liver and split liver transplantation in order to strengthen the argument very rightly made by the author.

Reduced size liver transplantation

The concept of reduced size liver transplantation [1, 3, 9] has been validated by several groups [4, 5, 14], including our own [11, 19, 20], and the long-term survival appears to be similar whether patients receive a full-sized or a reduced graft.

Of the 389 grafts transplanted in to 322 children in our center during the period 1984–1993 (all indications included), 175 (45 %) were full-sized grafts and 214 (55 %) were technical variants: 94 reduced livers, 98 partial liver grafts (implanted with preservation of the recipient inferior vena cava), 21 split liver grafts, and 1 living related graft.

The overall 5-year graft survival rate was 67 %: 72 % for the full-sized grafts, 64 % for the technical veriants, and 82 % for the split grafts. The 5-year survival rate of biliary atresia patients transplanted electively was 84 % for 106 children who received a full-sized graft and 83 % for 89 children who were transplanted with a technical variant.

Split liver transplantation

In spite of its merits, reduced size liver transplantation does little more than redistribute the adult liver donor pool to the advantage of children, thereby placing adult patients at a potential disadvantage. The fact that potentially usable liver tissue is discarded when performing a reduced size liver transplantation stimulated the development of split liver graft transplantation in four centers in 1988 [2, 6, 10, 12]. In this procedure, the adult donor liver is split on a back table into a segmental left graft (either the left liver lobe or the left lateral segment), usually to be transplanted into a pediatric recipient, and a right lobe graft, to be transplanted into an adult recipient. Split liver transplantation allows one to make maximum use of the cadaveric liver donor pool; however, it is a very demanding and elaborate surgical procedure that requires extensive experience with liver anatomy, major liver resections, and reduced or partial liver grafting.

Technique

The technique of splitting livers has evolved from knowledge and experience acquired with reduced or partial liver transplantation. From our own experience (1988–1993) splitting 15 donor livers, resulting in 29 split liver grafts transplanted into 28 patients, and from the European experience with 100 split liver grafts, reported during the first European workshop on split liver transplantation organized in Brussels on 19 March 1993 [18], a workshop in which nine European liver transplant teams participated, the optimal way to split a donor liver with a normal anatomy can be summarized as follows.

After procurement and cooling with UW solution, the liver graft is prepared according to the standard technique. The left and right lobes are divided along the main liver fissure, keeping the median hepatic vein to the right. The left liver split graft consists of the left lateral segment (Couinaud's segments 2 and 3) and the left median segment (Couinaud's segment 4); if necessary, due to the size of the recipient, the volume of the left split graft can be further reduced by resecting segment 4 along the right side of the umbilical fissure. The right split graft is implanted into an adult recipient according to the standard technique of orthotopic transplantation. The easiest and fastest technique of implantation is with a side-to-side cavocavoplasty, retaining the recipient infradiaphragmatic vena cava [7]. The left split graft is implanted as a partial graft, anastomosing the left hepatic vein of the graft onto the retained infradiaphragmatic vena cava of the pediatric recipient.

The division of the biliary tree, the portal vein, and the hepatic artery should ideally respect the following rules. Because the arterial supply to the extrahepatic biliary ducts is provided by the right hepatic artery, the left bile duct should be severed flush to the liver parenchyma, keeping the right bile duct in continuity with the hepatic duct and the main bile duct; the latter can be trimmed up to a better vascularized segment. The biliary reconstruction is usually made by performing a hepatico-(or choledocho-)choledochostomy for the right split graft and a (left) hepaticojejunostomy on a Roux-en-Y loop for the left split graft. The left portal vein is severed, keeping the right portal vein in continuity with the trunk of the portal vein. Alternatively, the latter can be kept in continuity with the left portal vein, depending on the status of the portal vein of the recipient. Since the left hepatic artery is usually smaller in size than the right hepatic artery, it is best to keep it in continuity with the common hepatic artery and the coeliac axis. As for the portal vein, the severing of the left hepatic artery may be the appropriate option.

To avoid ischemic damage to the extrahepatic bile ducts, dissection of the common sheaf of supportive tissue surrounding bile duct and hepatic artery should be avoided. The best option for precise identification of the anatomy in a peculiar case and of the level of confluence of the right and left bile ducts is to perform a cholangiography on the back table, marking with a hemoclip the level where the left bile duct should be transected. Similarly, the anatomy of the arterial tree should be established by an arteriography on the bench table. We like to use half-strength contrast medium diluted with fresh UW solution and to complete cholangiography and arteriography by thorough flushing with fresh UW solution.

Biliary and vascular variants of the normal anatomy do not preclude successful splitting of the liver. However, a precise identification of the anatomy is essential in order to determine the appropriate level of transection. The group from Groningen [21] has elegantly shown that NMR of the donor liver, while still immersed in the preservation solution and packed in the transportation container (which should not be made of steel), can very precisely identify the anatomy of the hepatic and portal veins.

It is well established that cold ischemia of a liver graft preserved with UW solution should not exceed 12–14 h in order to avoid late ischemic strictures of the bile ducts. Therefore, logistics should be adapted to transplant the two potential recipients in parallel. Shipping of one of the two split grafts to another well-trained liver transplant center is an option that should be encouraged.

Because of the complexity of the splitting procedure and the two ensuing transplants, only an ideal donor liver should be considered for splitting.

Results

Between 1988 and 1993, we split 15 donor livers. Of the 30 split grafts, 2 were not transplanted, due either to lack of capacity or to steatosis of the graft. Two right split grafts were shipped to another center (Munich), while we received three grafts (two left, one right) from another center (Groningen). In total then, 29 split grafts were transplanted (16 left grafts, 13 right grafts) into 28 recipients. Eleven right grafts were transplanted into adult patients and two into children; all left split grafts were transplanted into pediatric recipients. Seven transplants were performed electively while 14 were performed in urgent (hospital-bound) and 8 in highly urgent (ICU-bound) recipients.

The 6-month survival rate was 71 % and 67 % for the left and right split grafts, respectively; it was 85 % and 75 % for the recipients of either a left or a right split graft, respectively. Six grafts were lost as a result of death of the recipient (unrelated to the splitting procedure): multiple organ failure ($n = 2$), cardiac arrest ($n = 1$), tumor recurrence ($n = 1$), encephalitis ($n = 1$), and bleeding

from adhesions in the abdominal cavity ($n = 1$).

Two grafts were lost to either early severe dysfunction (26 h of cold ischemia time while the split counterpart, preserved for 10 h, functioned properly) or to primary nonfunction. One more graft was lost to chronic rejection. Surgical complications included three arterial thromboses, five biliary complications, and six cases of unusually profuse bleeding from the cut surface of the split graft (during the learning phase).

The collective European experience consisted of 100 split liver grafts prepared from 50 donor livers in nine transplant centers between March 1988 and March 1993 [18]. Two grafts were discarded due either to death of the recipient before implantation or to logistical reasons. Of the 49 right split grafts, 38 were transplanted into adult recipients and 11 into children; of the 49 left split grafts, 45 were transplanted into pediatric recipients (< 15 years). Analysis of the results excluded two left split grafts that were transplanted heterotopically.

The 6-month actual survival was 65 % for the 44 recipients of a left split graft (three patients were transplanted twice) and 75 % for the 49 recipients of a right split graft (P: NS). The 6-month survival rate was 71 % for the 53 pediatric recipients and 70 % for the 40 adult recipients. It was 52 %, 73 %, and 85 % for the 31 highly urgent, 30 urgent, and 33 elective recipients, respectively.

The 6-month survival rate was 65 % for the 47 left split grafts and 63 % for the 49 right split grafts. Of a total of 96 grafts, 20 were lost to a cause related to the graft itself: vascular thrombosis ($n = 7$,), primary nonfunction ($n = 4$), chronic rejection ($n = 4$), acute rejection ($n = 3$), Budd-Chiari syndrome ($n = 1$), and hepatitis ($n = 1$). Thirteen grafts were lost as a result of death of the recipient that was unrelated to the graft.

It may be concluded from this large collaborative and retrospective study that split liver transplantation has no major disadvantages as compared to the standard techniques, including reduced size liver transplantation. Splitting the donor liver into two grafts fit for use in two recipients is the only way to maximize a limited cadaveric donor liver pool.

We feel that our personal experience, the Groningen experience, and the collective European experience have validated the split liver procedure. When performed in elective patients by an experienced team, it yields results similar to transplantation of a full-sized graft; neither recipient is submitted to increased hazards, and specifically not the adult recipient of the right split graft. These data should reassure teams limiting their activity to adult patients that their patients will be provided with the best possible care and should encourage their collaboration with other teams already experienced in splitting procedures.

Indeed, splitting of the liver is a lengthy procedure. Because of its complexity as well as that of the two ensuing transplants, only an ideal donor liver should be considered for splitting. On the other hand, it is well established that cold ischemia of a liver graft preserved with UW solution should not exceed 12–14 h, in order to avoid late ischemic strictures of the bile ducts. Therefore, logistics should be adapted to transplant the two potential recipients in parallel. Shipping of one of the two split grafts to another well-trained liver transplant center, as Dr. Sloff's team is doing regularly, is an option that should be encouraged further.

Living related liver transplantation

The extensive use of reduced and split liver grafts has resulted in a decrease in the mortality of pediatric patients awaiting a donor. In our own center, it decreased from 13.5 % (until 1990) to 7.5 % in 1990 and to 5 % in 1991. At the same time, however, the ever-increasing number of adult patients on waiting lists has diminished the number of adult liver donor grafts available to pediatric recipients. Consequently, there has been a new increase in the mortality of the latter on our waiting list – up to 15 % in 1992 and 1993. This evolution was the incentive to start a program in 1993 of living related liver transplantation (LRLT), following a protocol that was carefully prepared during 1991–1992.

The first case of LRLT was performed in Brazil on 8 December 1988 [13]; however, the patient died shortly thereafter. The first successful case of LRLT was performed in Brisbane, Australia, in July of 1989 [17]. Here a child received the left liver lobe from his mother and became a long-term survivor (he later needed retransplantation for chronic rejection).

In Japan, LRLT was initiated at the University of Shimane Medical School in 1989 [8]; the recipient died of multiple organ failure about 6 months after transplantation. The main program of LRLT in Japan was started in June 1990 at Kyoto University [8]. The rapid expansion of LRLT to several other Japanese centers has been made possible by the intense efforts made by our Japanese colleagues who are not yet allowed to remove organs from brain-dead patients.

The University of Chicago Pritzker School of Medicine was the first to develop a prospective protocol of LRLT on the basis of a collaborative effort between clinical ethicists (led by M. Siegler) and clinical investigators (led by C. E. Broelsch, surgeon, and P. F. Whitington, pediatrician). The protocol was elaborated after a year-long series of seminars and discussions that were open to the entire community. Very remarkable was the publication of their protocol [15] before they performed their first case on 29 November 1989. Intense activity in this field has continued since then in Chicago, even after

Broelsch, who had been the pioneering surgeon, returned to Germany.

During recent years, several programs have been started in Western Europe and in the United States. The total number of LRLT performed worldwide until now is about 250 cases. There has been one donor fatality from pulmonary thromboembolism and this occurred in Hamburg on the 4th postoperative day (C. E. Broelsch, personal communication). In experienced centers, the overall patient survival rate is averaging 85 %.

In 1991–1992, at the University of Louvain Medical School in Brussels, we took the example from the model in Chicago to conduct several seminars, bringing together clinicians involved in liver transplantation and members of the Center of Bioethical Studies. All aspects of LRLT, including psychological, legal, and medical problems, were discussed in length and in depth. A protocol was developed on the basis of these reflections, and this was approved by the Ethics Committee of the Medical School and by the Board of Trustees of the University Hospital. Potential recipients are children with a chronic liver disease in a stable clinical condition, allowing for elective transplantation. Potential donors are either of the parents. Their good health and motivation are checked by an internist who is not a member of the transplantation team ("medical advocate of the donor"). Their willingness to donate without any coercion and their capacity to resist stressful situations are confirmed by a psychologist. A two-step informed consent procedure is carried out while two units of blood are donated in advance by the donor.

As already mentioned, we waited 1 year before implementing LRLT in order for every member of the team to become fully and honestly convinced that such a program was necessary to obviate the shortage of donors. The new rules set by the Board of Eurotransplant, excluding from the waiting lists candidates originating from non-EC countries, were a further impetus.

Our first case was performed on 28 July 1993; very remarkably the father who acted as donor to his son was himself a trauma surgeon who had travelled all the way from Santiago (Chile). Eight more cases were performed during the first 5 months of 1994. The longest hospital stay of the donor, after procurement, was 7 days; no complication of any sort occurred. The nine recipients have been successfully transplanted without any surgical complication, except for bowel perforation in one. The smallest recipient weighed 4 kg at the time of transplantation when he received the left lateral segment (Couinaud's segments 2 and 3) from his father, who weighed 64 kg; he died 2 months later due to hepatitis. Five of the donors were mothers and two were fathers.

In conclusion, the innovative techniques including reduced liver, split liver, and living related liver transplantation have substantially contributed to alleviating the shortage of liver grafts in pediatric transplantation. However, the medical community should be aware that too many good donor liver grafts are still being wasted. Indeed, an analysis performed by Jan Lerut (Brussels) of the unused livers within Eurotransplant during the first 3 months of 1993 and presented at the Founding Assembly of ELTA (the European Liver Transplant Association), a section of ESOT, in Rhodos in October 1993, has shown that at least one good liver is wasted every day in Eurotransplant countries. Similar data, collected in the United Kingdom, were presented by the Birmingham group.

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