

lesions were diagnosed in liver segment 7 Couinaud's classification, 4 cm in diameter, and segments 2 and 6, both 0.5 cm, by computed tomography (CT) scan; and the patient twice underwent TAE. In May 2000, multiple HCCs were detected in liver segments 2, 3, 4, 5, 7 and 8 with diameters from 1.5 to 0.5 cm. A reservoir port was implanted and he underwent continuous intraarterial chemotherapy through it for 4 weeks. Since then, he has undergone several treatments of intraarterial chemotherapy. In July 2003, because the multiple HCCs could not be controlled by any treatment, and as he complained of liver dysfunction caused by the progression of liver cirrhosis and the HCCs, he was referred to our hospital to undergo LDLT.

Physical examination revealed him to be moderately well built with stable vital signs and with no hepatosplenomegaly or superficial lymph-node enlargement.

Serum total protein level was 6.7 g/dl with an albumin level of 2.9 g/dl. Serum liver function test results showed slightly elevated levels of aspartate transaminase (136 IU/l), alanine aminotransferase (54 IU/l) and gamma GTP (79 IU/l). The value of total bilirubin and direct bilirubin were 4.4 and 3.1 mg/dl respectively. Prothrombin time-international normalized ratio was 1.15. Hepatitis C virus (HCV) antibody, tested by EIA, was positive, and the value of HCV-RNA was 18.5 KI/ml, tested by RT-PCR method. Tumour marker levels of alpha fetoprotein and protein induced by vitamin K antagonist II (PIVKaII) were 39 131 ng/dl and 37 600 U/ml respectively.

A CT scan of the abdomen revealed multiple HCCs in liver segments 2, 3, 4, 5, 7 and 8 with diameters from 5 to 1 cm. Abdominal angiography revealed a complete obstruction of the common hepatic artery and the blood supply to the right hepatic lobe was fed from a collateral artery from the gastroduodenal artery (Fig. 1a). Celiac arterial angiography revealed stenosis of the celiac axis and the splenic, and irregularities of left gastric arteries; the blood supply to the spleen was fed from collateral arteries from the celiac axis (Fig. 1b).

We decided to use the radial artery as an interpositional vascular graft between the graft artery and the aorta. A clinical assessment of the patient's nondominant (left) arm was performed preoperatively using a modified Allen's test. In addition, pulsatile flow in the digital artery of the thumb was confirmed using a Doppler probe, while the radial artery was compressed. With a diagnosis of multiple hepatocellular carcinoma associated with liver cirrhosis, LDLT using his son's right lobe was performed on 19 August 2003. The left radial artery was procured by a cardiothoracic surgeon, highly experienced in this procedure, using previously described techniques [7] (Fig. 2a). The radial artery graft had a diameter of 4 mm and was shortened to a length of 15 cm. Cross clamping

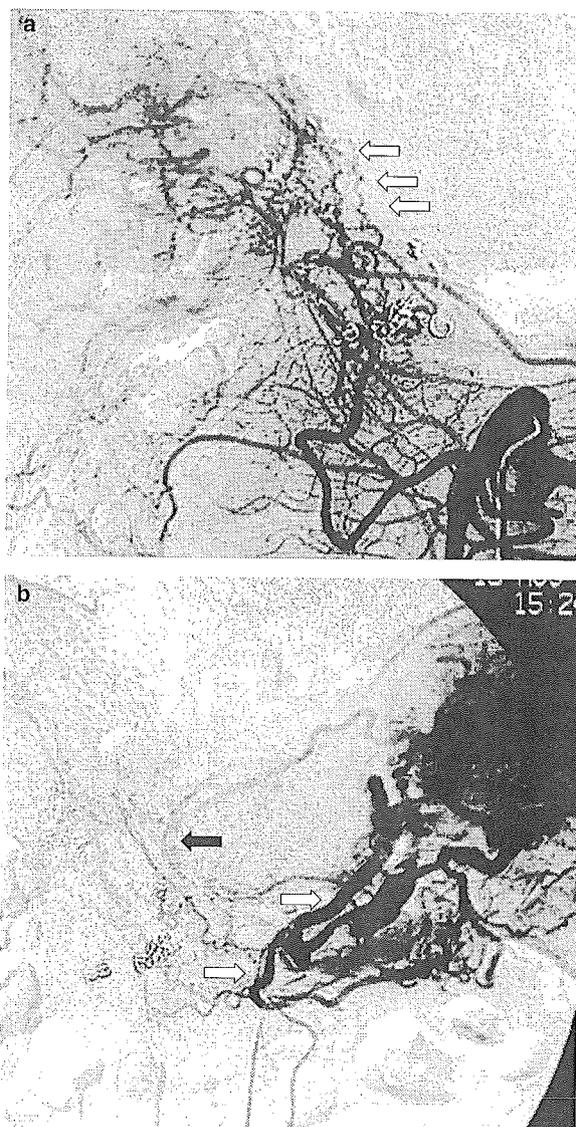


Figure 1 (a) Abdominal angiography demonstrates a complete obstruction of the common hepatic artery and the blood supply of the right hepatic lobe is fed from a collateral artery from the gastroduodenal artery, indicated by white arrows. (b) Celiac arterial angiography reveals stenosis of the celiac axis and the splenic artery, and irregularities of the left gastric arteries. The blood supply to the spleen was fed from collateral arteries from the celiac axis. A white arrow indicates collateral arteries from the celiac axis, black arrows indicate irregularities of the left gastric arteries.

was applied at the infrarenal portion of the aorta and an aortotomy was created with 4-mm aortic punch. Both ends of the radial artery were spatulated and the proximal anastomosis of the graft was carried out with 6-0 polypropylene running suture using parachute technique under 2.5 loupe magnification (Fig. 2a). The radial artery

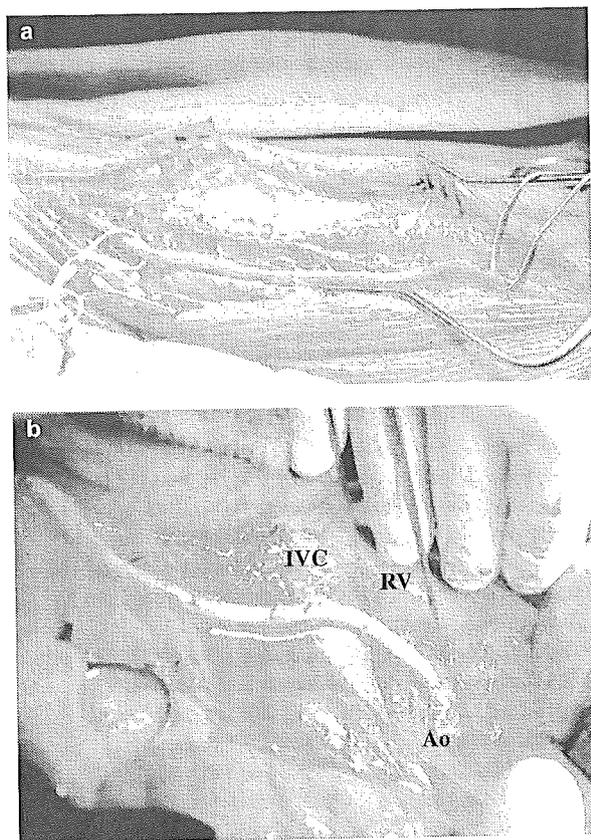


Figure 2 (a) Procurement of the left radial artery. (b) The radial artery graft is anastomosed to the infrarenal aorta. IVC, inferior vena cava; Ao, aorta; RV, renal vein.

graft was then anastomosed to the allograft hepatic artery using an interrupted 8-0 polypropylene suture under microscopic procedures. Good arterial inflow was then demonstrated by Doppler duplex ultrasound.

The patient had a good postoperative course and the patency of the radial artery graft has been very good. He was discharged on the 23rd postoperative day without any complications. He is currently well and free of disease, 3 months after the operation.

Discussion

In recent years, progress has been achieved in the radical treatment of HCC with several therapeutic modalities, including liver resection, percutaneous ethanol injection (PEI) and radiofrequency cytoablation (RFA) [8]. However, HCC patients with repeated recurrence, tumour progression, and advanced liver dysfunction have been increasing and are unable to undergo such radical treatment; most undergo TACE or intraarterial infusion chemotherapy through implanted reservoirs to prolong

survival [9]. On the contrary, liver transplantation is an excellent treatment for HCC patients because this procedure is able to cure not only the tumour but also the underlying cirrhosis. It is reported that in 56 HCC patients who underwent LDLT most had received treatments for HCC, including TACE in 39 cases, PEI or RFA in 24 cases and liver resection in eight cases [5]. Increasingly, HCC patients are waiting for LDLT; some recipients do not have an adequate artery to reconstruct it to the graft hepatic artery such as a hepatic, gastric or splenic artery because these arteries are often injured by repeated interventional therapies.

In this case, we needed an interpositional artery graft with a length of >15 cm because we had to reconstruct the artery graft to the infrarenal aorta and the graft's hepatic artery. The saphenous vein [1], iliac artery [2], inferior epigastric artery [3] and the cadaveric iliac artery [4] have been described as interpositional arterial grafts. However, these grafts would not have sufficient length or diameter except for the saphenous vein graft. However, there have been several reports of complications of pseudoaneurysms of saphenous vein grafts after coronary bypass [10,11] and it was believed that an autologous arterial conduit would provide better long-term patency.

This is supported in the cardiac surgery literature with reports of <50% patency of vein grafts at 10 years and intraluminal disease in those grafts that were patent. In all angiographic studies, the patency rate for arterial grafts is consistently greater than for vein grafts at any point after coronary surgery [12]. The unsatisfactory patency of saphenous vein grafts compared with that of internal mammary artery grafts in these studies has stimulated a revival in the usage of the radial artery as a coronary artery bypass graft, based on the belief that it should improve long-term results from coronary operations. Carpentier *et al.* [13] first described an arterial conduit in myocardial revascularization in 1971 and the radial artery is now frequently used with excellent long-term patency rates [7,14,15]. A recent report showed an 83% angiographic patency rate of radial artery grafts at 5 years [16]. The excellent long-term patency of radial artery grafts in myocardial revascularization prompted us to use a radial artery graft for the interpositional artery graft in LDLT for this patient. Advances in minimal traumatic arterial-harvesting techniques have limited postoperative morbidity and virtually eliminated ischaemic complications. Because there are some possible complications of the donor arm such as developing of ischaemia or motor dysfunction and there are minor complications of stitch abscesses, skin dehiscence, superficial infection, and small haematomas or seromas, it is important to note that a radial artery graft should be harvested by a surgeon with experience in this technique [17].

Liver transplantation is acknowledged as the treatment of choice for patients with early, unresectable HCC and the Milan criteria have been widely accepted for selection of HCC patients for transplantation [18,19]. On the contrary, Kaihara *et al.* [5] reported that the 20 HCC patients beyond the Milan criteria showed tumour-free survival of approximately 50% at 2 years after LDLT. These results demonstrated the considerable possibility that even HCC patients, who had been excluded by the Milan criteria, can survive for long periods after transplantation. In our institution, all HCC patients have the extent of tumour involvement evaluated with abdominal, chest and brain CT scans, and by bone scintigraphy within the 2 months before transplantation; but condition, number and size of the tumours are not criteria for exclusion. The present patient underwent LDLT for HCC beyond the Milan criteria. However, as he would get the opportunity for long-term survival, long-term arterial graft patency would be necessary.

In conclusion, we believe that this report is the first documented use of an autologous radial artery for interpositional artery graft in LDLT for HCC patients. Although the radial artery is not a first-line arterial conduit, it can safely and successfully be used when a suitable recipient's artery is unavailable and the use of a saphenous vein or other conduits is believed to be undesirable. Autologous radial artery grafts should be added to the transplant surgeon's armamentarium as needed for interpositional artery graft in LDLT patients who have undergone repeated intraarterial chemotherapy for HCC.

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Impact of Right Lobe with Middle Hepatic Vein Graft in Living-Donor Liver Transplantation

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Technical improvements in adult-to-adult living-donor liver transplantation (LDLT) have led to the use of right-lobe grafts to overcome the problems encountered with 'small-for-size grafts'. The major controversy remains that the venous drainage from anterior segment substantially depends on tributaries of the middle hepatic vein (MHV), and deprivation of such tributaries may critically influence the postoperative graft function. Right-lobe grafts with MHV could resolve the potential problem of congestion in anterior segment. From December 2000 to January 2004, we performed 217 right-lobe LDLTs for adult patients. Of these, 40 patients received a right lobe with MHV graft (18.4%). The overall cumulative 3-year graft survival rate of a right lobe with (n = 40) and without MHV (n = 177) was 86.2% and 74.8% (p = NS). The proximal side of the MHV and the drainage vein of segment IV to the MHV (the left medial superior vein) were preserved in 24 patients. All of them needed venous interposition graft for anastomosis. All patients had a patent right hepatic vein (RHV) and MHV anastomosis during the follow-up period. We adopted the right lobe with MHV graft in 40 LDLT cases. Vein graft is essential for safe MHV anastomosis in cases which preserve proximal side of the MHV.

Key words: Hepatic vein reconstruction, liver transplantation, living donor, right-lobe graft

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Introduction

The accumulating results of living-donor liver transplantation (LDLT) are comparable to those of cadaveric transplan-

tation (1). Experience of and technical improvements in left-lobe donation have led to the use of right-lobe grafts in adult-to-adult LDLT to overcome the problems encountered with 'small-for-size grafts'. We have reported that the use of 'small-for-size grafts' (<1.0% of recipient body weight) leads to lower graft survival, probably through enhanced parenchymal cell injury and reduced metabolic and synthetic capacity (2).

The major controversy about right-lobe LDLT remains that the venous drainage from the anterior segment depends substantially on tributaries of the middle hepatic vein (MHV), and deprivation of such tributaries may influence the postoperative graft regeneration (3). We have reported that the regeneration of the posterior segment was significantly greater than that of the anterior segment. Despite deprivation of MHV tributaries, a graft will regenerate to meet the metabolic demand (4). However, some patients substantially suffered from complications related to 'small-for-size graft'. In some right-lobe grafts, regional volume of the MHV might be dominated over the right hepatic vein (RHV), and the functional liver volume could be reduced in such type of the grafts. To maximize the benefit of right-lobe graft, several technical modifications have been reported, such as additional venous reconstruction of segment V and VIII (5–8).

The application of right lobe with MHV graft could resolve the potential problem of congestion in the anterior segment (6). However, sufficient drainage veins of the remnant donor liver might not be certified due to the presence of tributaries from segment IV to the MHV (left medial superior vein) (9). Preservation of the drainage veins of segment IV to the MHV in the donor might be important for surgical innovation in right lobe with MHV LDLT.

Recent developments in imaging studies have made it possible to visualize the distribution of the hepatic vessels without hepatic dissection (10). Preoperative three-dimensional (3D) computed tomography (CT) volumetry and computer-assisted volumetric analysis according to the hepatic venous anatomy (MeVis, Germany) were adopted as a noninvasive and objective evaluation for application of a right lobe with MHV graft (11). The computer-assisted preoperative donor risk analysis is helpful for providing volumetric calculations, relating the volume of the compromised areas to total graft or remnant liver. We describe the surgical techniques and outcome in 40 cases of

hepatic vein reconstruction in LDLT using right lobe with MHV grafts, while preserving the significant drainage veins of segment IV to the MHV remaining in the donor.

Patients and Methods

During the period from June 1990 to January 2004, 966 LDLTs were performed in 922 patients at Kyoto University Hospital. Right-lobe LDLT was first carried out in February 1998, and we have since carried out 345 right-lobe LDLTs. Since the initiation of the right lobe with MHV graft procedure for adult patients (>18 years old) in December 2000, we have performed a total of 217 cases of right-lobe LDLTs for adult patients in the same period. Of these, 40 patients received a right lobe with MHV graft (18.4%). Nineteen cases of right-lobe LDLT with additional vein reconstruction of the anterior segment were excluded from the study.

The patients were 29 males and 11 females, with a median age of 49.7 years (range: 18.8–65.7), and a median weight of 64.3 kg (range: 37.1–99.0). Median model for end-stage liver disease (MELD) score was 19.0 (range: 4.0–37.0). The indication for transplantation was hepatocellular carcinoma with hepatitis C virus (HCV) cirrhosis in 17 patients; hepatocellular carcinoma with hepatitis B virus (HBV) cirrhosis in 4; liver cirrhosis in 9 (HCV in 6, HBV in 1 and alcoholic in 2); biliary atresia in 3; fulminant hepatic failure in 2; primary biliary cirrhosis in 2; glycogen storage disease in 1; retransplantation in 1 and a metastatic neuroendocrine tumor (pancreatic polypeptide-secreting tumor) in 1. Six patients received blood-type incompatible grafts (Table 1).

Immunosuppression consisted of tacrolimus and low-dose steroids (12). Patients who received blood-type incompatible transplants had preoperative plasma exchange or double-filtration plasmapheresis in order to reduce the anti-ABH antibody titer. Prostaglandin E1, cyclophosphamide and additional steroids were administered from the portal vein or hepatic artery postoperatively (13).

Donor evaluation

Potential donors were evaluated through the use of liver function tests, determination of blood type, HLA typing and determination of anatomical

variation and graft size using 3D CT volumetry. The potential indication for right lobe with MHV grafting was a graft-to-recipient weight ratio (GRWR) of less than 1.0% with right-lobe graft, as determined by preoperative 3D CT volumetry. If the regional volume of the MHV dominated over the RHV and the remnant liver volume in the donor was shown to be over 35% of the whole liver volume, then the entire MHV could be included with the graft. If not, the proximal side of the MHV, which is the confluence of the segment IV drainage vein (left medial superior vein), should be left in the donor to reduce the risk of venous congestion in segment IV. The MHV dominance in right lobe was defined as follows:

$$\text{regional volume of vein 5} + \text{vein 8} / \text{right-lobe volume} \times 100 > 40\%$$

Donor operation

Before parenchymal transection, the right lobe was mobilized and the sizeable right inferior hepatic vein (RIHV; >5 mm) was preserved with a caval cuff for reconstruction. After careful definition of biliary anatomy in the hepatic hilum using intraoperative cholangiography, the right hepatic duct was transected. The right portal vein and the right hepatic artery were temporally clamped to clarify the parenchymal transection line.

The surface markings of the donor liver consisted of a line from a point to the middle of the gallbladder fossa anteriorly and inferiorly/dorsally to the left side of the RHV entry to the vena cava. An 8-mm Penrose drain was passed between the RHV superiorly and the portal bifurcation inferiorly to maintain the cutting plane during parenchymal dissection (hanging maneuver technique) (14).

The initial parenchymal transection line should be same as the standard right-lobe donation. When encountering the MHV or V5 peripherally, the cutting line was modified to the left side of the MHV. Parenchymal transection was continued until the junction of the MHV and left hepatic vein without inflow occlusion. The MHV was transected distal to the common trunk with the left hepatic vein. When the hepatic vein from segment IV (left medial superior vein) had a significant drainage region in the remnant liver as determined by 3D CT volumetry, the proximal side of the MHV and the drainage vein of segment IV to the MHV were preserved in the donor (right lobe with partial MHV graft). Perfusion of the graft was done through

Table 1: Characteristics of 217 Right-Lobe Living-Donor Liver Transplantation With or Without Middle Hepatic Vein

	With MHV (n = 40)	Without MHV (n = 177)	p-value
<i>Donor demographics</i>			
Age (years)	41.3 ± 11.8 (range: 21–61)	40.1 ± 11.4 (range: 19–64)	NS
Weight (kg)	58.5 ± 10.5 (range: 40–80)	63.6 ± 10.9 (range: 42–107)	NS
Operation time (min)	432 ± 74.8 (range: 308–528)	402 ± 82.1 (range: 198–660)	NS
Blood loss (g)	243 ± 217 (range: 25–1030)	239 ± 241 (range: 5–2300)	NS
Blood-type combination (identical: compatible: incompatible)	29:5:6	109:34:34	NS
<i>Recipient demographics</i>			
Sex	Male, 29; female, 11	Male, 83; female, 94	
Age (years)	50.1 ± 12.8 (range: 18–66)	42.9 ± 15.2 (range: 16–69)	NS
Weight (kg)	64.3 ± 13.8 (range: 37.1–99.0)	60.0 ± 11.4 (range: 28.3–96.0)	NS
MELD score*	18.8 ± 7.1 (range: 6–37)	20.5 ± 9.2 (range: 6–54)	NS
<i>Operation profiles</i>			
Cold ischemic time (min)	128 ± 83 (range: 30–372)	99 ± 85 (range: 30–372)	NS
Warm ischemic time (min)	59 ± 16 (range: 27–100)	45 ± 16 (range: 22–114)	<0.001
Operation time (min)	781 ± 200 (range: 400–1415)	730 ± 178 (range: 337–1291)	NS
Blood loss (g)	5977 ± 6776 (range: 320–33 000)	7088 ± 9768 (range: 350–60 000)	NS
Graft weight (g)	678.9 ± 165.2 (range: 445–1270)	699.3 ± 120.9 (range: 425–1080)	NS
GRWR** (%)	1.10 ± 0.26 (range: 0.70–1.70)	1.20 ± 0.28 (range: 0.60–2.40)	NS

*Model for end-stage liver disease.

**Graft-to-recipient weight ratio.

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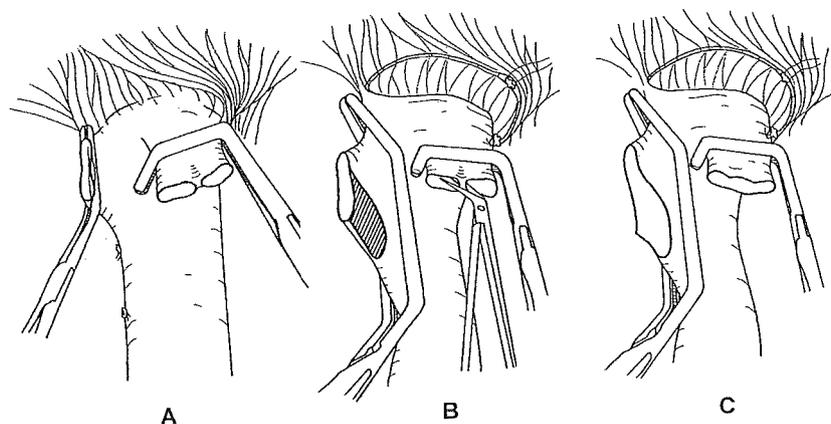


Figure 1: Skeltonization of the inferior vena cava and the hepatic veins to allow adequate spacing for the hepatic vein anastomosis (A,B). The orifice of the RHV was enlarged with a downward incision and an anterior wall excision making an oval orifice to obtain sufficient outflow (B,C).

the right portal vein with a histidine-triophan-ketoglutarate solution (Dr. Franz Köhler Chemie, Alsbach-Hähnlein, Germany).

Back-table operation

In the case of a right lobe with partial MHV graft, the stump of the MHV was too short to be anastomosed directly to the recipient MHV, and the MHV orifice was not always close enough to the RHV to make a common cuff plasty. The vein graft, i.e. the recipient's portal branch, left portal vein or inferior mesenteric vein or donor's ovarian vein, was prepared according to the size of MHV and was anastomosed as an interposition graft to the MHV stump on the back table (6-0 polypropylene, Prolene, Ethicon, Japan).

Recipient operation

After a total hepatectomy, the top vena cava was freed from its diaphragmatic attachments, by dividing the phrenic veins, and was skeltonized to allow adequate spacing for the hepatic vein anastomosis (Figure 1). During the anhepatic period, a portosystemic shunt was made between the right portal branch and the inferior vena cava (IVC) to prevent portal hypertension in the patients without collaterality. The orifice of the RHV was enlarged with a downward incision and an anterior wall excision making an oval orifice to obtain sufficient outflow. Anastomosis of the RHV was accomplished in an end-to-end fashion with a continuous suture (5-0 Prolene). Significant RHV was anastomosed to the sidewall of the IVC, the recipient RHV or the stump of the portosystemic shunt. The interposition vein graft was anastomosed to the recipient's MHV with an interrupted suture in the anterior wall. The patch graft technique was used with an interrupted suture if tension was seen in the anterior wall of the MHV anastomosis. Portal and arterial reconstructions were carried out according to our previous report (15). Biliary reconstruction was carried out with duct-to-duct anastomosis in 36 cases, and with Roux-en-Y hepaticojejunostomy in four cases with 6-0 polydioxanone suture.

Statistical analysis was performed using the generalized Wilcoxon test. Actuarial survival rate was calculated with the nonparametric Kaplan-Meier method and was compared with the Wilcoxon test throughout the study. *p*-values < 0.02 were considered significant.

The study was approved by the international review board and informed consent was obtained in all the cases.

Results

Donor outcome

A comparison was made between right lobe with MHV grafts from living donors (*n* = 40) and graft cases without MHV (*n* = 177).

The median right lobe with MHV graft donor operation time was 420 min (range: 308–528), and median blood loss was 195 g (range: 25–1030). No blood transfusion was given during the donor operation. Four (10%) out of 40 donors experienced complications that required treatment, including two cases of biliary leakage, one of biliary stricture and one of liver failure. Biliary leakage was successfully resolved with percutaneous aspiration. Biliary stricture was treated by reexploration surgery. The liver failure was caused by unsuspected nonalcoholic steatohepatitis and small remnant liver volume. The donor underwent domino liver transplantation, but died from sepsis 9 months after the initial operation (16).

Of 177 donors of a right lobe without MHV graft in our center, duration of the donor operation was 402 ± 82.1 min and blood loss was 239 ± 241 g. There was no significant difference in duration of surgery or blood loss in the donors between right lobe with or without MHV graft operation. Nineteen (10.7%) out of 177 donors experienced complications that required treatment: 14 cases of biliary leakage; 1 of pulmonary embolization; 3 of wound infection and 1 of wound hernia. Nine donors with biliary leakage required endoscopic nasobiliary tube drainage (17).

To evaluate the impact of right-lobe donation, postoperative liver function tests in the donors were analyzed in relation to the type of graft carried out. However, aspartate aminotransferase (AST) and serum bilirubin levels showed no significant difference between right-lobe donation either with or without MHV graft (Figure 2).

Recipient outcome

The median recipient operation time for right lobe with MHV graft was 753 min (range: 400–1415), and the median blood loss was 4100 g (range: 320–33 000). The median cold and warm ischemic time was 103 (range: 30–372) and 57 min (range: 27–100). The median graft weight was 675 g (range: 445–1270), and the median GRWR was 1.10% (range: 0.70–1.70%).

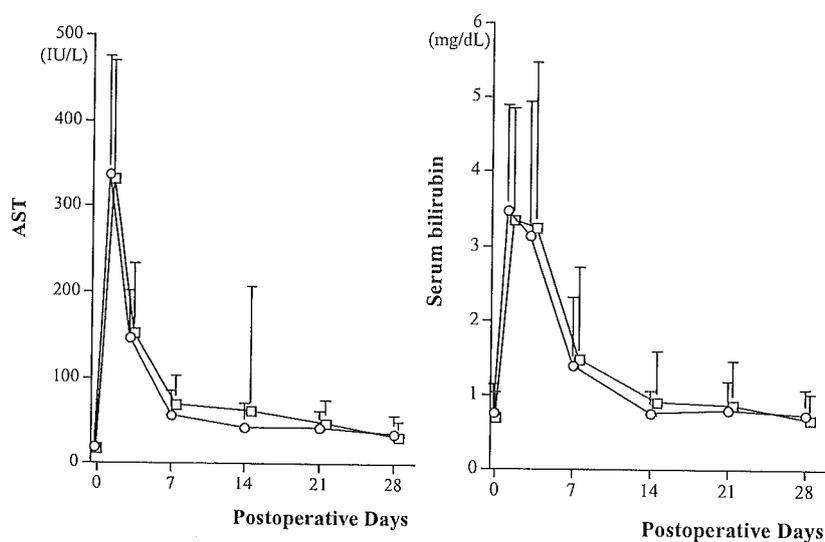


Figure 2: Postoperative liver function tests in the donors. ○: Right lobe with middle hepatic vein graft; □: Right lobe without middle hepatic vein graft.

Among 177 recipients of a right lobe without MHV graft, duration of the recipient operation was 730 ± 178 min and blood loss was 7088 ± 9768 g. The graft weight and GRWR range was 699.3 ± 120.9 g and $1.20 \pm 0.28\%$. The cold and warm ischemic time was 99 ± 85 and 45 ± 16 min, respectively. There was no significant difference in duration of surgery, blood loss and GRWR in the recipients between right lobe either with or without MHV graft. However, the warm ischemic time was significantly longer in the right lobe with MHV graft group ($p < 0.001$).

With regard to liver function tests, there was no significant difference in AST or prothrombin levels between the two groups. Although preoperative serum bilirubin level was significantly lower in the right lobe with MHV graft group ($p < 0.02$), serum bilirubin clearance was much delayed and persistent hyperbilirubinemia was observed in the right lobe without MHV graft group (Figure 3).

Venous reconstruction

With regard to the patients who had right lobe with MHV graft, a direct MHV anastomosis was possible in 12 patients in an end-to-end fashion (30.0%). Of these cases, the common cuff technique of the MHV and RHV in the graft after venoplasty, as reported by Lo et al. (18), was indicated in four. The proximal side of the MHV and the drainage vein of segment IV to the MHV (left medial superior vein) were preserved in 24 donors and a venous interposition graft was necessary in these cases: native portal vein in 19 cases; native inferior mesenteric vein in 2; donor's ovarian vein in 2 and native portal vein patch graft in 1. A Y-shaped portal vein graft was adopted in 13 cases, an I-shaped vein graft in 10 and a patch graft in 1, according to the distance between graft and recipient MHV (Figure 4).

Fourteen RIHV were reconstructed in 13 patients (46.4%). All patients had a patent RHV and MHV anastomo-

sis confirmed by routine Doppler ultrasonography and/or CT/magnetic resonance imaging (MRI) at least 1 month after transplantation. There were no complications related to the hepatic vein anastomosis during the follow-up.

One patient had portal vein thrombosis 19 days after LDLT, and this was successfully treated by reexploration surgery. Two patients developed biliary leakage, which was resolved by percutaneous aspiration. Four cases developed retrograde biliary drainage (19). Causes of death were sepsis in one patient, intraabdominal bleeding in one, multiple organ failure secondary to small intestinal perforation in one and severe pneumonia in one. The overall cumulative 3-year graft survival rate of right lobe with MHV graft was 86.2%, with a median follow-up of 18 months (range: 6–36). The cumulative 3-year graft survival rate of 143 right lobe without MHV graft for the same period was 74.8% (Figure 5; $p = 0.38$, NS).

Discussion

Right-lobe LDLT can provide an adequate graft size to compensate for the metabolic demands in most adult recipients, and the clinical outcome has improved in our series (5). One of the controversies in right-lobe LDLT is the potential congestion in the graft anterior segment due to the deprivation of the MHV tributaries. Techniques of venous reconstruction and the graft selection remain an open question.

Our standard technique of harvesting the right-lobe graft requires the transection of the MHV tributaries from the anterior segment to leave the entire MHV in the donor (20,21). To prevent congestion in the anterior segment, several technical modifications were reported. Fang et al. have adopted an extended right-lobe graft with the MHV

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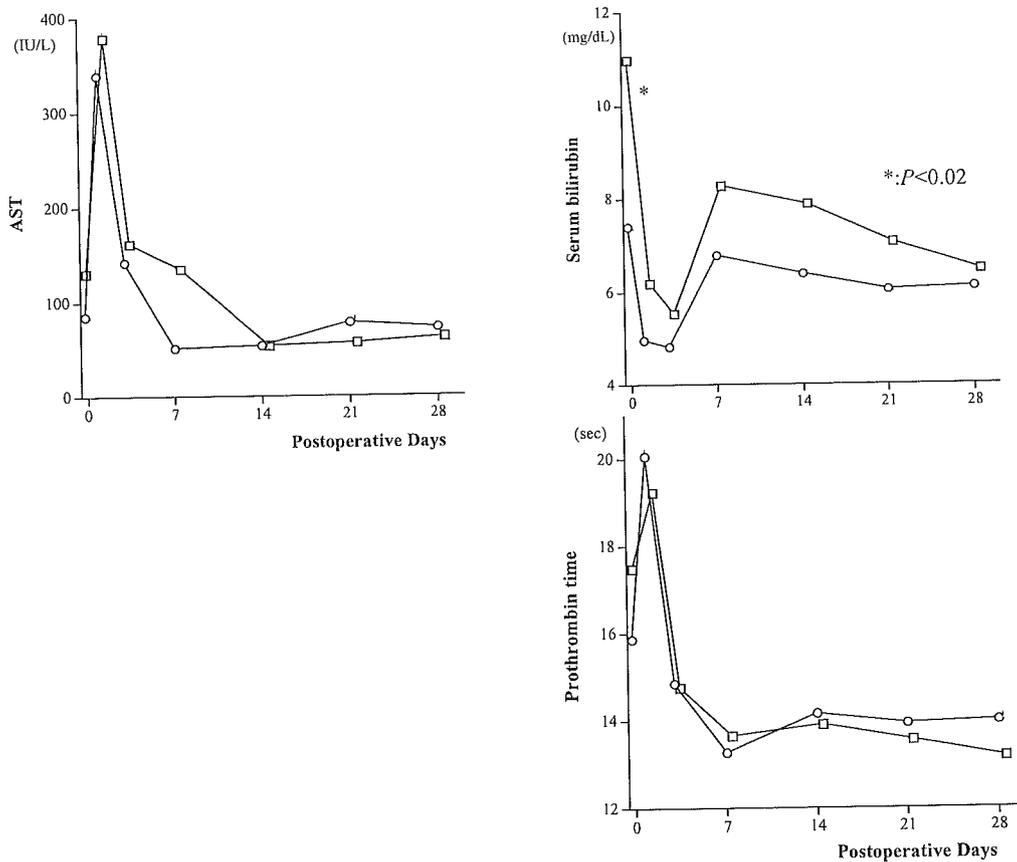


Figure 3: Postoperative liver function tests in the recipients. ○: Right lobe with middle hepatic vein graft; □: Right lobe without middle hepatic vein graft.

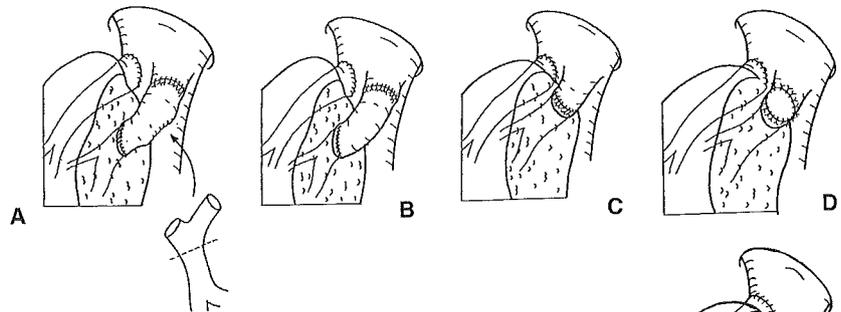


Figure 4: The type of middle hepatic vein anastomosis with/without the use of interposition vein graft. (A) Y-shaped portal vein graft (n = 13), (B) I-shaped vein graft (n = 10), (C) direct anastomosis (n = 12), (D) patch graft (n = 1); and (E) venoplasty (n = 4).

- A. Y-shaped portal vein graft (n=13)
- B. I-shaped vein graft (n=10)
- C. Direct anastomosis (n=12)
- D. Patch graft (n=1)
- E. Venoplasty (n=4)

(6,22), and reconstruction of the MHV with an interposition vein graft has also been adopted by the Toronto group (23). Reconstruction of the segment V/VIII branches using jump grafts has been reported both with and without the intraoperative MHV clamp test to confirm graft congestion

in some centers (8,24). However, additional venous reconstruction of the anterior segment did not significantly reduce graft congestion defined on MRI despite the patency of reconstructed drainage veins in our previous series (25).

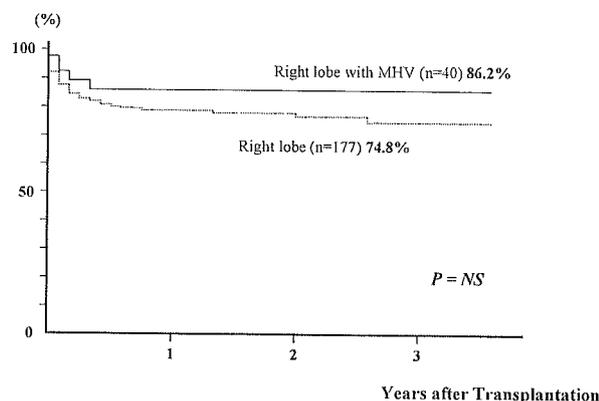


Figure 5: The overall cumulative graft survival rate in right-lobe with/without middle hepatic vein.

Based on our previous study, graft congestion in the anterior segment could be well tolerated and improved through intrahepatic anastomosis when the portal and arterial inflow and the RHV outflow were preserved (5,25). Although the regeneration of the posterior segment was shown to be superior to that of the anterior segment, the lack of anterior segment regeneration was resolved by a compensatory regeneration of posterior segment and the graft congestion in the anterior segment did not affect the overall graft regeneration (4). After the initiation of right-lobe with MHV graft, however, we experienced some patients who suffered from complications related to 'small-for-size graft'.

Our recent study revealed that right-lobe with MHV graft showed no congestion on MRI imaging (26). However, it remains open to question whether or not right-lobe with MHV graft should be indicated in all adult recipients. Nakamura et al. suggested that 26.5% of the MHV had proper branches that internally drained from the anterior segment (27). Kinkhabwala et al. reported that 26% of the accessory venous reconstruction from the anterior segment was necessary in right-lobe LDLT (28). We agree with these results that the reconstruction of MHV tributaries was not always necessary and should be indicated according to the preoperative imaging study.

A graft without MHV reconstruction would be given a 'functional liver volume' that corresponded to area drained by the RHV (and RIHV if reconstructed), while a graft with MHV reconstruction would have the anterior segments included in the right-lobe calculation with 3D volumetry. In our preliminary study of 3D CT volumetry in right-lobe LDLT series, the regional volume of V5 and V8 in right-lobe was $29.4 \pm 11.1\%$ (range: 12.4–56.7%) and 18.0% of the grafts showed MHV dominant ($n = 52$; data not shown). The importance of drainage vein in the anterior segment could be emphasized in the MHV dominant graft. Moreover, the tolerability of congestion in anterior segment and the compensate regeneration of posterior segment might not be

guaranteed in the MHV dominant right-lobe graft. We recommend right-lobe with MHV graft or additional vein reconstruction of the anterior segment in the MHV dominant right-lobe graft.

Recently, the Kaohsiung group provided an adequate algorithm for determining the extent of donor hepatectomy in right-lobe LDLT either with or without MHV. The decision to take MHV with the graft was made based on the donor-to-recipient body weight ratio and the size of the MHV tributaries from the anterior segment (29). The initial indication for right-lobe with MHV graft in our institution was the GRWR $< 1.0\%$ using right-lobe graft. Figure 6 shows our current algorithm for the graft selection after the initial experience of 40 right lobes with MHV LDLTs. The graft selection should be made according to the RHV/MHV dominance, GRWR and remnant liver volume. It is important for avoiding the possibility of anterior segment congestion having information of the MHV dominant before an operation with 3D volumetry. If the graft selection is inconclusive, further discussion should be necessary to secure the recipient benefit as well as donor safety considering the graft quality and metabolic load of the recipient.

The inflow modulation of in 'small-for-size graft' might be an another important issue. Our study showed that elevated portal vein pressure (>20 mmHg) is strongly associated with poor patient survival attributable to 'small-for-size syndrome'. Further elucidation of the pathogenesis behind this phenomenon and efforts to modify portal vein pressure will be a key to improving results (30). Moreover, our recent study suggested that partial diversion of portal flow to systemic circulation and splenic artery ligation might be effective for avoiding injuries that occur in 'small-for-size graft' (31). The same technical modification was adopted in some centers in order to avoid graft congestion and failure by portal overperfusion (32,33). The decrease of portal vein pressure may be able to be used as an effective method to attenuate the 'small-for-size syndrome'. Further discussion about portocaval shunt and splenic artery ligation should be necessary to make a conclusion for the graft selection in right-lobe LDLT.

In determining whether a donor can provide adequate liver volume at acceptable risks, it is important to know not just the remnant liver volume but also the anatomical factors that may affect the functional capacity of the donor remnant liver. It was reported that 9.5% of patients had a left medial superior vein originating from the MHV and draining predominantly the left medial superior segment (27). The impairment of regeneration and functional recovery of segment IV after right lobectomy with MHV has been reported, while the overall regeneration of the remnant liver was not affected by the MHV harvesting in right-lobe LDLT (34).

The mean regional volume of the left medial superior vein in 3D CT evaluation was 159.3 ± 28.8 mL and the

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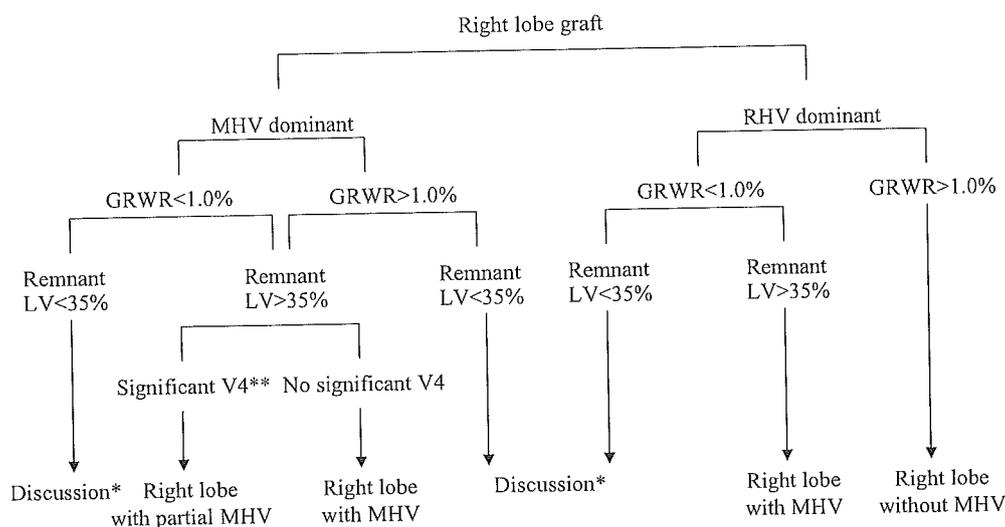


Figure 6: Algorithm for the graft selection. RHV: right hepatic vein; MHV: middle hepatic vein; GRWR: graft-to-recipient weight ratio; LV: liver volume. RHV dominant: regional volume of vein 5 + vein 8/right-lobe volume $\times 100 < 40\%$ MHV dominant: regional volume of vein 5 + vein 8/right-lobe volume $\times 100 > 40\%$ *Discussion for; additional vein reconstruction of V5/8, dual graft, auxiliary liver transplantation, ligation of splenic artery and/or partial portocaval shunt, exclude from potential donor candidate **V4: drainage vein of segment IV to the MHV (left medial superior vein).

percentage of the regional volume of left medial superior vein in remnant liver was $40.5 \pm 8.0\%$ (range: 27.9–49.9%) in our series ($n = 52$, data not shown). To obtain more evidence of the segment IV drainage vein and RHV, a further study of '3D volumetric analysis' is now underway in order to clarify the exact role of these drainage veins. Evaluation of the regional volume of the left medial superior vein is important for the donor safety.

If the regional volume of the left medial superior vein was significant, then the proximal side of the MHV and the left medial superior vein were preserved in the donor, given that the MHV was divided at the side proximal to the left medial superior vein. If the remnant liver volume was revealed to be less than 35% of the whole liver volume, the potential donor was excluded and another donor candidate or option was considered, such as auxiliary liver transplantation, dual liver transplantation and additional vein of the anterior segment reconstruction (35–37).

Manner of the MHV reconstruction is controversial. It was reported that 7.6% of MHV anastomoses were found to be occluded intraoperatively even in an experienced center (22). Direct end-to-end MHV reconstruction was possible in 40.0% of the patients with entire MHV graft. Skeltonization of the IVC and the hepatic veins are important to allow adequate spacing for the hepatic vein anastomosis. In the case of a MHV divided proximal to the left medial superior vein, vein graft should be used to prevent torsion and tension in the anastomosis, as the MHV is considered too short for safe anastomosis. Recently, the common cuff of the MHV and RHV in the graft after venoplasty has been reported (18). While it is an excellent technique, reconstruction of

the outflow of the RHV and distal part of the MHV into a single opening may not be possible if their orifices are far apart, and both may need to be implanted separately into the recipient IVC.

In conclusion, we adopted right lobe with MHV graft in 40 LDLT cases. Although no significant differences were revealed in the donor and recipient liver function tests nor in patient survival between right-lobe LDLT with or without MHV, right lobe with MHV graft should be indicated in very selected patients according to algorithm for the graft selection paying special attention to donor safety. It is hoped that as experience increases and refinements are made to the technique, improved outcomes in right-lobe LDLT will be seen.

Acknowledgment

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Living-donor liver transplantation for situs inversus: 2 case reports

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Index words:

Living-donor liver
transplantation;
Situs inversus

Abstract Two cases of living-donor liver transplantation performed in patients with situs inversus are reported. The authors discuss the operative management for a situs inversus recipient to undergo liver transplantation.

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Liver transplantation has been accepted as the treatment of choice for patients with end-stage liver disease. Biliary atresia is one of the most common indications in children for liver transplantation. The disorder is associated with other congenital abnormalities in 10% to 27% of patients, which includes situs inversus [1].

Situs inversus is characterized by a mirror image orientation of the abdominal and thoracic viscera relative to the midline. The etiology of this disease is unclear, and the incidence is very low, as it occurs in less than 0.005% of the general population [2]. Situs inversus may occur in up to 28% of children with biliary atresia [3,4].

Situs inversus was once considered a contraindication to liver transplantation because of technical difficulties inherent in the procedure. Patients with a combination of vascular anomalies, including an interrupted inferior vena cava (IVC), a preduodenal portal vein, and an anomalous hepatic arterial anatomy, have been highly questionable candidates for liver transplantation [5], but it is very controversial.

We present 2 cases of living-donor liver transplantation performed in patients with situs inversus. In this report, we discuss the operative management for a situs inversus recipient to undergo liver transplantation.

1. Case report

1.1. Case 1

A 5-year-old boy presented with end-stage liver disease for living-related liver transplantation. He had a history of biliary atresia and had undergone a Kasai portoenterostomy at the age of 13 months. At that time, he was noted to have situs inversus, polysplenia, intestinal malrotation, and preduodenal portal vein.

After the Kasai operation, ascending cholangitis frequently occurred, and he developed liver failure. The father, who was selected as an organ donor, had normal abdominal anatomy by computed tomography scan. A left lateral segment was harvested as a graft. The procedure was performed as reported previously [6].

In the recipient operation, complete situs inversus, including nonrotation of the gut, polysplenia, and a preduodenal portal vein, was verified. The retrohepatic IVC was absent, and the hepatic veins drained directly into

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the right atrium. The right and left hepatic arteries independently originated directly from the supraceliac aorta. The graft was placed in the midline position to align the vascular anastomoses.

The donor left hepatic vein was anastomosed directly to the shared hepatic vein ostium in an end-to-end fashion. Because of sclerosis and narrowing of the wall, the portal vein of the recipient was resected at the confluence of the splenic vein and the superior mesenteric vein superior to the pancreas. The inferior mesenteric vein of the donor, which was the interposition vein graft, was anastomosed to the recipient portal vein in an end-to-end fashion. On the opposite side, transversing over the duodenum, it was anastomosed to the donor left portal branch in an end-to-end fashion. In spite of transversing over the duodenum, the anastomotic site was not under tension. The recipient hepatic artery was anastomosed to the donor left hepatic artery using microvascular techniques [7]. The bile duct was anastomosed to the previously created Roux-en-Y limb. A 4F polyvinylalcohol tube was inserted as an external stent to prevent anastomotic stenosis or obstruction.

Postoperatively, the graft function was excellent. During the 9-year follow-up, the patient did well without any surgical complications.

1.2. Case 2

A 2-year 4-month-old girl presented at Kyoto University Hospital with progressive hepatic failure secondary to biliary atresia after a Kasai portoenterostomy. She had undergone the procedure at the age of 2 months, at which time she was noted to have situs inversus with dextrocardia, polysplenia, intestinal malrotation, and a preduodenal portal vein. After the Kasai operation, the patient had frequent episodes of ascending cholangitis and had developed liver failure 2 years after the initial Kasai operation.

Her parents were evaluated as potential organ donors for liver transplantation, and both of them had normal anatomic findings on computed tomography scan. The mother was selected as the organ donor because the father had a fatty liver. A left lateral segment from her mother was harvested as a graft.

In the recipient operation, complete situs inversus, including nonrotation of the gut, polysplenia, a left-positioned vena cava, and a preduodenal portal vein, was verified. The proper hepatic artery arose directly from the supraceliac aorta and bifurcated into a left and right hepatic artery.

The graft was placed in the left side of the abdominal cavity. The graft had separate segments 2 and 3 veins, and both veins were independently anastomosed to the recipient hepatic vein orifice, because they were too far apart to make a single anastomosis. An orifice was created to connect the left and middle hepatic veins by incising the IVC, and this structure was then anastomosed end-to-end to the graft segment 2 vein. The right hepatic vein of the recipient was sutured from the left corner to adjust the size and anasto-

Table 1 Profiles of cases

	Case 1	Case 2
Age (y)	5	2
Weight (kg)	15	10.5
Native liver abnormalities	Absence of retrohepatic IVC preduodenal PV right and left HA direct from aorta independently	Left-sided IVC preduodenal PV proper HA direct from aorta
Donor relation	Father	Mother
Blood type combination	Identical	Identical
GRWR	1.56	2.28

GRWR indicates graft-to-recipient weight ratio; PV, portal vein; HA, hepatic artery.

mosed end-to-end to the graft segment 3 vein. Because of sclerosis and narrowing of the wall, the portal vein of the recipient was resected superior to the pancreas. Then, the donor ovarian vein, which was the interposition vein graft, was anastomosed to the recipient portal vein in an end-to-end fashion. On the opposite side, transversing the duodenum, the vein graft was anastomosed to the donor left portal branch in an end-to-end fashion without tension. The recipient right hepatic artery was anastomosed to the donor left hepatic artery using microvascular techniques. The bile duct anastomosis was created with the Roux-en-Y limb in the usual fashion, and a 4 French polyvinylalcohol tube was inserted. Postoperatively, the graft function was excellent. Currently, 2 years and 9 months after liver transplantation, the patient is doing well.

2. Discussion

The prevalence of situs inversus in the general population is difficult to establish. The estimated incidence is between 0.002% and 0.1% [8]. Nearly 80% of these patients are affected with other congenital malformations, including visceral and vascular anomalies and biliary atresia, which is one of the most common indications for liver transplantation [3,9]. Biliary atresia in association with other congenital structural anomalies has a poor prognosis, and these patients continue to have poor bile secretion after Kasai portoenterostomy [10]. Complex vascular anomalies associated with situs inversus increased the technical difficulty of the operation and resulted in a high mortality rate in these patients, especially in the context of an interrupted IVC, a preduodenal portal vein, and an anomalous hepatic artery origin. The technical aspects of performing liver transplantation in these patients are more challenging than simply overcoming the mirror-image liver anatomy.

Mattei et al [11] described the results of 26 patients with situs inversus who had undergone liver transplantation. In that report, they stated that the anatomic variations

encountered most frequently were a preduodenal portal vein (69%), an absent infrahepatic IVC (50%), and an aberrant hepatic artery distribution (35%), which included an accessory artery. Despite these anatomic variations, the majority of vascular anastomoses were performed in a standard fashion.

We encountered 2 variations in the IVC anatomy: a left-sided IVC and an absent infrahepatic IVC (Table 1). In both cases, hepatic vein reconstruction was performed by our standard technique, the preparation for IVC anastomosis was managed easily, and the postoperative hepatic venous outflow was excellent.

The predominant portal vein anomaly in situs inversus patients is a preduodenal portal vein. This anomaly rarely interferes with a simple end-to-end anastomosis, and vascular grafts are usually not necessary, when the preduodenal portal vein is sufficiently mobilized and not injured. The portal vein of the recipient with biliary atresia is often atrophic and sclerotic because of repeated episode of cholangitis. Interposition vein grafting is useful to prevent an anastomosis under tension, especially if transversing the duodenum. The discrepancy of the distance from the portal vein to the hepatic vein between graft and recipient may be problematic. This discrepancy may result in kinking of the reconstructed portal vein, which can lead to portal vein thrombosis and graft failure. In the case of patient with preduodenal portal vein, the portal vein was reconstructed in a preduodenal position resulting in a straight line. Preduodenal reconstruction of the portal vein is a feasible and effective method to deal with mismatched distance [12].

An aberrant hepatic artery supply is commonly encountered in patients with situs inversus. However, current microvascular techniques permit the construction of an end-to-end anastomosis that maintains adequate arterial flow.

In liver transplantation to situs inversus patients, the evaluation of the donor is important. Familial situs inversus has been reported only sporadically, but a case of living-donor liver transplantation from a situs inversus to another has been reported. Therefore, donor selection should properly evaluate liver anatomy [13].

Situs inversus is not a contraindication to liver transplantation, and prolonged survival can be achieved. The anatomic variants encountered can be managed with conventional techniques but sometimes demand creative surgical solution. Reconstruction of preduodenal portal vein with interposition vein graft is useful to confirm the enough length and prevent overstretching of anastomosis, especially when it is atrophic and sclerotic.

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Proinflammatory and Antiinflammatory Cytokine Production During Ischemia-Reperfusion Injury in a Case of Identical Twin Living Donor Liver Transplantation Using No Immunosuppression

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ABSTRACT

Background. Bolus steroids are usually administered prior to graft reperfusion in an attempt to provide protection against ischemia reperfusion injury (IRI). However, the anti-IRI properties of steroids have not been established. Living donor liver transplantation (LDLT) between identical twins provides a unique opportunity to study the natural production of cytokines during transplantation without the confounding influences of the alloimmune response or of immunosuppression in particular steroids.

Methods. A 38-year-old male with hepatitis C virus-related cirrhosis and multiple hepatocellular carcinomas received a hepatic right lobe graft from his identical twin. No immunosuppression was administered, not even intraoperative bolus steroids. IRI was assessed by serum transaminases as well as by proinflammatory interleukin (IL) IL-1 β , tumor necrosis factor (TNF)- α , IL-8 cytokines and for potent regenerative/anti-inflammatory (IL-6, IL-10) mediators.

Results. Despite no administration of steroids, low peak levels of serum transaminases were observed. Serum IL-6 and IL-10 dramatically and rapidly increased during liver transplantation, namely, 160 and 20 times higher than baseline, respectively. In contrast, IL-1 β and TNF- α remained low during and after transplantation and an increase in IL-8 was less obvious.

Conclusion. Syngeneic LDLT without intraoperative bolus steroids is feasible, yielding no penalty in terms of IRI. A predominance of protective cytokines was observed in the absence of steroids. Thus, the concept that intraoperative administration of steroids is necessary to protect liver transplants from IRI must be revisited.

IT has long been assumed that proinflammatory cytokines play a pivotal role in liver tissue damage during hepatic ischemia-reperfusion injury (IRI). Bolus steroids are usually administered prior to liver graft reperfusion based on the assumption that steroids protect against IRI by suppressing production of proinflammatory cytokines. This assumption has been recently challenged, however, by the results of clinical and rodent experiments demonstrating that steroids can paradoxically aggravate IRI by impairing hepatocyte regeneration.¹⁻³ In the meantime; a beneficial role has been experimentally established for hepatocyte regenerative and antiinflammatory protective cytokines, such as interleukin (IL)-6 and IL-10.^{4,5}

We report a case of living donor liver transplantation

(LDLT) between identical twins without any immunosuppression, including intraoperative bolus steroids. This case provided a unique opportunity to study the natural produc-

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Table 1. Changes in AST and ALT Serum Levels

	Before	Reperfusion	1 hr	6 hr	12 hr	18 hr	Day 1	Day 2	Day 3	Day 5	Day 7
AST	139	167	464	<u>550</u>	435	359	369	328	212	99	81
ALT	97	80	<u>511</u>	481	445	475	490	511	390	229	169

Peak values of AST and ALT are underlined.

tion of proinflammatory and hepatocyte protective cytokines during hepatic IRI because of the absence of confounding effects due to an alloimmune response or immunosuppression.

MATERIALS AND METHODS

Syngeneic LDLT

A 38-year-old man underwent right lobe LDLT on November 11, 2003 to treat hepatitis C virus-related cirrhosis and hepatocellular carcinomas. The liver donor was the patient's twin brother. Their HLA phenotypes were confirmed to be identical by HLA DNA typing. The weight of the graft was 810 g, and the recipient's body weight was 63 kg (graft/body weight ratio, 1.29%). Cold and warm ischemia times were 23 minutes and 50 minutes, respectively, compared with 85.5 ± 105.6 minutes and 43.5 ± 14.2 minutes for other LDLT patients receiving a right lobe.

Immunosuppression

No immunosuppression was administered, not even intraoperative bolus steroids.

Measurement of Serum Aminotransferases and Cytokines

Blood samples were sequentially collected before and at the beginning of the operation; at reperfusion; and 10 minutes, 1, 2, 3, 6, 12, and 18 hours later followed by once daily for 3 days posttransplant. IRI was assessed by measuring serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Proinflammatory cytokines (interleukin [IL]-1 β , tumor necrosis factor [TNF]- α , IL-8) and hepatocyte protective cytokines (IL-6, IL-10) were evaluated by ELISA in an independent laboratory in a blinded manner.

RESULTS

Despite no steroids being administered, peak levels of serum transaminases (ALT/AST: 511/550 IU/L; Table 1) were low and comparable to those usually observed in our LDLT patients receiving intraoperative steroids mean \pm SD (AST/ALT: $449 \pm 952/476 \pm 609$ IU/L; $n = 117$). The kinetics of the serum cytokines (Fig 1) showed IL-6 to dramatically increase after removal of the native liver, rapidly reaching its highest value at the time of reperfusion (843 pg/mL, 160 times higher than the baseline value at the beginning of the operation; Fig 1A). IL-10 also rapidly increased: the peak value was 39 pg/mL at 1 hour after reperfusion, 20 times higher than the baseline value at the beginning of the operation (Fig 1B). In marked contrast, TNF- α was undetectable both during and after LTx at all time points (Fig 1C). The pretransplant IL-1 β level was relatively high, but showed an abrupt decline during the anhepatic phase remaining low thereafter (Fig 1D). IL-8

slowly increased during LTx but reached its highest value only postoperatively: namely, peak value of 58.4 pg/mL at 6 hours after reperfusion, which is 20 times higher than the baseline value at the beginning of the operation (Fig 1E). No surgical complications were observed post-LTx.

DISCUSSION

TNF- α and IL-1 are the two proinflammatory cytokines most commonly implicated in hepatic IRI. Both, mediators induce production of IL-8—a chemoattractant for neutrophils.⁶ Some cytokines such as IL-6 appear to have dual functions, participating in both inflammatory responses and cellular regeneration. IL-6 knockout mice show an aggravation of warm IRI with impaired hepatocyte regeneration.⁴ In contrast, antiinflammatory cytokines, such as IL-10, may also play an important role in protection of the liver by counteracting the inflammatory response.⁵ Therefore, it may well be that intraoperative steroids, although effective in blocking inflammatory responses, negatively affect beneficial hepatocyte protective cytokines, which are important for graft recovery from IRI. Since we plan to continue the use of small-for-size grafts for adult LDLT, the ability of the liver to initiate regeneration or counteract inflammatory responses has become especially important.

In animal experiments on reperfusion injury, the kinetics and function of various cytokines are usually investigated in syngeneic organ transplant models that have an absence of an alloimmune response and no immunosuppression. However, cases of syngeneic organ transplants especially liver transplants, between identical twins have been rare. Our case reported here has, therefore, provided a unique and important opportunity to study the natural production of proinflammatory and hepatocyte protective cytokines during human hepatic IRI.

In contrast to the classic concept of the role of proinflammatory cytokines in hepatic IRI, the increase in serum IL-1 β , TNF- α , and IL-8 was not prominent despite the absence of steroids. In contrast, serum levels of IL-6 and IL-10 were dramatically and rapidly elevated after removal of the native liver. Some investigators have also found that liver surgery induces cytokine responses characterized predominantly by an early appearance of IL-6 and IL-10, whereas the levels of TNF- α remain low and IL-1 β is undetectable.⁷ Therefore, this cytokine imbalance may naturally occur during surgical operations on the liver.

In conclusion, we have found that, despite the complete absence of steroid administration, posttransplant peak levels of serum ALT/AST were unexpectedly low, while serum IL-6 (cytokine essential for liver regeneration) and IL-10 (antiinflammatory cytokine) were dramatically and rapidly

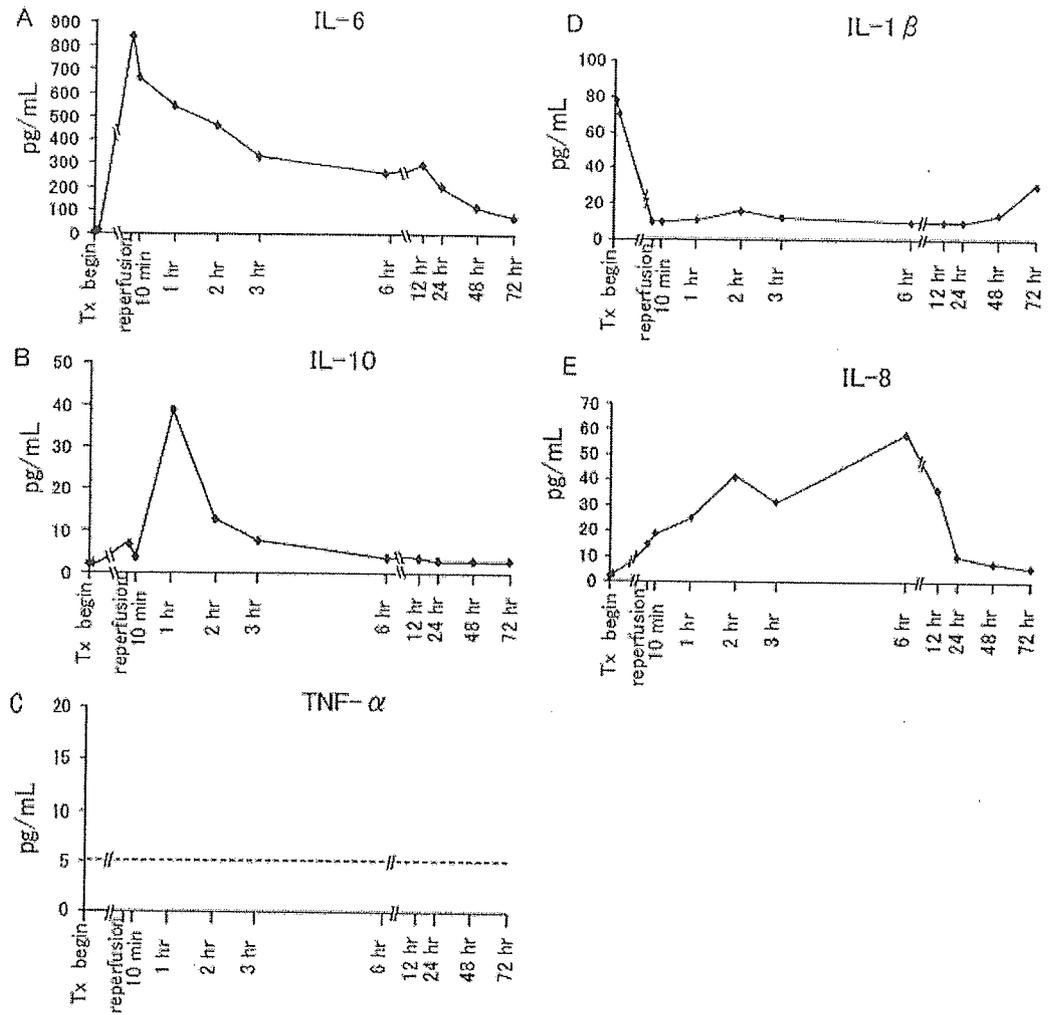


Fig 1. Kinetics of serum cytokines. IL-6 rapidly increased after removal of the native liver and reached its maximum value 2 hours after reperfusion (A). IL-10 strongly and rapidly increase and peaked 1 hour after reperfusion (B). In contrast, TNF- α was not detectable either during or after transplantation at all the time points tested (C), while IL-1 β levels declined during anhepatic time and remained low thereafter (D). IL-8 slowly increased but reached its highest value post-operatively (E). Tx: transplantation.

increased during LTx. In contrast, increases in serum IL-1 β , TNF- α , and IL-8 (proinflammatory cytokines) were not prominent. The predominant balance of hepatocyte protective cytokines (IL-6 and IL-10) during LTx may contribute to the protection of liver grafts from IRI. Of special interest is that this naturally occurring favorable balance was observed in the complete absence of steroids. Therefore, the concept that intraoperative administration of steroids is necessary to provide protection against IRI in LTx warrants reexamination.

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Portal Vein Complications in the Long-Term Course After Pediatric Living Donor Liver Transplantation

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ABSTRACT

The frequency and the outcome of patients with portal vein (PV) complications in the long-term course after pediatric living donor liver transplantation (LDLT) have rarely been reported. Between June 1990 and September 2003, 527 pediatric patients underwent primary LDLT with left lobe grafts, among which 479 patients with functioning grafts at 3 months after LDLT were included in this analysis. The ages ranged from 29 days to 17 years, 3 months (median: 1 year, 9 months) and body weight from 3.1 kg to 62.4 kg (median: 9.6 kg). Biliary cirrhosis was the most common cause for LDLT (81%). The PV was anastomosed with or without a vein graft. Thirty-nine patients (8%) showed a PV complication (stenosis: 16; obstruction: 17; thrombus: 2; twist: 3). Their ages ranged from 4 months to 17 years, 3 months (median: 1 year) and their body weight from 3.8 kg to 44.8 kg (median: 8.5 kg) at operation. PV complications were detected between 4 and 116 months (median: 14 months) after the transplant. Splenomegaly and decreased platelet counts were observed in more than 90% of the patients with a PV complication. In 27 patients (71%), interventional venoplasty was successful. Eleven patients had obstruction of the PV (2.3%) including three who showed cirrhosis; one with severe pulmonary hypertension; one death after retransplantation; and one alive after retransplantation. Moderate fibrosis was found in two patients at 3 and 2 years after the procedure, one of whom had the complication of a moderate intrapulmonary shunt. Early detection of PV stenosis with these two markers can lead to successful angioplasty and avoid graft loss.

MORE THAN 10 YEARS have passed since the introduction of living donor liver transplantation (LDLT) for pediatric patients with end-stage liver disease. Segmental liver grafts from adult donors have larger vessel pedicles compared to those of small pediatric patients. Furthermore, the vessel pedicles in the grafts are short compared with those in whole liver grafts from deceased donors.¹ In addition, the option to obtain vessel grafts is limited in LDLT.² These inconveniences require technical refinements for the anastomoses of segmental liver grafts with the recipient vessels. So far, vascular complications during the long-term course after pediatric LDLT have rarely been reported. In this report, we review portal vein (PV) complications in the long-term course of 527 pediatric LDLTs over the last 13 years.

PATIENTS AND METHODS

From June 1990 to September 2003, 527 pediatric patients received primary LDLT with left-side grafts, including lateral segment, left

lobe grafts, and monosegments. We reviewed the records of the medical courses in 479 patients with functioning grafts at 3 months after LDLT. Their ages ranged from 29 days to 17 years, 3 months (median: 1 year, 9 months) body weight, from 3.1 kg to 62.4 kg (median: 9.6 kg) at the time of LDLT. Primary diseases were biliary cirrhosis in 384 patients (81%); metabolic diseases in 35 patients (7%); fulminant hepatic failure in 24 patients (5%); liver cirrhosis in 15 patients (3%); tumors in 15 patients (3%); and other

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Table 1. Outcomes of Venoplasty for Portal Vein Complications

	Stenosis	Obstruction	Thrombus	Twist	Total
Number	16	17	2	3	38
Succeeded	16 (100%)	8 (47%)	0 (0%)	3 (100%)	27 (71%)
Failed	0 (0%)	9 (53%)	0 (0%)	0 (0%)	9 (24%)
No change	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (5%)
Recurrence	5 (31%)	4 (23.5%)	1 (50%)	0 (0%)	10 (26%)

etiologies in 6 (1%). Fifty-two percent of patients were under 2 years old. The donor and recipient operations were performed at the same time. When the native portal vein of the recipient was stenotic, we obtained a vein graft using either the ovarian vein of maternal donors or the inferior mesenteric vein of paternal donors. Segmental grafts were transplanted in piggyback fashion.³ The graft PV was anastomosed directly with the trunk or the branch patch of the recipient PV, when there were no stenotic changes in the recipient PV.⁴ When the PV trunk was stenotic, the native PV was removed and anastomosed to the confluence of the splenic vein and the superior mesenteric vein, or to an interposed vein graft, according to the distance between graft PV and the native PV. If the vein graft was small in diameter, it was patched. Blood flow in the portal vein was confirmed after reperfusion of the grafts by Doppler ultrasonography during operation and once or twice in a week while the patients stayed in the hospital. Patients were followed by blood tests every 1 to 2 months and by Doppler ultrasonography every 3 to 6 months. When a PV complication was suspected by clinical signs, it was confirmed by the Doppler ultrasonography and addressed by interventional venoplasty. However, in some patients, Doppler ultrasonography first revealed a PV complication requiring interventional venoplasty. We analyzed the frequency, age, and body weight at transplant, graft-versus-recipient body weight ratio, time from LDLT to diagnosis, symptoms and signs, findings on portography, results of interventional venoplasty, and long-term outcomes of patients with PV complications.

RESULTS

PV complications occurred in 39 patients (8%) of ages ranging from 4 months to 17 years, 3 months (median: 1 year) and body weights ranging from 3.8 kg to 44.8 kg (median: 8.5 kg). The period between LDLT and the diagnosis of a PV complication was between 4 and 116 months (median: 14 months). The graft-versus-recipient body weight ratios were significantly larger in 39 patients with PV complication (range: 0.86 to 5.6, mean: 2.97) than those in 440 patients without a PV complication (range: 0.6 to 7.68, mean: 2.52; $P < .03$). The diagnosis of a PV complication occurred within the first 6 months in five patients; between 6 months and 1 year in 10 patients, between 1 year to 2 years in nine patients; between 2 years and 3 years in eight patients; between 3 years and 5 years in six patients; and later than 5 years in one patient. Symptoms of a PV complication included gastrointestinal bleeding in 23%; liver dysfunction in 64%; splenomegaly in 95%; and decreased platelet counts below the lower limits of the normal ranges in 100%. Eleven patients (33%) had a vein graft placed at the time of LDLT. Portography was performed in 38 patients (97%). One patient did not receive portography because it took almost 2 years for the treat-

ment of repeated stenosis of the choledochojejunostomy by external biliary drainage.

The radiological findings were classified into four groups: PV stenosis at the anastomotic sites with detectable blood flow in 16 patients (42%); obstruction of the PV with no blood flow in 17 patients (45%); partial thrombus in the PV with detectable blood flow in two patients (5%); and twist of the anastomotic sites with elastic expansion by the balloon pressure in three patients (7.5%; Table 1). In all 38 patients, interventional venoplasty was performed. In 27 patients (71%), venoplasty was successful with recovery of portal flow without the major pressure gaps between pre- and poststenotic sites. These patients had displayed PV stenosis ($n = 16$), PV obstruction ($n = 8$) twist ($n = 3$). In nine patients with PV obstruction, venoplasty failed (24%). Two patients with a PV thrombus received thrombolytic therapy after venoplasty through a catheter placed into the PV with no major effects; one patient showed complete obstruction of the PV after splenectomy; and one patient underwent surgical thrombectomy but had a recurrent PV thrombus. Repeated venoplasty was required due to recurrence of the PV complication in five patients out of 16 stenotic patients; 4 out of 17 obstructed patients, and one patient with a partial thrombus. In 26 out of 27 patients with successful-interventional venoplasty, the platelet counts significantly increased from a median of $9.5 \times 10^4/\mu\text{L}$ (range: 2.9 to 18.8) before venoplasty to the median of $17.5 \times 10^4/\mu\text{L}$ (range: 2.0 to 21.8; $P < .0001$). The long-term outcomes in 11 patients with obstructed PVs, including nine patients with failed venoplasty, one patient with no treatment for PV thrombus due to long-term external biliary drainage for repeated stenosis of choledochojejunostomy, and one patient who previously had a PV thrombus and had complete obstruction of PV after splenectomy are shown in Fig 1. Cirrhosis was histologically evident in three patients, one of whom has been alive for 9 years after the diagnosis of PV occlusion with the complication of severe hepatopulmonary syndrome. At the moment, the pulmonary hypertension is severe excluding retransplantation. Another two patients lost their grafts at 5 years and at 2 years after the diagnosis due to biliary cirrhosis. One died early after retransplantation due to sepsis and the other is alive for more than 3 years after retransplantation. Moderate fibrosis was seen at 40 months and 25 months after the diagnosis of PV occlusion in two patients, the former being complicated by a moderate intrapulmonary shunt. No fibrotic changes were found in three patients at 50, 27, and 23 months after the diagnosis of PV occlusion without specific complica-

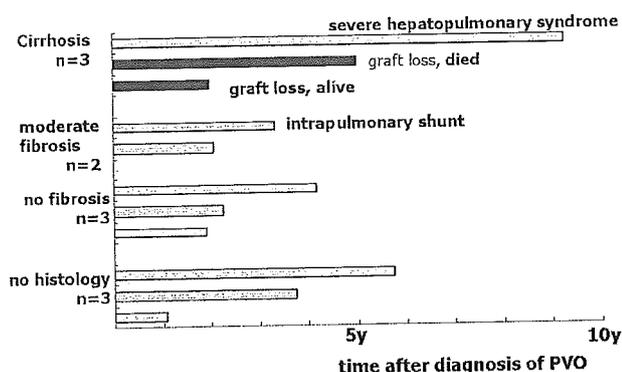


Fig 1. Outcomes of patients with PV obstructions ($n = 11$, 2.3%).

tions. The other three patients are alive for 69, 45, and 13 months after the diagnosis of PV occlusion, although they did not undergo a liver biopsy nor a radiological examination in the last 1 to 2 years. Patients without PV obstruction after venoplasty are all alive.

DISCUSSION

In pediatric LDLT, size mismatch between graft vessels from adult donors and the recipient native veins and short pedicles demands frequent usage of vein grafts that can affect the patency of the anastomotic sites in the long term. In addition a major indication for LDLT is biliary atresia in smaller patients age less than 2 years. The patients' PVs are sometimes complicated by sclerosis or narrowing due to repeated cholangitis or repeated previous laparotomies. However, the frequency and long-term outcomes of vascular complications in pediatric LDLT have rarely been reported. Buell et al reported vascular complications in pediatric patients with whole liver grafts and segmental grafts in a large series of 600 transplants.⁵ The incidence of PV complications was high among LDLT (27%) compared to that in reduced an split-liver transplantations (1%) or in whole liver transplantation (1%) from a deceased donor. They also reported that the patients with LDLT, especially those requiring a PV anastomosis with vein grafts, showed 71% PV complications, while LDLT without vein grafts in the PV anastomosis showed 13% PV complications. Therefore, they concluded not to use vein grafts for the PV anastomosis, which resulted in a significant decrease in the complication rates.

Our series is large and includes only LDLTs for pediatric patients. The rate of long-term PV complication was low (8%), although vein grafts were used when indicated. The Chicago group often used cryopreserved vein grafts from deceased donors in pediatric LDLTs that may be a reason why the rate of long-term PV complication was so high. We used mostly fresh ovarian veins from maternal donors or fresh inferior mesenteric veins from paternal donors. Among patients with PV complications, the rate of PV

anastomosis with vein grafts was high (33%) in this series. Therefore the use of a vein graft remains a risk factor for PV complications. The graft-versus-recipient body weight ratio was significantly larger with the median of 3.1% among the patients with PV complications, which means that this ratio is a risk factor for a PV complication. The frequency of diagnosis of PV complications was high in the first year, followed by the second to fifth years after LDLT. As to the symptoms and signs of a PV complication, gastrointestinal bleeding, splenomegaly, and/or liver dysfunction were confirmed as previously observed in patients with PV complications. One of the most characteristic findings was a decreased platelet count. Significant recovery of the platelet count was observed in all patients with successful venoplasty at 6 months to 1 year after treatment. Thrombocytopenia was a distinctive feature of chronic liver dysfunction with fibrotic changes.

PV obstruction in the long-term course was rare in our series (2%). However, two patients received re-LDLT due to graft dysfunction with biliary cirrhosis. In patients with long-term PV obstruction after liver transplantation, ischemic damage to the hepatic parenchyma and ischemic biliary pathology may cause biliary cirrhosis of the graft, even though cavernous formation of the PV developed around the obstructed PV. Even when hepatic grafts are free from severe fibrosis, portosystemic shunt may cause an intrapulmonary shunt or pulmonary hypertension, as observed in one patient with moderate fibrotic changes in the liver graft and with moderate intrapulmonary shunt. With the progress of hepatopulmonary syndrome, retransplantation may be required. One patient with long-term PV obstruction already showed severe pulmonary hypertension when diagnosed, which exceeded the application of retransplantation at the moment.

To avoid graft loss from ischemia-induced biliary cirrhosis or to avoid the severe complication of hepatopulmonary syndrome requiring retransplantation, early detection of a PV complication is essential. Platelet counts and spleen size should be monitored regularly in the long-term follow-up of pediatric patients after LDLT, combined with regular evaluation of PV flow by Doppler ultrasonography, to detect a PV complication early and avoid graft loss.

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