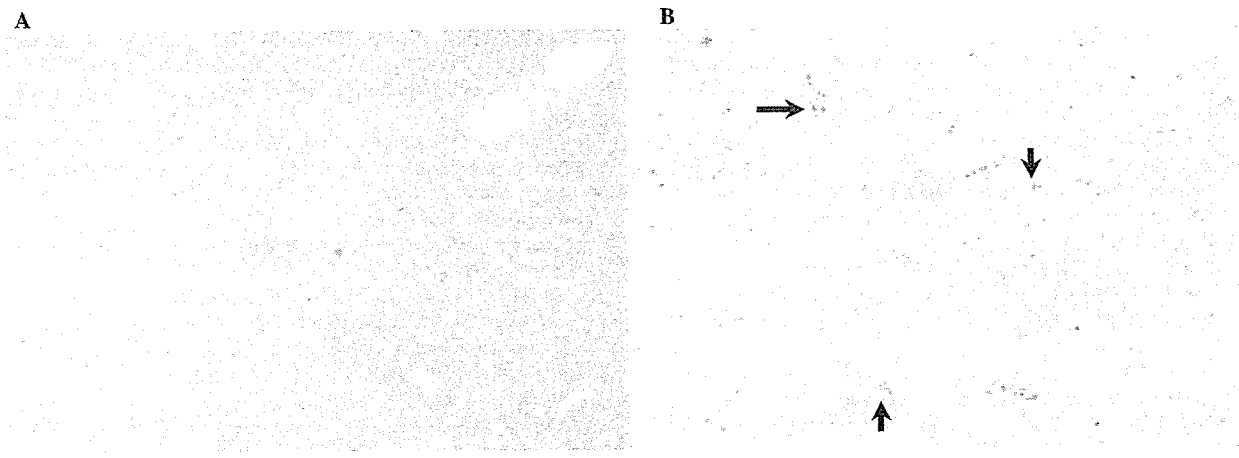

Fig. 3. Results of immunohistochemical staining with an anti-CD20 antibody (A, magnification ×40) and an anti-CD138 antibody (B, magnification ×40). B-lymphocytes are not seen (A), but abundant plasma cells (arrows) are present (B).

levels γ-globulin below 400 mg/dL was continued two wk after transplantation and he died of sepsis because of intra-abdominal abscess at two months after transplantation. Regarding the need for a splenectomy, Sawada et al. (4) confirmed the presence of plasma cells in the spleen by immunostaining of splenectomy tissue after pre-operative rituximab administration. Our immunostaining analyses revealed that the tissue was negative for CD20 (Fig. 3A) and positive for CD138 (Fig. 3B) in all three cases, and it was possible to confirm that plasma cells remained in the spleen. In case 1, an acute increase in the anti-blood-type antibody titer up to 256 was observed following the LDLT, even though the B lymphocyte level was suppressed to $<1\%$ by rituximab administration. However, after steroid pulse therapy, the titer was suppressed again and there was no acute increase necessitating a PE. Based on these findings, it is impossible to rule out the possibility that plasma cells left behind in the spleen as well as in the bone marrow contribute to the production of anti-blood-type antibodies, and the protocol in our department therefore includes a combined splenectomy. Similarly, even some patients with low pre-operative anti-blood-type antibody titers experience an acute increase in the anti-blood-type antibody titer immediately after surgery, and there are cases that pursue a fulminant course and progress to graft-liver failure. Thus, the dose and timing of the rituximab administration must be taken into consideration, and preventive administration would seem to be important. In addition, there have been reports (15–17) that rituximab administration is effective against humoral rejection and post-transplant lymphoproliferative disorder (PTLD) that has already occurred, and future studies investigating rituximab as a therapeutic agent, rather than just a preventive agent, appear necessary.

In conclusion, we have reported three cases of ABO-incompatible LDLT in which pre-operative rituximab administration and a splenectomy resulted in ABO-antibody titer suppression after transplantation. Although the protocol of rituximab administration was a conventional and safe regimen with no major side effects, all three cases had CMV infection and one of them was dead caused by infection with bone suppression. Finally, reconstruction for the rituximab administration protocol is needed for prevention of the infection and bone suppression.

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ORIGINAL ARTICLE

Donor outcome and liver regeneration after right-lobe graft donation

Hajime Yokoi, Shuji Isaji, Kentaro Yamagiwa, Masami Tabata, Hiroyuki Sakurai, Mosanobu Usui, Shugo Mizuno and Shinji Uemoto

First Department of Surgery, School of Medicine, Mie University, Mie, Japan

Keywords
computed tomography volumetry, hepatectomy, living donor liver transplantation, postoperative complication, steatosis.

Correspondence
Hajime Yokoi MD, First Department of Surgery, School of Medicine, Mie University, 2-174 Edobashi, Tsu, Mie 514-8507, Japan.
Tel.: +81-59-232-1111; fax: +81-59-232-8095;
e-mail: yokoi288@clin.medic.mie-u.ac.jp

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Summary

Sufficiently detailed information on donor safety and the liver regeneration process following right-lobe living donation has been unavailable, so we evaluated donor outcome and liver regeneration in 13 males and 14 females (39.0 ± 14.8 years old) who provided 27 right-lobe grafts without the middle hepatic vein. Preoperative total liver volume (TLV), graft volume, and postoperative changes in residual liver volume (RLV) were measured by volumetric computed tomography. Histological steatosis of the liver was graded as none, minimal (≤10%), and mild (11–30%). The median follow-up period was 337 days. Estimated graft volume and actual graft weight were linearly correlated ($Y = 177.85 + 0.795X$, $R^2 = 0.812$, $P < 0.0001$). Graft-to-recipient weight ratio was 1.08 ± 0.19%. Four donors had postoperative complications, but they resolved in response to conservative treatment. Postoperative hospital stay was 15.2 ± 5.5 days. Peak liver enzyme values were significantly higher in donors with mild steatosis ($n = 7$) than without steatosis ($n = 16$) ($P < 0.05$). Donor RLV was 40.8 ± 6.6% of original TLV at surgery, 79.8 ± 12.0% by 6 months, and 97.2 ± 10.8% by 12 months. At 3 months the liver of the older donors (≥50 years) had grown significantly more slowly than in younger donors (70.4 ± 9.2% vs. 79.3 ± 9.6%, $P = 0.0391$). In conclusion, right hepatectomy without middle hepatic vein of living donors is a safe procedure with acceptable morbidity, and the residual liver regenerated to its preoperative size by 1 year. However, meticulous care should be taken in donors with liver steatosis and aged donors.

Introduction

Living-donor liver transplantation (LDLT) was first used in 1988 to treat children because of the severe shortage of pediatric donors [1]. After the first success [2], LDLT using a left lateral segment became widely accepted as a treatment of choice for end-stage liver disease in pediatric patients. LDLT has now become an accepted alternative for any patients waiting for cadaveric liver transplantation, especially in countries like Japan where cadaveric organ harvesting is very limited. After expansion of the indication of LDLT for adult populations by using left-lobe grafts, small-for-size grafts with relatively high morbidity remained a significant barrier to more widespread use [3]. The subsequent evolution of LDLT has led to its applicability to right-lobe donation with good initial results [4,5]. Right-lobe grafts are now commonly used in many LDLT programs, because the right lobe represents approximately 60% of the entire liver volume, and provides sufficient viable tissue for many adult recipients of average size. Although LDLT using right-lobe grafts is rapidly being accepted worldwide, donor safety should be the top priority. The undisputed disadvantage of LDLT is the risk of serious complications or death in an otherwise healthy donor, but published complication rates in right-lobe living donors have differed widely from programs to

program [6–10], and there is still no standardized method for reporting surgical outcome. As a result, sufficiently detailed information on donor safety is not yet available, and controversy has been remaining. Moreover, few studies on regeneration of the residual liver in the living donor have been reported [6,7,10–12], and little is known about the long-term process of liver regeneration in right-lobe living donors.

In the present study, we evaluated our experience with regard to donor outcome and liver regeneration after donor surgery harvesting the right-lobe for use as a graft.

Patients and methods

Donors

Between March 2002 and November 2003, 38 consecutive LDLTs were carried out in Mie University Hospital, Japan, after obtaining the approval of the Ethics and Indications Committee of Mie University, and the 27 donors who donated their right lobe without the middle hepatic vein were enrolled in this study. The 11 donors who were excluded consisted of three who donated right-lobe grafts with the middle hepatic vein, two who donated left-lobe grafts with the middle hepatic vein, and six who donated the left lateral segment graft. The ages of the donors ranged from 18 to 62 years. In terms of their relationship to the recipient, the donors consisted of 10 spouses (one husband and nine wives), 10 offspring (eight sons and two daughters), three sisters, one father, one grandson, one cousin, and one son-in-law. Significant medical history consisted of hypothyroidism, hypertension with diabetes mellitus, gastric ulcer and well-controlled depression in one donor each. There were three donors with a history of abdominal surgery, and the procedures consisted of appendectomy in three and gynecological surgery in one. One donor was ABO incompatible with her recipient.

Donor selection

Donor candidates were limited to blood relatives up to the third degree and the spouse, or equivalent of the recipient, if they manifested a strong desire to donate part of their liver of their own free will. After first obtaining their informed consent, donor candidates were medically screened by means of blood tests, abdominal ultrasonography (US), and tests for general anesthesia. Final candidates were examined for vascular anomalies by 5-mm slice volumetric computed tomography (CT) with three-dimensional images, and biliary sytem was evaluated by three-dimensional drip infusion cholangiography (DIC)-CT. The total liver volume (TLV), graft volume and residual liver volume (RLV) of the donors were calculated by CT volumetric analysis. Graft-to-recipient weight ratio (GRWR) was estimated using graft volume instead of the actual graft weight (estimated GRWR = graft volume/recipient body weight × 100). The CT of the liver for volume determination was performed as described elsewhere [13]. Briefly, the scheduled graft and the whole liver were traced on 5-mm CT slices, and areas enclosed were calculated and integrated.

Selection criteria for donors were, in principle, age 20–60 years, healthy, ABO compatible, estimated GRWR >1.0%, and estimated RLV (preoperative estimated TLV – estimated graft volume) >30% of TLV. Each application for LDLT was submitted to the Ethics and Indications Committee of our University, and Committee discussed the applications with regard to donor safety and the indications of the recipients. The Committee gave its final approval to perform the transplant only after interviewing the potential donor and her or his family. The donor was informed that she or he could withdraw at any time.

Pretransplant evaluation of the donor

The pretransplant evaluation of the anatomy of the donor's liver was based on Doppler US and CT scan and did not include angiography or endoscopic retrograde cholangiopancreatography. In one emergency case the preoperative CT scan was omitted because the equipment was not available. The liver was evaluated for steatosis by US and CT alone, and preoperative liver biopsy was not routinely performed. Donor candidates who were suspected of having steatosis were placed on a diet and exercise program, and their candidacy was evaluated again at a later date. To prevent postoperative pulmonary emboli, all candidates were screened by US for deep vein thrombi of lower extremities before surgery.

Donor surgery

The surgical procedure used in the donors has been described in detail elsewhere [5,14]. Briefly, after the abdomen was entered, a liver biopsy specimen was collected to evaluate for hepatic steatosis. Before parenchymal transection of the liver, the right lobe was mobilized, and the short hepatic veins were transected except right inferior hepatic veins of significant size. Short hepatic veins along the left side of inferior vena cava were left intact. After dissection and isolation of the vessels at the hepatic hilum, the transection plane was determined by referring to the demarcation line obtained by temporary clamping of the right portal branch and right hepatic artery. The transection line was then marked by electrocautery on the surface of the liver just to the right of the demarcation line. After releasing the clamps of hepatic blood flow,

parenchymal transection was carried out without any interruption of the hepatic blood flow. Intraoperative cholangiography prior to transection of right hepatic duct was omitted when the anatomy of biliary system was clearly demonstrated by preoperative three-dimensional DIC-CT. Parenchymal transection was started at the liver edge and proceeded down to the bile duct, and after transecting the right hepatic duct at its bifurcation, the parenchymal transection was continued cranially toward the right hepatic vein. The grafts were flushed with histidine–tryptophan–ketoglutarate solution *ex situ* via the portal vein, and then weighed on the back-table and preserved in the same solution. Graft weight was considered equivalent to its volume, because the specific gravity of the liver is similar to that of water. Before closing the abdomen, intraoperative cholangiography was performed to test for bile leakage with clamping of common bile duct at the supraduodenal portion.

Postoperative care

After surgery the donors were cared for in a surgical recovery room. Early oral nutrition was encouraged, and progressed as tolerated. Postoperative pain was managed by routine epidural infusion of analgesics. As the prevention and early detection of deep vein thrombosis is one of the most important points in postoperative care of living donors, an intermittent pneumatic compression device was used during surgery and the early postoperative period until the donor was ambulatory. Serial Doppler US of the deep veins was performed postoperatively, and intravenous heparin, 10 000 units daily, was given after removal of the epidural catheter until the donor became ambulatory.

Postoperative evaluation of graft and liver regeneration

The ratio of graft size to recipient body weight was evaluated by using actual GRWR (actual graft weight/recipient body weight × 100). Estimated-actual %RLV of donors immediately after donation was calculated as: estimated-actual %RLV = (preoperative estimated TLV − actual graft weight)/preoperative estimated TLV × 100. Postoperative liver regeneration is expressed as a percentage of the original TLV based on follow-up CT liver volume measurements. Follow-up CT volumetry was performed 7, 14, 30, 90, 180, and 360 days postoperatively on 23, 22, 22, 22, 17, and 7 donors respectively.

Evaluation of the degree of steatosis

All liver biopsy specimens were examined histologically. The specimens were classified into three groups based on the degree of macrovesicular steatosis observed: none (0% steatosis), minimal (≤10%), and mild (11–30%).

Evaluation of postoperative liver functions and complications

Postoperative changes in liver function test values were analyzed in relation to donor age, histological degree of steatosis of the liver, and estimated-actual %RLV. The donors were also assessed for postoperative complications during and after the initial hospital stay. The follow-up periods of the donors ranged from 134 to 666 days (median 337).

Statistical analysis

Values are expressed as mean ± SD. Variables were compared by using the unpaired Student's *t*-test, and statistical significance was defined as $P < 0.05$. All statistical analyses were performed using the Stat View 5.0 software package for Macintosh (SAS Institute Inc., Cary, NC, USA).

Results

Liver volumetry and graft profiles

Preoperative CT volumetric analyses and postoperative graft profiles are summarized in Table 1. Estimated graft volume ranged from 476.0 cm^3 to 1064.8 cm^3, and actual graft weight ranged 460 to 1180 g. The values for estimated graft volume and actual graft weight showed a positive linear correlation ($Y = 177.85 + 0.795X$, $R^2 = 0.812$, $P < 0.0001$). Preoperative estimated GRWR, calculated using estimated graft volume instead of actual graft weight, ranged from 0.79 to 1.89%, and in one case it was <0.8%. All of the actual GRWR values were >0.8%. Preoperative estimated %RLV, defined as (estimated

Table 1. CT volumetric analysis and graft profile.

Preoperative ($n = 26$)	
Estimated TLV (cm^3)	1145.8 ± 199.7 (806.1–1694.9)
Estimated graft volume (cm^3)	721.0 ± 129.0 (476.0–1064.8)
Estimated %RLV	37.0 ± 4.1 (25.4–44.3)
Estimated GRWR (%)	1.16 ± 0.25 (0.79–1.89)
Postoperative ($n = 26$)	
Actual graft weight (kg)	679.4 ± 144.4 (460–1180)
Estimated-actual %RL	40.8 ± 6.6 (27.2–51.4)
Actual GRWR (%)	1.08 ± 0.19 (0.83–1.57)

Values are expressed as mean ± SD. Numbers in parentheses indicate range.

TLV, total liver volume; RLV, residual liver volume; GRWR, graft-to-recipient weight ratio; Estimated % RLV = (TLV − estimated graft volume)/TLV × 100; Estimated-actual %RLV = (TLV − actual graft weight)/TLV × 100.

TLV – estimated graft volume)/estimated TLV × 100, ranged from 25.4% to 44.3%. Two donors had a preoperative estimated %RLV below 30%. The actual transection lines in both donors were intentionally shifted to the right, and as a result their postoperative estimated-actual %RLV, calculated by actual graft weight instead of preoperative estimated graft volume, was more than 30%. Finally, only one donor, a donor with a preoperative estimated %RLV of 33.8%, had estimated-actual %RLV of 27.2% postoperatively.

Histological examination of the liver biopsy specimen during surgery revealed minimal (≤10%) and mild (11–30%) macrovesicular stestosis in 4 and 7, respectively, of the 27 grafts. None of the grafts exhibited histological steatosis of >30%.

Surgery and complication

Surgical factors related to the harvesting procedure in the 27 donors and the postoperative complications are summarized in Table 2. The patients with complications consisted of three males and one female, and they ranged in age from 18 to 54 years old (32.8 ± 15.6 years). They required a significantly longer postoperative hospital stay than the other donors (25.0 ± 7.4 days vs. 13.5 ± 2.8 days, $P < 0.0001$), but all of them recovered in response to conservative treatment. None of the donors with a significant medical history experienced a recurrence or exacerbation postoperatively. All donors are being followed, and they are alive and well.

Postoperative liver function

Changes in postoperative liver function test values are shown in Fig. 1. The values for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time international normalized ratio (PT-INR) of all of the donors peaked on postoperative day (POD) 1 or 2, and rapidly returned to within the normal range by 1 month. The serum total bilirubin (T-Bil) values also peaked on POD 1 or 2, and they were all below 5 mg/dl, except in one case with a peak value of 9.8 mg/dl. That patient was a 55-year-old male with a body height of 173 cm, body weight of 85 kg, and normal preoperative liver function test values. His preoperative estimated TLV was 1458 ml and actual graft weight was 840 g. Right hepatectomy was performed uneventfully with an intraoperative blood loss of 616 ml. Postoperative estimated-actual RLV was calculated at 42.4% of original TLV. His T-Bil value increased to 9.8 mg/dl on POD 2 after the peak liver enzymes values (AST 844 IU/l, ALT 628 IU/l) occurred on POD 1, and the histological examination of his liver had revealed mild macrovesicular steatosis (up to 30%). The T-Bil values of all donors, including this donor, decreased to within the normal range within 1 month. The postoperative peak liver function tests values were analyzed in relation to donor age (<50 years, ≥50 years), intraoperative blood loss (<500 ml, 500–1000 ml, >1000 ml), estimated-actual %RLV (<40%, ≥40%), and histological degree of macrovesicular steatosis of the liver (none, minimal, mild). The results showed that only histological degree of steatosis affected the postoperative peak AST and ALT values, which were significantly higher in the donors with mild macrovesicular steatosis than in those without steatosis (AST; $P = 0.0380$, ALT; $P = 0.0166$). However, there were no significant differences in postoperative peak T-Bil and PT-INR value according to degree of macrovesicular steatosis in the liver (Table 3).

Table 2. Operative results ($n = 27$).

Operation time (min)	365.7 ± 71.9 (225.0–551.0)
Blood loss (ml)	822.2 ± 572.1 (175–1597)
Blood transfusion	
Autologous	6
Heterologous	0
Postoperative complications	
Bile leakage	1
Persistent fluid collection with fever	1
Duodenal ulcer	1
Fever of unknown origin	1
Hospital stay (days)	15.2 ± 5.5 (9–34)

Values are expressed as mean ± SD or numbers of cases. Numbers in parentheses indicate range.

Postoperative liver regeneration

The residual liver of the donors was 40.8 ± 6.6% of original TLV immediately after right hepatectomy, i.e. at time 0. The residual liver grew rapidly, resulting in an increase to 61.6 ± 10.8% and 68.3 ± 9.4% of original TLV by 1 week and 2 weeks, respectively, after surgery. Thereafter, the liver volume gradually increases to 79.8 ± 12.0% and 97.2 ± 10.8% of original TLV by 6 months and 12 months, respectively, after the donation.

Postoperative changes in liver regeneration of donors were compared according to donor age (<50 years, ≥50 years), gender (male, female), intraoperative blood loss (<500 ml, 500–1000 ml, >1000 ml), estimated-actual %RLV (<40, ≥40%), and histological degree of macrovesicular steatosis of the liver (none, minimal, mild). The results showed no significant differences in liver regeneration according to any of these factors except donor age. Postoperative changes in liver volume according to donor age are shown in Fig. 2. The mean liver volume 90 days following donation by donors 50 years of age or older was significantly lower than in younger donors

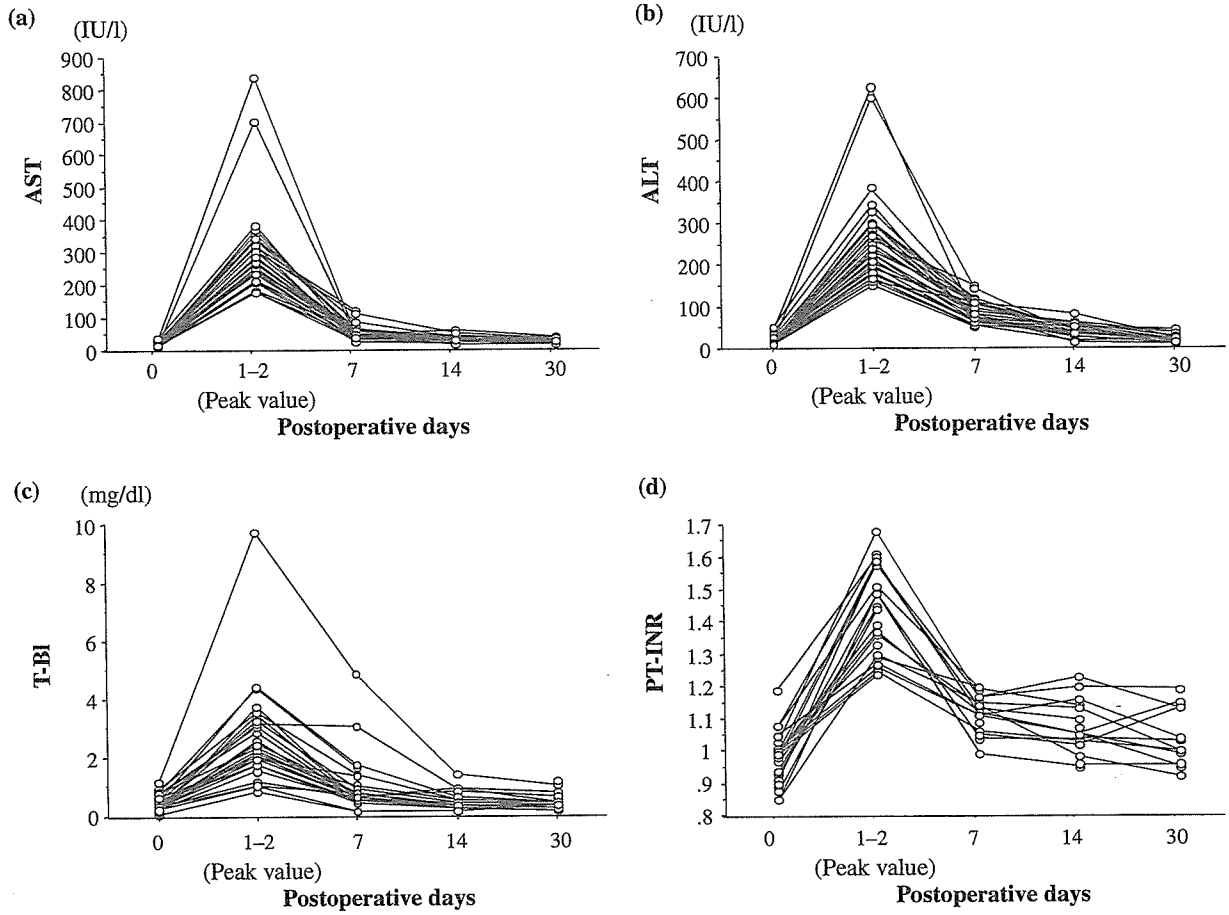

Figure 1 Changes in postoperative liver function test values. (a) Aspartate aminotransferase (AST); (b) alanine aminotransferase (ALT); (c) total bilirubin (T-Bil); (d) prothrombin time international normalized ratio (PT-INR).

Table 3. Histological degree of steatosis and postoperative liver function test values.

	Postoperative peak values (mean ± SD)			
	T-Bil (mg/dl)	AST (IU/l)	ALT (IU/l)	PT-INR
Total (n = 27)	2.74 ± 1.71	312.5 ± 146.9	270.0 ± 116.3	1.44 ± 0.14
Degree of steatosis				
None (0%) (n = 16)	2.69 ± 1.07	277.8 ± 124.4	233.1 ± 106.4	1.46 ± 0.15
Minimal (≤10%) (n = 4)	2.00 ± 0.56	282.3 ± 46.6	252.8 ± 46.2	1.42 ± 0.15
Mild (11–30%) (n = 7)	3.27 ± 2.99	423.4 ± 187.2*	364.3 ± 122.7**	1.39 ± 0.11

*P = 0.0380 versus none, **P = 0.0166 versus none.

(70.4 ± 9.2% of original TLV vs. 79.3 ± 9.6% of original TLV, P = 0.0391), and it was still lower at 180 postoperative days, but the difference was not statistically significant (73.4 ± 9.5% of original TLV vs. 84.3 ± 12.0% of original TLV, P = 0.0655).

Discussion

The LDLT was initially introduced to overcome shortage of organs for pediatric patients, and the evolution of the modality has led to right-lobe living donation for adult-to-adult liver transplantation. Furthermore, an extended right liver graft, including the trunk of middle hepatic vein, was devised by the Hong Kong group [15]. However, the safety criteria for right-lobe donation should be strict. The harvesting of the middle hepatic vein with a right-lobe graft allows an optimal venous drainage for the recipient but can also have adverse effects for the donor. The operative risk of right-lobe donation is considered higher than for donation of other types of liver grafts,

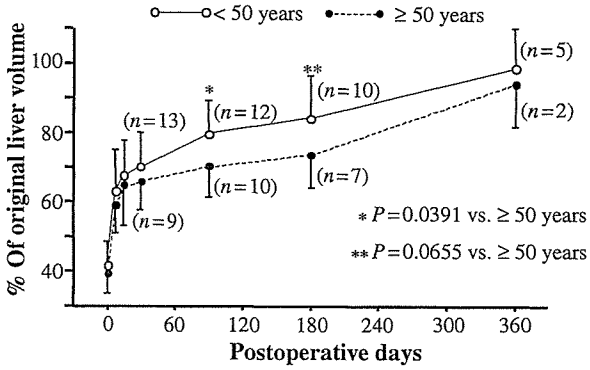

Figure 2 Changes in residual liver volume by age after right hepatectomy for living donation. The percentages of original liver volume at postoperative day 0, 7, 14, 30, 90, 180, and 360 are expressed as mean ± SD.

because the liver volume remaining in the donor is smaller. Indeed, Surman [16,17] reported that eight donor deaths had occurred worldwide after partial-liver donation. Three of these deaths had occurred in the United States, and two of the three were right-lobe donors. The mortality rate of living donors has been reported to be 0.8% in Europe [18] and 0.2% in the United States [19]. The Japanese Liver Transplantation Society reported no perioperative donor deaths among the total of 1853 living liver donors operated in 48 Japanese centers between November 13, 1989 and April 11, 2002 [20]. However, on May 4, 2003, the first death of living donor who donated the right-lobe with middle hepatic vein occurred in Japan[21], and donor safety committee of the Japanese Liver Transplantation Society made an inspection of this donor. Consequently, the donor was diagnosed as nonalcoholic steatohepatitis (NASH) and the RLV was too small (around 25% by estimation), and the committee proposed the avoidance of NASH as living donor and the volume guarantee of residual donor liver as more than 30% by estimation. Recent studies of right-lobe donors have reported morbidity rates that included minor complications of 18–40.5% [6–10], and bile leakage has been found to be more frequent in right-lobe donors than after left-sid procedures [20,22]. We instituted a LDLT program in March 2002 and have performed 27 right-lobe donations without middle hepatic vein. There was no donor who died or received heterologous blood transfusion. Four donors experienced minor postoperative complications, but all of them resolved in response to conservative treatment without any surgical intervention. In the present study, three donors who donated right-lobe with middle hepatic vein were excluded, because of small number and short postoperative follow-up periods, but all of them had uneventful postoperative course. According to the results of this, right hepatectomy without middle hepatic vein from living donors is a safe procedure with acceptable morbidity, however, living donor surgery requires greater care when the right-lobe is being donated.

In previous studies on postoperative changes in liver function test values following liver donation by living adults, the peak AST, ALT, and T-Bil values were found to be higher in right-lobe donors than left-lobe donors [22]. Moreover, the liver enzyme and T-Bil values of right-lobe donors on POD 1 have been reported to be significantly higher in older donors, donors with smaller RLV, and donors with macrovesicular steatosis of the liver [8,13]. In the present study, however, only one of these factors, steatosis of the liver, had a significant influence on the postoperative peak values of AST and ALT. Although one of the donors in our series who had mild macrovesicular steatosis of the liver had a peak postoperative T-Bil value of 9.8 mg/dl, his preoperative data, operative factors, and RLV were all within the averaged range in our series. It is well known that implantation of cadaveric livers with severe fatty infiltration (>60%) is frequently associated with early hepatic dysfunction and an increased incidence of primary nonfunction. A more recent study showed that even 30% steatosis negatively affected graft and recipient survival in cadaveric transplantation [23]. In contrast to the cadaveric grafts, Hayashi *et al.* [24] and Soejima *et al.* [25] reported that moderate (up to 50% or 60%) fatty liver grafts from living donors was followed by graft and recipient survival comparable with that obtained with normal control liver grafts because of the shorter duration of cold preservation of the graft. They also reported the absence of any specific postoperative complications in the donors related to the steatosis of the liver [24,25]. However, a retrospective study after major hepatic resection for benign or malignant liver disease showed that postoperative liver failure occurred in 9% of even the patients with no more than 30% steatosis [26]. The results of our study suggested that even mild steatosis of the liver could be a risk factor of right hepatectomy from living donors.

There have been numerous studies on the liver regeneration after hepatic resection for benign and malignant tumors, but few studies have characterized the process of liver regeneration in living donors. To the best of our knowledge, Kawasaki *et al.* [11] were the first to report on the liver regeneration in donors and recipients. They measured regeneration by CT volumetry after LDLT with a left lateral segment or left-lobe graft in a small series of four pediatric patients and their donors, and reported that the residual liver of the donors tended to grow more slowly than the grafted liver in the recipient throughout the first postoperative year. By contrast, Marcos *et al.*

[12] reported on liver regeneration in right-lobe living donors by volumetric magnetic resonance imaging. They found that the liver of most donors regenerated rapidly during the first week and had almost completely regenerated within 60 days after surgery. Moreover the time course of the liver regeneration did not differ significantly between the donors and recipients. More recent studies have reported different results. Pomfret *et al.* [10] reported that maximum growth of the residual liver occurred within 1 month after right-lobe donation, and was followed by gradual increases in volume throughout the rest of the first postoperative year, whereas the mean volume of the residual liver in the donors had increased to only 83.4% of the preoperative original volume by 1 year. Ghobrial *et al.* [6] and Pascher *et al.* [7] reported a similar time course of liver regeneration, with the liver volume of the donors reaching 80–85% of its original volume by 1 year. The time course of liver regeneration during the first 6 months after surgery in our series was similar to their findings, and the volume of the residual liver had regenerated to 97.2% of the original liver volume by 1 year after donation. The difference in our results may be attributable to the smaller number of cases at 1 year in our series. Thus, it may require at least 1 year after donation for the liver of right-lobe donors to attain its original volume.

Normal liver regeneration is a complicated process that depends on the activation of more than 100 genes and involvement by numerous growth factors, cytokines, and transcriptional factors, and the mechanisms controlling liver regeneration are not yet sufficiently understood. There has been no consensus as to factors that have a significant impact on the process of liver regeneration in right-lobe donors. Marcos *et al.* [12] reported that volume of the residual liver affects the duration of the regeneration process, with a smaller initial liver volume prolonging the course. Pomfret *et al.* [10] reported finding no effect of donor age, body mass index, operative blood loss, or perioperative liver function test values on liver regeneration, but that liver regrowth was slower in female donors than in male donors. In our study, the residual liver of the donors 50 years or older had grown significantly less at 3 months than in those under 50 years old, but gender, intraoperative blood loss, RLV, and steatosis of the liver had no influence on the rate of liver regeneration. These results may be attributable to the fact that the LDLT programs used similar donor selection criteria, which generally exclude high risk donors, i.e. older donors, donors with severe steatosis, and donors in whom the residual liver would be expected to be small.

In conclusion, our LDLT program showed that right hepatectomy without middle hepatic vein in healthy living donors is a safe procedure with acceptable morbidity and that the residual liver regenerated to its preoperative size volume by 1 year after donation. However, right-lobe living donor surgery requires more meticulous care, especially in donors with steatosis of the liver and aged donors.

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Clinical Transplantation

Impact of venous drainage on regeneration of the anterior segment of right living-related liver grafts

Mizuno S, Iida T, Yagi S, Usui M, Sakurai H, Isaji S, Uemoto S. Impact of venous drainage on regeneration of the anterior segment of right living-related liver grafts.
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Abstract: The effect of additional venous reconstruction on morphologic and functional regeneration of the anterior segment of right-lobe liver grafts was compared among three groups according to graft type: right liver graft without the middle hepatic vein (MHV) or MHV tributaries (n = 7), with MHV tributaries (n = 25) and with the MHV (n = 10). Whole graft volume (GV) and anterior segment volume (ASV) were estimated from CT scans and post-operative laboratory data and daily ascitic fluid volume were examined. Peak GV in each group was reached two or three wk after surgery. The ASV/GV ratios of the grafts with the MHV or MHV tributaries were higher than those of grafts without additional venous reconstruction. However, the asparate aminotransferase and ascitic fluid volume values in the group that received grafts with MHV tributaries were higher than in the group that received grafts with the MHV in the same period. Although rapid enlargement of the anterior segment of right-lobe grafts with MHV tributaries occurred in the early post-operative period, complete functional liver regeneration may not occur even after additional tributary reconstruction. These results suggest that the selection of right-lobe grafts with the MHV is more beneficial for recipients, as long as donor safety is protected and that as many MHV tributaries as possible should be reconstructed in right-lobe grafts without MHV.

Shugo Mizuno, Taku Iida, Shintaro Yagi, Masanobu Usui, Hiroyuki Sakurai, Shuji Isaji and Shinji Uemoto

First Department of Surgery, Mie University School of Medicine, Tsu, Mie, Japan

Key words: congestion – liver regeneration – living donor liver transplantation

Corresponding author: Shugo Mizuno, Department of Surgery, Mie University, 424-1 Mukohiro, Hisai, Mie, Japan.
Tel.: +81 59 252 1555; fax: +81 59 252 1383;
e-mail: mizuamido@mtj.biglobe.ne.jp

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Because of the critical shortage of cadaveric donor organs in Japan, living donor liver transplantation (LDLT) is performed much more frequently than cadaveric liver transplantation. Right-lobe liver grafts are now used more commonly for LDLT in adult patients and often provide an adequate graft volume (GV) for recipients (1). However, tissue congestion sometimes occurs in the anterior segment (right paramedian sector) of right-lobe grafts without the middle hepatic vein (MHV) (2, 3), and several technical modifications in terms of hepatic venous reconstruction to prevent congestion in the anterior segment have been proposed and assessed (4, 5). Moreover, it has been reported that the MHV of most donors can be safely included with living donor right-lobe grafts (6) although such grafts increase the extent of the operation in the donor, and it therefore remains a major ethical issue in LDLT (7). Faced with this situation, the aim of the present study was to evaluate the efficacy of such grafts in mitigating graft congestion using the method of additional reconstruction of drainage veins.

Materials and methods

Patients

Between March 2002 and January 2005, 54 patients underwent primary LDLT at Mie university hospital: eight received lateral segment liver grafts, four received left-lobe liver grafts and 42 received right-lobe grafts. The 42 patients who received a right-lobe graft were the subjects of this

study. After obtaining written informed consent, all patients underwent follow-up computed tomography (CT) examination. The study protocol was approved by the Medical Ethics Committee of Mie University and the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. The 42 subjects consisted of 30 men and 12 women, with a male–female ratio of 5:2, ranging in age from 20 to 68 yr (median 52 yr). Body weight ranged from 42 to 87 kg (median 61 kg). LDLT was performed to treat hepatitis C virus-related cirrhosis in 19 cases (12 of which were complicated by hepatocellular carcinoma), hepatitis B virus-related cirrhosis in six cases (four of which were complicated by hepatocellular carcinoma), cryptogenic cirrhosis in four cases (one of which was complicated by hepatocellular carcinoma), primary biliary cirrhosis in four cases, acute liver failure in three cases, alcoholic cirrhosis in three cases (one of which was complicated by hepatocellular carcinoma), primary sclerosing cholangitis in two cases (one of which was complicated by bile duct cancer) and biliary atresia in one case. ABO blood groups were identical in 33 cases, compatible in six and incompatible in three.

Donors

The donors consisted of 17 men and 25 women, and their ages ranged from 18 to 62 yr (median 39 yr). According to their relation to the patient, they comprised 17 children, 16 spouses, four siblings, two cousins, one parent, one nephew and one grandson. Right-lobe liver volume was pre-operatively estimated by CT scans. The policy was to select right-lobe grafts with the MHV, as long as donor safety is protected, and to reconstruct as many MHV tributaries as possible. Candidate donors whose right lobe liver comprised more than 70% of their whole liver volume were rejected as prospective donors. An estimated graft-to-recipient weight ratio (GRWR) of 0.8 was the lower limit for right-lobe liver transplantation. Extended right liver harvesting was indicated when the remnant left liver was estimated to be more than 35% of the whole liver and there were no major MHV tributaries draining the left hepatic lobe. Otherwise, right liver harvesting without the MHV trunk was indicated. All MHV tributaries that measured more than 7 mm in diameter were reconstructed with interpositional vascular grafts harvested from the recipients' left portal, inferior mesenteric, umbilical, paraumbilical, left external jugular and left external iliac veins, and the donors' ovarian veins. When umbilical veins were used as interpositional vein grafts, they were first recanalized by opening the obliterated lumen, because they do not possess an endothelium. All MHV tributaries larger than 7 mm were reconstructed because we occasionally could not easily reconstruct 5 mm MHV tributaries, though there are many centers in which all MHV tributaries of more than 5 mm are reconstructed. The sizable right inferior hepatic vein (RIHV; > 5 mm) was preserved with a caval cuff for reconstruction. The 42 subjects were divided into three groups according to graft type: a group that received a right-lobe graft without reconstruction of the segmental hepatic vein tributaries draining into the MHV (group I: n = 7), a group that received a right-lobe graft with reconstruction of the segmental hepatic vein tributaries draining into the MHV using interpositional vein grafts (group II: n = 25), and a group that received an extended right-lobe graft with reconstruction of the MHV (group III: n = 10).

Operative procedure

The right portal vein was routinely anastomosed to the trunk of the recipient's portal vein end-to-end. Autogenous vein grafts for interposition were harvested from the recipient or donor and the interpositional vein grafts were anastomosed to the MHV tributaries at the bench. The anastomoses between the graft veins and inferior vena cava (IVC) were created end-to-side with 5–0 or 6–0 prolene stitches as described previously (8). The right hepatic vein (RHV) anastomoses were performed by incising the IVC at the caudal corner of the RHV orifice and removing a piece of the anterior IVC wall to make the orifice oval shaped. A new hole was created in the IVC wall for the anastomoses of the MHV tributaries. Significant RIHV was anastomosed to the sidewall of the IVC. Reconstruction of the hepatic arteries was performed by end-to-end anastomosis under a surgical microscope. The bile duct was reconstructed by duct-to-duct anastomosis in 39 of the patients and hepaticojejunostomy was performed in the three patients with primary sclerosing cholesistitis or biliary atresia.

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids. The target trough level for tacrolimus in whole blood was 10–15 ng/mL during the first two wk, approximately 10 ng/mL during the next two wk and 5–10 ng/mL thereafter. Methylprednisolone, 10 mg/kg body weight intravenously was administered immediately before perfusion of the graft portal vein followed by a dose of 1 mg/kg

intravenously on post-operative days (PODs) 1–3 and then 0.5 mg/kg/d on PODs 4–6. A switch was made to oral prednisolone, 0.5 mg/kg/d on POD 7, and the dose was reduced to 0.1 mg/kg/d at one month. If the patient's liver function was stable, the patient was weaned off steroids at around 3–6 months post-operatively.

Post-operative evaluation

Total bilirubin (T-bil) and asparate aminotransferase (AST) levels were measured daily for two wk after LDLT. Ascitic fluid volume was estimated daily for one month as the amount of fluid discharged from a closed suction drain that was placed into the abdominal cavity. Vascular flow in the graft and interposition vein patency were monitored daily by Doppler ultrasonography until POD 14, and weekly thereafter until discharge from the hospital. Interpositional graft patency in group II was estimated by Doppler ultrasonography three wk after LDLT.

Volumetric computed tomography of the liver graft

Helical CT studies were conducted with a High-Speed Advantage QX-1 Scanner (GE Medical Systems, Tokyo, Japan). The scanning parameters were 120 kV, 200 mA, collimation 5 mm and a table speed of 15 mm per rotation, with reconstruction increments of 5 mm. GV and anterior segment volume (ASV) in the recipients were calculated by volumetric CT approximately 1, 2, 3 wk, 1, 3, 6 months and 1 yr after LDLT. Standard liver volume (SLV) was calculated according to the formula proposed by Urata et al. (9).

Statistical analyses

All statistical calculations were carried out using StatView-J 5.0 statistical software (SAS Institute, Cary, NC, USA). Values were reported as means ± standard deviation, unless stated otherwise. Discontinuous data were analyzed by Mann–Whitney tests, continuous data by Student's *t*-test, categorical data by chi-squared tests and Kaplan–Meier survival curves by Cox–Mantel tests. All p-values less than 0.05 were considered statistically significant.

Results

Morbidity and mortality

No patients in group I died after LDLT. Seven patients in group II and one patient in group III died after LDLT, although all had been free of vascular complications. The one-yr survival rate was 100% in group I, 72.0% in group II and 85.7% in group III, and there were no statistical differences among the three groups. The causes of death of the seven patients in group II consisted of deep fungal infection (n = 2) on POD 56 and 76, respectively, sepsis (n = 1) on POD 9, severe acute rejection due to ABO incompatibility (n = 1) on POD 54 and unforeseen complications (i.e. cerebral hemorrhage; n = 1) on POD 41 and multiple organ failure secondary to hemorrhagic shock caused by rupture of a splenic aneurysm (n = 1) on POD 62. The cause of the one death in group III on POD 242 was recurrence of bile duct cancer (n = 1).

Intra-abdominal hemorrhage developed in one case in group I, four cases in group II and one case in group III, and occurred on POD 1 in two cases and on POD 2 in the other four cases. Biliary anastomotic stenosis developed in one case each in group I and group II. One was managed successfully by percutaneous transhepatic balloon dilatation on POD 89 and the other was treated by hepaticojejunostomy on POD 278. Biliary leakage developed in two cases in group II, and percutaneous drainage on POD 17 and POD 13, respectively, was followed by recovery. There was one case of stenosis of the hepatic artery anastomosis and it was successfully managed by balloon dilatation on POD 6.

The RIHV was reconstructed in 16 patients (38.1%; two patients in group I, 10 patients in group II and four patients in group III). All patients had a patent RIHV anastomosis confirmed by routine Doppler ultrasonography and/or CT at least a month after LDLT. Stenosis of the hepatic venous anastomosis of the graft developed in one case on POD 13 and stenosis of the IVC developed in two cases, on POD 9 and 18; all were successfully treated by stent placement, which prevented any progression of graft dysfunction (10).

Since the focus of the study was on liver regeneration and reconstruction of the hepatic vein in LDLT patients, eight patients who died after LDLT and three who experienced outflow block were excluded from the study below.

Table 1 shows the pre-operative and intra-operative characteristics of the recipients in each of the three groups. Recipient age, gender, Child–Pugh score and Model for End-Stage Liver Disease (MELD) score at the time of LDLT were similar in all three groups. There were no significant differences among the three groups in operation time, blood loss, graft weight or GRWR. The number of cases with more than 1.2% GRWR was two in

Table 1. Patient background

	Group I (n = 6)	Group II (n = 18)	Group III (n = 10)
Age (yr)	56.7 ± 10.6	50.9 ± 11.6	51.9 ± 11.6
Male/female	5/2	18/7	7/3
Child-Pugh score	9.1 ± 3.5	9.8 ± 2.4	10.2 ± 2.8
MELD score	13.1 ± 10.1	16.2 ± 7.7	14.9 ± 8.9
Operation time (min)	824 ± 179	900 ± 227	879 ± 142
Cold ischemic time (min)	55.4 ± 32*	101.6 ± 38.8*	69.0 ± 48.5
Warm ischemic time (min)	40.8 ± 15.9	45.5 ± 15.4	51.0 ± 10.7
Blood loss (mL)	7830 ± 4354	9782 ± 3279	7382 ± 4526
Graft weight (g)	663 ± 103	652 ± 128	669 ± 142
GRWR	1.13 ± 0.19	1.07 ± 0.26	1.09 ± 0.24
GV/SLV at transplantation (%)	0.633 ± 0.125	0.567 ± 0.199	0.618 ± 0.157
Steatosis (%)	16.7	22.2	10.0

GRWR, graft-to-recipient weight ratio; GV, graft liver; SLV, standard liver volume; steatosis, mild (<30%) or moderate (<60%) macrovesicular steatosis; MELD, Model for End-Stage Liver Disease.
*$p < 0.05$.

group I and one in groups II and III, with no significant differences among the three groups. The only significant difference was the variation in cold ischemic time between group I and group II ($p = 0.015$), but there were no significant differences between group II and group III ($p = 0.062$). There were also no significant differences among the three groups with regard to the etiology of the patients' liver disease. Groups II and III did not show significant differences in any of these clinical parameters.

Patency of the interpositional venous graft

The number of reconstructed MHV tributaries per patient ranged from one to three (Table 2). Multiple V5 or V8 tributaries were reconstructed in 18 (75%) of the 24 right liver grafts without the MHV. The patency of the interpositional venous grafts is shown in Table 3 and 21 (84%) of the 25 reconstructed venous grafts were patent at three months after LDLT. The rate of umbilical vein patency was low, but there were no significant differences in rates of patency associated with the type of venous graft performed.

Table 2. Details of the interpositional vein grafts in group II

Number of V5 veins reconstructed	Number of V8 veins reconstructed	Number of patients
1	0	5
0	1	7
1	1	3
2	0	2
2	1	1

Table 3. Patency of the interpositional venous grafts

Venous graft	Patency (%)
Recipient's left portal vein	7/8 (87.5)
Donor's ovarian vein	4/5 (80)
Recipient's inferior mesenteric	4/4(100)
Recipient's paraumbilical vein	3/3 (100)
Recipient's umbilical vein	2/3 (66.7)
Recipient's left external jugular vein	0/1 (0)
Recipient's left external iliac vein	1/1 (100)

Liver regeneration after LDLT

The changes in the GV/SLV ratio during the year after LDLT are shown in Fig. 1. GV/SLV rapidly reached 1.0 by one wk after LDLT in every group and it remained over 1.0 for the first month. The peak GV/SLV in each group was observed two or three wk after LDLT, and in group II GV/SLV reached 1.2 at two wk after LDLT. However, the differences among the three groups were not significant. Changes in the ASV/SLV ratio during the year after LDLT are shown in Fig. 2. There were no significant differences among the three groups before LDLT. ASV/SLV was significantly higher in group II than in group I at both one and two wk after LDLT (group I/group II at 1 wk: 0.485 ± 0.074/0.621 ± 0.086, $p = 0.0022$; and at 2 wk: 0.528 ± 0.071/0.642 ± 0.085, $p = 0.0074$). ASV/GV in group III was significantly higher than in group I for three wk (group I/group III at 1 wk: 0.485 ± 0.074/0.603 ± 0.077, $p = 0.0094$; 2 wk: 0.528 ± 0.071/0.638 ± 0.075, $p = 0.0118$; and 3 wk: 0.496 ± 0.081/0.639 ± 0.085, $p = 0.0051$). The changes in ASV/GV ratio during the year after LDLT are shown in Fig. 3. The ASV/GV ratio in group I was below 0.5 for the entire year. However, the ratios in groups II and III were 0.5 or higher. ASV/GV was significantly higher in group II than in group I at both one and two wk after LDLT (group I/group II at 1 wk: 0.431 ± 0.065/0.534 ± 0.071, $p = 0.0048$; and at 2 wk: 0.453 ± 0.046/0.529 ± 0.057, $p = 0.0073$). ASV/GV in group III was significantly higher than in group I for three wk (group I/group III at 1 wk: 0.431 ± 0.065/0.518 ± 0.045, $p = 0.0067$; 2 wk: 0.453 ± 0.046/0.534 ± 0.054, $p = 0.0085$; and 3 wk: 0.472 ± 0.042/0.544 ± 0.053, $p = 0.0135$).

Laboratory data

In all groups, AST and T-bil peaked on POD 1 and gradually decreased thereafter (Figs. 4 and 5). Fig. 3 shows that the serum AST levels in group III were significantly lower than in group II on PODs 1 and 3 (group II/group III on POD 1:

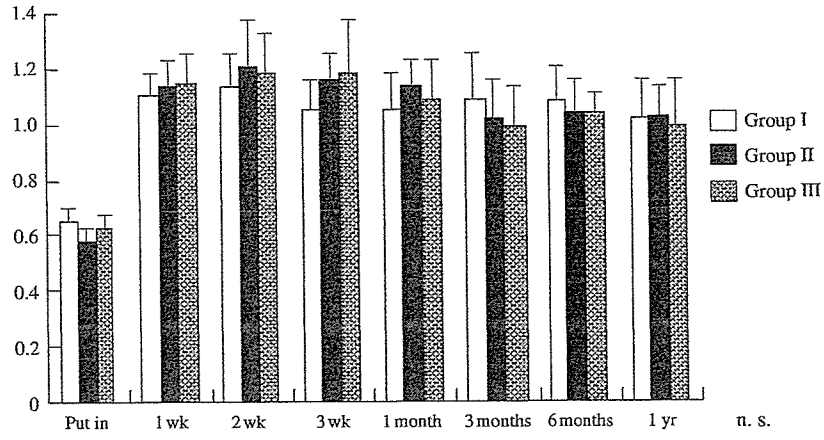

Fig. 1. The changes in GV/SLV during the first year after LDLT. There were no significant differences among the three groups. GV, graft volume; SLV, standard liver volume; LDLT, living donor liver transplantation; wk, week; mo, month; yr, year.

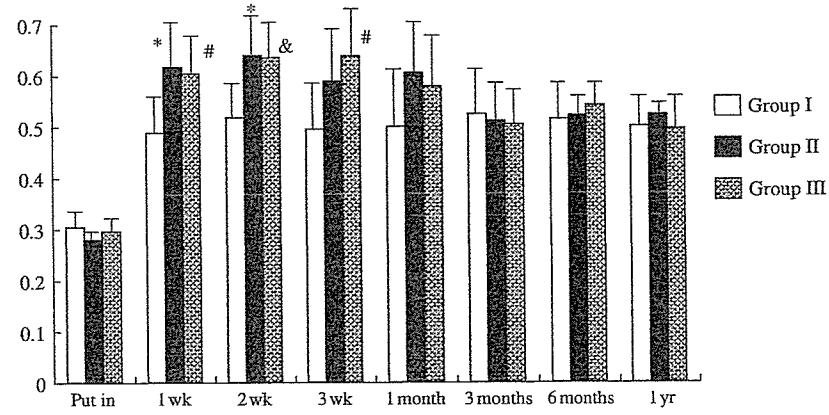

Fig. 2. The changes in ASV/GV during the first year after LDLT. There were significant differences between group I and group II at one and two wk, $^{*}p < 0.001$. There were significant differences between group I and group III at one and two wk, $^{\#}p < 0.001$ and at three wk, $^{\&}p < 0.05$. ASV, anterior segment volume; GV, graft volume; LDLT, living donor liver transplantation.

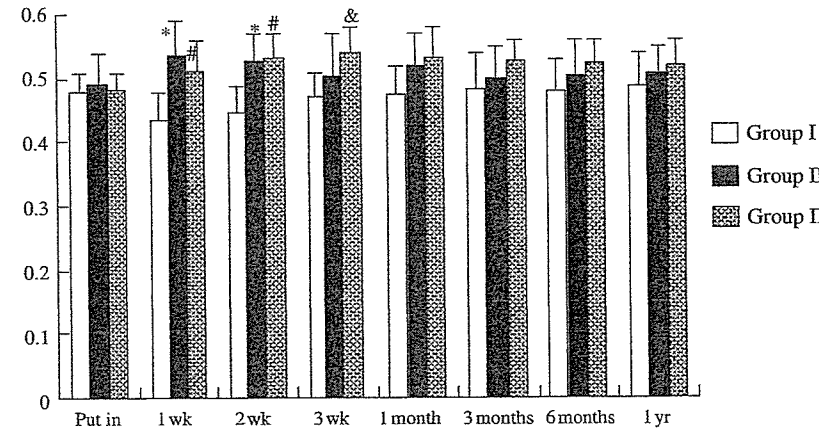

Fig. 3. The changes in ASV/GV during the year after LDLT. There were significant differences between group I and group II at one and two wk, $^{*}p < 0.001$. There were significant differences between group I and group III at one and two wk, $^{\#}p < 0.001$ and at three wk, $^{\&}p < 0.05$. ASV, anterior segment volume; GV, graft volume; LDLT, living donor liver transplantation.

307.6 ± 192.1/165.8 ± 109.5 IU/L, $p = 0.042$ and on POD 3: 207.2 ± 141.1/108.1 ± 67.9 IU/L, $p = 0.048$). There were no significant differences among the three groups in the level of serum T-bil (Fig. 4).

Daily ascitic fluid volume

In all groups, the daily ascitic volume peaked on POD 1 and gradually decreased thereafter (Fig. 6). The daily ascitic fluid volume in group III was significantly lower than in group II on both POD 3 and POD 5 (group II/group III at POD 3: 1389 ± 764/843 ± 402 mL, $p = 0.046$; and POD 5: 1268 ± 652/753 ± 434 mL, $p = 0.035$).

Discussion

There have been few reports concerning congestion of the anterior segment of the right graft liver after

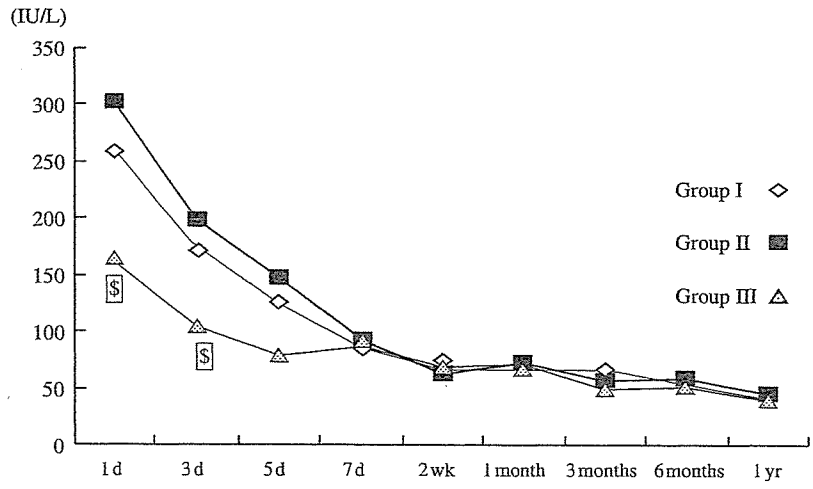

Fig. 4. The course of serum AST level during the year after LDLT. There were significant differences between group II and group III at one and three d, $^{\$}p < 0.05$. AST, asparate aminotransferase; LDLT, living donor liver transplantation.

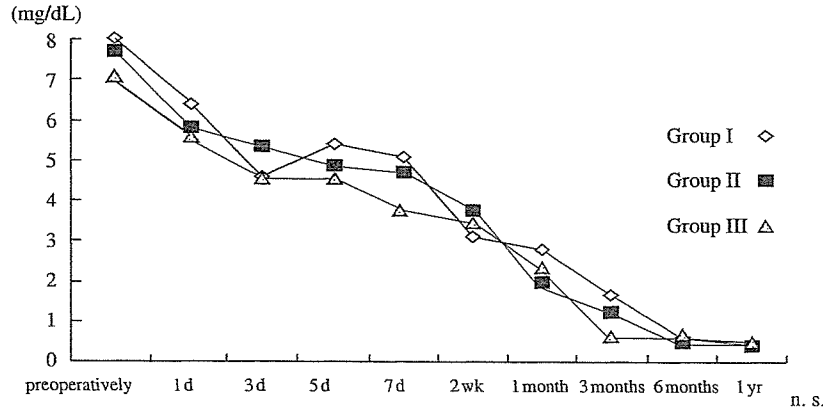

Fig. 5. The course of serum T-bil level during the year after LDLT. There were no significant differences among the three groups. T-bil, total bilirubin.

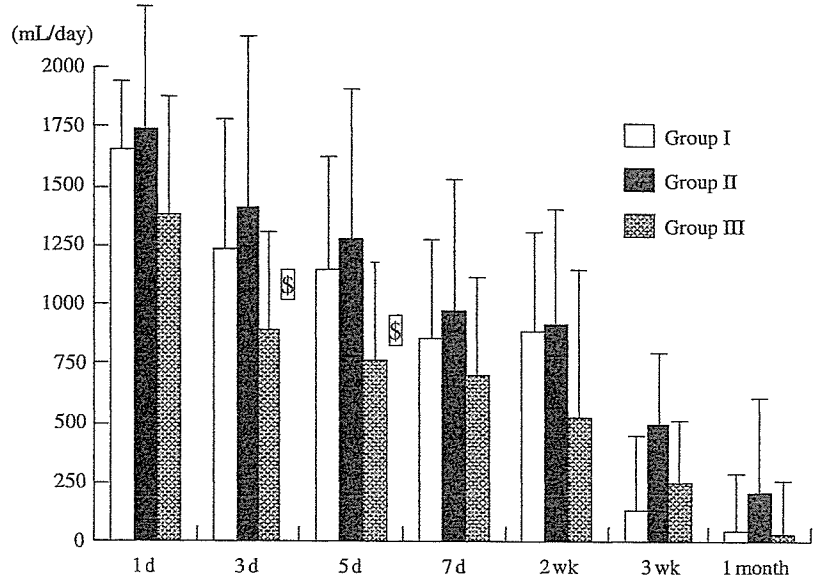

Fig. 6. The changes in daily ascitic fluid volume during the month after LDLT. There were significant differences between group II and group III at three and five d, $^{\$}p < 0.05$. LDLT, living donor liver transplantation.

LDLT (11, 12). Akamatsu et al. (11) estimated from CT scans that the regeneration rate of the right paramedian sector was lowest in right liver grafts without MHV trunk or MHV reconstruction, and it has been suggested that tissue congestion in grafts without the MHV was not completely

eradicated by additional reconstruction of V5/V8 as estimated by magnetic resonance imaging (12).

In the early post-operative period of this study, from one to three wk after LDLT, the ASV/GV ratios in liver grafts with MHV or MHV tributary reconstruction were significantly higher than in those without MHV or MHV tributary reconstruction. The GV in all three groups also peaked in this period, but there were no significant differences among the three groups. In addition, from one to three wk after LDLT, comparison of the changes in ASV/SLV with those in GV/SLV showed more proportionate increases in the posterior segment volume of the graft in group I than in group II or III. On the other hand, the laboratory values and daily ascitic fluid volume of the patients who had received right-lobe grafts with MHV tributary reconstruction were higher than in the patients who had received right-lobe grafts with the MHV. Although this study was not a randomized trial since patients were essentially pre-determined to be in one group or another based on donor venous anatomy, there is a discrepancy in the results because an increase of liver GV was thought to be equal to the improvement of the graft function and regeneration of the graft liver after LDLT. These results also appear to show that the right-lobe grafts with additional reconstruction of MHV tributaries do not completely reduce tissue congestion and the increase in liver GV as estimated from CT scans does not necessarily indicate regeneration of the liver graft. One explanation for these observations may be related to the latent occurrence of tissue congestion in the anterior segment as a result of the ligation of many tiny venous branches to the MHV and the possibility that latent congestion impairs the functional capacity of grafts (3).

It is very important to select an adequate type right-lobe graft with or without the MHV or MHV tributaries. However, the policy for selection of graft type varies with the institution. Our policy has been, after accounting for donor safety, to select right-lobe grafts with the MHV and to reconstruct as many MHV tributaries as possible. More specifically, we consider extended right liver harvesting to be indicated when it is estimated that the remnant left liver will consist of more than 35% of the whole liver and there are no major MHV tributaries draining the left hepatic lobe. Otherwise, right liver harvesting without the MHV trunk was indicated and we reconstructed all MHV tributaries that measured more than 7 mm in diameter with interpositional vascular grafts, although we cannot precisely examine the volume of the graft drained by the MHV. Kasahara et al. (13) used pre-operative CT volumetry and computer-assisted volumetric analysis based on the hepatic venous anatomy to evaluate the need for application of a right lobe with MHV graft. On the other hand, Sano et al. (14) emphasized that intraoperative ultrasonography with vessel clamping was a useful indicator when deciding whether to reconstruct MHV tributaries. This method has been commonly used because it enables identification of the area of tissue congestion of each tributary. Therefore, if we had decided to reconstruct the MHV tributaries using this method, the results might have been slightly different from those of this study. Ito et al. (12) reported that when marginal grafts were encountered in marginal recipients (e.g. small-for-size grafts, older grafts, steatotic grafts or grafts with a smaller RHV than MHV), an effort should be made to harvest grafts with the MHV attached rather than just tributaries.

As for the vein graft, there are several reports about other kinds of vein grafts that we have not attempted. Lee et al. (15) reported a good result of reconstruction of MHV drainage tributaries of the anterior segment using the great saphenous vein. Sugawara et al. (16) suggested that venous reconstruction using cryopreserved veins, such as the vena cava or iliac vein, seemed to be technically feasible for outflow reconstruction in a right liver graft. We might use the saphenous vein graft if we have a chance to do so, though we never have because the diameter seemed too small for reconstruction. Indeed, venous reconstruction using cryopreserved veins might be the best way to keep outflow and make the reconstruction technically simple. Unfortunately, we do not have access to cryopreserved veins. In addition, we used various kinds of venous grafts in this study, but the number of each graft was low, preventing an assessment of the quality of each type of vascular interposition graft.

There were no cases of graft loss that were directly due to graft congestion in this series, even among the patients who received right-lobe grafts without MHV or MHV tributaries. However, stenosis of the hepatic venous anastomosis developed in one case and stenosis of the IVC developed in two cases. All three of them were successfully treated by stent placement. All these complications due to venous reconstruction occurred in right-lobe grafts with MHV tributary reconstruction. The pathogenesis of IVC stenosis may be due to narrowing caused by the multiple anastomoses of major hepatic tributaries to the cut surface of the graft and compression due to hypertrophy of the grafted liver (10). Sugawara et al. (17) reported

that if reconstruction of MHV tributaries is necessary, they anastomose the MHV tributaries to the stump of the recipient's MHV or left hepatic vein; the harvested venous grafts can reach to the MHV or LHV stump of the recipients without tension. These methods enable the formation of a single orifice of the multiple reconstructed MHV tributaries instead of making numerous anastomoses to the IVC. Also, right grafts with MHV tributaries appeared to be accompanied by more bleeding and operation time than those without MHV or MHV tributaries, although the only statistically significant difference between the two groups involved cold ischemic time. Indeed the right grafts with MHV tributaries were not so simple, but those reconstructions made the outflow from the grafts increase. On the other hand, the right-lobe grafts without MHV tributary reconstruction selected on the basis of our indication did not have large MHV tributaries, and thus they would not have developed a large area of congestion if the MHV tributaries had not been reconstructed. In other words, all types of right liver grafts selected based on our policy prevented graft congestion, and that improved morbidity and mortality. In terms of liver function and ascitic fluid volume, latent graft congestion may occur in the early post-operative period in right-lobe grafts with or without MHV tributary reconstruction. However, it gradually improves after a few months. The reason for the improvement may have been the effectiveness of certain salvage mechanisms, including intrahepatic anastomosis between the MHV and the RHV (18, 19). However, if right-lobe graft without the MHV were used in cases with small for-size graft, steatosis liver graft or old-aged liver graft, there might be a detrimental impact on graft survival.

In conclusion, satisfactory outcome in our series was independent of the type of graft used. Although the anterior segment of right-lobe grafts with MHV tributaries rapidly enlarges in the early post-operative period, complete functional liver regeneration may not occur even when additional reconstruction of MHV tributaries is performed. These results suggest that as long as the health of the donor is not compromised, it is in the best interest of the recipients to select right-lobe grafts with the MHV and to reconstruct as many MHV tributaries as possible in right-lobe grafts without MHV.

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Impact of Portal Venous Pressure on Regeneration and Graft Damage after Living-Donor Liver Transplantation

Shintaro Yagi, Taku Iida, Kentaro Taniguchi, Tomohide Hori, Takashi Hamada, Koji Fujii, Shugo Mizuno, and Shinji Uemoto

Several reports claim that portal hypertension after living-donor liver transplantation (LDLT) adversely affects graft function, but few have assessed the impact of portal venous pressure (PVP) on graft regeneration. We divided 32 adult LDLT recipients based on mean PVP during the 1st 3 days after LDLT into a group with a PVP ≥ 20 mm of Hg (H Group; n = 17), and a group with a PVP < 20 mm of Hg (L Group; n = 15). Outcome in the H Group was poorer than in the L Group (58.8 vs. 92.9% at 1 year). Peak peripheral hepatocyte growth factor (HGF) during the 1st 2 weeks was higher in the H Group (L: 1,730 pg/mL, H: 3,696 pg/mL; $P < .01$), whereas peak portal vascular endothelial growth factor (VEGF) level during the 1st week was higher in the L Group (L: 433 pg/mL, H: 92 pg/mL; $P < .05$). Graft volume (GV) / standard liver volume (SLV) was higher in the H Group (L / H, at 2, 3, and 4 weeks, and at 3 months: 1.02 / 1.24, .916 / 1.16, .98 / 1.27, and .94 / 1.29, respectively; $P < .05$). Peak serum aspartate aminotransferase, bilirubin levels, and international normalized ratio after LDLT were significantly higher in the H Group, as was mean ascitic fluid volume. In conclusion, early postoperative PVP elevation to 20 mm of Hg or more was associated with rapid graft hypertrophy, higher peripheral blood HGF levels, and lower portal VEGF levels; and with a poor outcome, graft dysfunction with hyperbilirubinemia, coagulopathy, and severe ascites. Adequate liver regeneration requires an adequate increase in portal venous pressure and flow reflected by clearance of HGF and elevated VEGF levels. (*Liver Transpl 2005;11:68–75.*)

Because of the shortage of deceased donor liver grafts, demand for living-donor liver transplantation (LDLT) has been increasing worldwide. Although grafts regenerate quickly after LDLT, the prognosis for recipients of transplanted small-for-size grafts is poor.[1] Since elevation of portal venous pressure (PVP) was thought to trigger liver regeneration after hepatectomy[2,3] and portal vein embolization,[4] we have deliberately increased the portal venous flow and PVP after liver transplantation. However, recently Boillot et al.[5] reported a case in which a recipient transplanted with a small-for-size graft was successfully treated by breaking down PVP with a mesocaval shunt. Several subsequent reports have claimed that portal hypertension after LDLT adversely affects graft function and the graft survival rate;[6–14] however, since few studies have assessed the impact of PVP on liver regeneration after LDLT, we retrospectively investigated its impact on graft regeneration and damage in adult recipients.

Patients and Methods

Patients

Between March 2002 and February 2004, 32 adult patients underwent LDLT in our institution. After obtaining written informed consent, all patients underwent follow-up computed tomography, and regeneration factors were measured in peripheral and portal venous blood specimens. The study protocol was approved by the Medical Ethics Committee of Mie University, and the study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki. The patients ranged in age from 20 to 68 years (median: 53 years), and the male-female ratio was 21 : 11. Body weight ranged from 42 to 87 kg (median: 60 kg). The reasons for LDLT were: hepatitis C virus–related cirrhosis in 16 cases (11 of which were complicated by hepatocellular carcinoma); hepatitis B virus–related cirrhosis in 4 (3 of which were complicated by hepatocellular carcinoma); alcoholic cirrhosis in 3 (2 of which were complicated by hepatocellular carcinoma); primary biliary cirrhosis in 5; acute liver failure in 2; and primary sclerosing cholangitis in 2. Grafts were: a right lobe graft in 27 cases, a left lobe graft in 1, and a right lobe with middle hepatic vein graft in 4. ABO blood group compatibility was identical in 26 cases, compatible in 5, and incompatible in 1.

Basically, the right hepatic vein or common trunk of the left and middle hepatic veins were anastomosed to the inferior vena cava in an end-to-side fashion, as described elsewhere.[15,16] The middle hepatic vein in the right lobe graft was anastomosed to the inferior vena cava or middle hepatic vein of the recipient using an autologous venous graft. Drainage

Abbreviations: LDLT, living-donor liver transplantation; PVP, portal venous pressure; GV, graft volume; SLV, standard liver volume; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; LSEC, liver sinusoidal endothelial cell; POD, postoperative days.

From the First Department of Surgery, Mie University School of Medicine, Tsu City, Mie Prefecture, Japan.

Address reprint requests to Shintaro Yagi, MD, First Department of Surgery, Mie University School of Medicine, 2-174, Edobashi, Tsu City, Mie Prefecture, 514-8507, Japan. Telephone: 81-59-232-1111; FAX: 81-59-232-8095; E-mail: shintaro@clin.medic.mie-u.ac.jp

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veins from segment V or VIII in the liver graft were anastomosed to the inferior vena cava using autologous venous grafts when the diameter of those drainage veins was more than 7 mm. Reconstruction of the hepatic arteries was performed with end-to-end anastomosis using a surgical microscope. The bile duct was reconstructed with duct-to-duct anastomosis in 30 patients; hepaticojejunostomy was used in the 2 patients with primary sclerosing cholangitis.

Immunosuppression

The immunosuppression protocol consisted of tacrolimus and low-dose steroids. The target trough level for tacrolimus in whole blood was 10–15 ng/mL during the 1st 2 weeks, approximately 10 ng/mL during next 2 weeks, and 5–10 ng/mL thereafter. Methylprednisolone, 10 mg/kg of body weight, was administered intravenously immediately before perfusion of the graft portal vein. Methylprednisolone, 1 mg/kg intravenously, was given on postoperative days (PODs) 1–3, followed by .5 mg/kg per day on PODs 4–6. The steroid was then switched to oral prednisolone .5 mg/kg per day on POD 7, and the dose reduced to .1 mg/kg per day at 1 month. If a patient's liver function was stable, they were weaned off steroids at around 3–6 months postoperatively.

Monitoring of PVP

A 16-gauge antithrombotic catheter (Medicut UK-LCV Kit; Nippon Sherwood Medical Industries, Tokyo, Japan) was inserted via the inferior mesenteric vein before the recipient's liver was removed. The tip of the catheter was positioned in the recipient's portal vein or splenic vein and fixed in place by ligation and 2 rubber bands. The other end was drawn outside the body via the surgical wound as described elsewhere.[7] A transducer was used to continuously monitor PVP during the operation and while patients were in the intensive care unit. We divided the 32 recipients into 2 groups based on their mean PVP during the 1st 3 days after LDLT: a higher PVP group, with PVP $\geq$ 20 mm of Hg (H Group; n = 17), and a lower PVP group, with PVP < 20 mm of Hg (L Group; n = 15). We removed the catheter on the ward 7 days after LDLT. If systemic infection related to catheterization was suspected, we withdrew it immediately.

Computed Tomography Volumetry of Liver Graft

Helical computed tomography studies were conducted with a High Speed Advantage QX-I (GE Medical Systems, Tokyo, Japan). The scanning parameters were 120 kV, 200 mA, collimation 5 mm, and a table speed of 15 mm/rotation, with reconstruction increments of 5 mm. Contrast-enhanced images were not acquired after LDLT in all patients. Graft volume (GV) was calculated with volumetric computed tomography for recipients approximately 1, 2, 3, and 4 weeks, and 3 and 6 months after LDLT. The standard liver volume (SLV) was calculated according to the formula as described by Urata et al.[17]

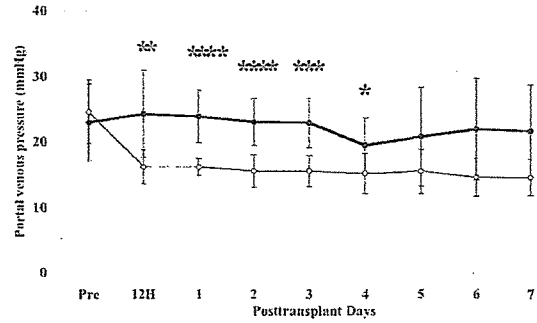

Figure 1. Serial changes of portal venous pressure of both groups. Open circles and closed circles represent GV / SLV of L Group and H Group, respectively. *P < .05 vs. L Group; **P < .0005 vs. L Group; ***P < .000005 vs. L Group; ****P < .0000005 vs. L Group. Abbreviations: H, hours; Pre, pretransplantation; GV, graft volume; SLV, standard liver volume.

Measurement of Serum Transaminases, Bilirubin, International Normalized Ratio, Hepatocyte Growth Factor, and Vascular Endothelial Growth Factor

Serum aspartate aminotransferase, alanine transaminase, bilirubin, and international normalized ratio were measured daily, and blood samples were obtained from a peripheral vein at 6 and 12 hours, and 1, 3, 5, 7, and 14 days after portal reperfusion. Portal venous blood was collected from the portal vein catheter 6 and 12 hours, and 1, 3, 5, and 7 days after portal reperfusion. Samples were collected into a serum separator tube and centrifuged for 10 minutes at 3,000*g*, and serum was stored at −80°C until assayed. Hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) concentrations were measured with HGF and VEGF enzyme-linked immunosorbent assay (ELISA kit; R&D Systems, Minneapolis, MN) according to the manufacturer's instructions.

Statistical Analyses

All statistical calculations were carried out using StatView-J 5.0 statistical software (SAS Institute, Cary, NC). Values are presented as mean ± standard deviation unless stated otherwise. Discontinuous data were analyzed by Mann-Whitney tests, continuous data by Student's *t*-test, categorical data by chi-squared tests, and Kaplan-Mayer survival curves by Cox-Mantel tests. P values < .05 were considered statistically significant.

Results

Changes in mean PVP in both groups during the week after LDLT are shown in Figure 1. PVP was significantly higher during the 1st 4 days after the operation in the H Group. Mean PVP during the 3 days after LDLT