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LIVER REGENERATION AND SURGICAL OUTCOME IN DONORS OF RIGHT-LOBE LIVER GRAFTS

ELIZABETH A. POMFRET,[1,4] JAMES J. POMPOSELLI,[1] FREDRIC D. GORDON,[1] NAZLI ERBAY,[2] LORI LYN PRICE,[3] W. DAVID LEWIS,[1] AND ROGER L. JENKINS[1]

Introduction. **Previous studies of healthy live-liver donors have suggested that complete liver regeneration occurs within a matter of weeks; however, there have been no long-term studies evaluating liver regeneration and few studies documenting long-term donor outcome.**

Materials and Methods. **Fifty-one donors who provided right-lobe grafts underwent volumetric spiral computed tomography scans preoperatively and postoperatively at time intervals of 1 week and 1, 3, 6, and 12 months. Patient demographics, surgical data, and postoperative outcome were correlated with liver regeneration data. Donor surgical outcome was followed prospectively and recorded in a comprehensive database.**

Results. **Thirty-three males and 18 females (mean age 36.0±9.6 years) provided 51 right-lobe grafts. Mean follow-up was 9.8±3.4 months. No donor operation was aborted, and surgical morbidity and mortality rates were 39% and 0%, respectively. Donor remnant liver volume was 49.4±5.7% of the original total liver volume (TLV). Overall liver regeneration was 83.3±9.0% of the TLV by 1 year. Female donors had significantly slower liver regrowth when compared with males at 12 months (79.8±9.3% vs. 85.6±8.2%, $P<0.01$). There was no effect of age, body mass index, operative time, estimated blood loss, postoperative complications, or perioperative liver function tests on liver regeneration.**

Discussion. **Liver regeneration continues throughout the first postoperative year. Only one donor achieved complete liver regeneration during this time period; however, all donors have maintained normal liver function without long-term complications. Longer follow-up is needed to determine whether donors ever achieve original TLV.**

Donor safety and surgical outcome has been a critical issue and is currently being debated in medical, surgical, ethical, and public communities (*1–5*). Most authors agree that a comprehensive database containing the surgical outcome of all live donors and recipients of live-donor adult liver transplantation (LDALT) is needed. Proper recording and reporting of the physiologic responses and postoperative complications of donors provides the best opportunity to ensure adequate informed consent. Hopefully, such reporting may help allay public fears regarding inadequate information. Published donor complication rates differ widely between programs because standardized reporting of surgical outcome does not currently exist (*6–9*).

Previous studies have suggested that complete liver regeneration occurs within a matter of weeks in the live-liver donor, although no long-term studies are available (*10–12*). In addition, there is a paucity of reports looking specifically at donor surgical outcome. In this report, we have analyzed the outcome of 51 live-liver donors who have undergone right hepatectomy.

PATIENTS AND METHODS

Donor Selection

Between December 1998 and February 2002, a single surgical team performed 51 LDALT using right-lobe grafts from healthy donors. One hundred sixty-four potential donors, between 18 and 55 years of age, sharing either a genetic or a significant "emotional" relationship with the recipient, were evaluated. No "Good Samaritan" liver donors were considered for evaluation.

The donor evaluation protocol followed at the Lahey Clinic Medical Center has been previously published (*6*, *13*). Briefly, a multidisciplinary screening committee composed of representatives from internal medicine, transplant surgery, anesthesia, blood bank, nursing, social work, psychiatry, and ethics meet weekly to review each potential donor's candidacy. The screening committee reviewed all data to determine the suitability of the donor-recipient pair as candidates for LDALT. Evaluation of recipient risk is also factored into the decision to proceed with LDALT. For example, recipients with very low Model of End Stage Liver Disease (MELD) scores with 1-year survival probability greater than that offered with transplantation were deferred until their disease progressed. Each donor provided 1 to 2 units of autologous blood before surgery. Informed consent was obtained for both donor and recipient operations approximately 1 week before surgery by the surgeon performing each procedure.

All donors were given nutritional support in the form of total parenteral nutrition (TPN). In our experience, enteral nutrition was poorly tolerated during early postoperative period. Donors were prescribed TPN formulas that contained 25 kcal/kg per day and were provided 1.5 grams/kg per day of protein. Micronutrients including phosphorus were also administered to help avoid complications (*14*).

Multiphase abdominal computed tomography angiography (CTA) with three-dimensional renderings for determining liver morphology, volume, and vascular anatomy was performed preoperatively and postoperatively at 1 week and 1, 3, 6, and 12 months in all patients. The CTA protocol used to assess donor-liver volume has been previously described (*15*). Although the ideal donor could provide a graft with the estimated right-lobe liver volume to recipient

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[1] Division of Liver Transplantation and Hepatobiliary Surgery, Lahey Clinic Medical Center, Burlington MA.

[2] Department of Radiology, Lahey Clinic Medical Center, Burlington MA.

[3] Division of Clinical Care Research, Tufts University, Boston, MA.

[4] Address correspondence to: Dr. Elizabeth A. Pomfret, Director Live Donor Liver Transplantation, Lahey Clinic Medical Center, Department of Liver Transplantation and Hepatobiliary Surgery, 41 Mall Road, Burlington, MA 01805. E-mail: Elizabeth.A.Pomfret@lahey.org.

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body weight ratio (GBWR) of greater than 1.0%, an estimated graft size of greater than 0.8% GBWR was also accepted (*16*).

Donor complications, defined as any unexpected or untoward event, were collected prospectively and recorded in a comprehensive database. Because any complication in a healthy donor is significant, both minor and major complications were recorded. Donors were monitored for 1 year postoperatively for surgical, medical, and psychiatric complications.

Statistical Analysis

Donor remnant volume (DRV) was calculated as the estimated total liver volume (TLV) minus the actual graft weight (AGW). Regeneration was expressed as a percent of the original TLV using follow-up computed tomography (CT) liver volume. Only donors with complete data were used for statistical analyses. Data are expressed as mean±standard deviation. Pearson's correlation was used to analyze associations between two continuous variables. Continuous variables were analyzed using the one or two sample Student's *t* test, as appropriate. Categorical variables were analyzed with the chi-square test. All analyses were performed using SAS software (version 8.2, SAS Institute Inc., Cary, NC). $P \leq 0.05$ was considered to be statistically significant.

RESULTS

One hundred sixty-four potential donors with compatible blood type were evaluated, and 51 (31.1%) underwent right hepatectomy. Of all donors evaluated, 50% (n=83) were rejected for either donor or recipient reasons as shown in Table 1. Twenty-two (13.4%) potential donors elected not to participate in the live-donation process after the initial interview with the transplant surgeon.

Thirty-three (64.7%) men and 18 (35.3%) women underwent right hepatic resection for LDALT. Most donors were blood group O (76.5%), relatively young (36.0±9.6 years), and had normal body weight (body mass index 26.5±3.5). Donors had an estimated TLV of 1845.3±350.2 mL. Helical CT scan with three-dimensional renderings was excellent in predicting mean right-lobe liver volume (predicted 1025.4±222.7 mL vs. actual 935.0±189.4 g; $P<0.0001$ by paired *t* test). Actual graft volume was 91% of the CT predicted right-lobe liver volume. The mean GBWR was 1.24%. Mean follow-up was 9.8±3.4 months.

TABLE 1. Reasons for rejecting donors.

Reason	Percent
Recipient reasons for rejection (n=42)	
Recipient too sick	28.6
Recipient died	21.4
Received cadaveric organ	26.2
Hepatocellular cancer (>5 cm or metastases)	21.4
Recipient portal vein thrombosis	2.4
Donor reasons for rejection (n=41)	
Inadequate liver volume	19.5
Abnormal live function tests/serologies	14.6
Unsafe vascular anatomy	14.6
Fatty liver	22.0
Medical	24.4
Abnormal liver biopsy	2.4
Psychosocial	2.4

Donors were rejected for both donor and recipient reasons. The most common reason for donor rejection was acute decompensation of the recipient, making them too ill for transplantation with a partial liver graft or recipient death. Common donor specific reasons were inadequate liver volume or steatosis.

Forty-four percent of donors had a significant accessory inferior right hepatic vein (≥5 mm) that was preserved for reimplantation, whereas only two donors (3.8%) had a significant segment VIII vein that required reconstruction in the recipient. The donor operative time was 6.3±1.1 hours with an estimated blood loss of 835±762 mL. Blood transfusion using a single unit of allogeneic blood occurred in one patient requiring reoperation on postoperative day 16 for evacuation of a perihepatic hematoma. Hospital length of stay for all donors was 8±3 days.

Surgical morbidity rate was 39% and is shown in Table 2. No donor operation was aborted, and no donor deaths occurred. Sixty-one percent of donors had no complications, whereas 20 patients had a total of 25 complications. The majority of the observed complications were minor and self-limited. Two (3.5%) donors developed symptomatic right pleural effusions and required thoracentesis. One patient had a small bile leak that required prolonged Jackson Pratt drainage until the first postoperative visit. Four patients developed small postoperative bile collections that required percutaneous drainage.

Reoperation was necessary in two (3.8%) patients for portal vein thrombosis and evacuation of a postoperative hematoma, respectively. The portal vein thrombosis was most likely the result of a technical error in the closure of the right portal vein branch stump. This was exacerbated by postoperative liver edema that resulted in acute angulation between the main and left portal veins. Simple thrombectomy and closure of the longitudinal venotomy in a vertical fashion corrected the problem. The patient was discharged home in 10 days with a patent portal vein and without anticoagulation. The patient's portal vein has remained patent after follow-up for greater than 2 years.

The second patient requiring reoperation developed anemia on postoperative day 3 and was found to have a perihepatic hematoma. The patient's hematocrit stabilized after transfusion of 2 units of autologous blood and was followed expectantly. The hematoma was confirmed by CT scan and initially associated only with early satiety. Approximately 2 weeks postoperatively, the patient developed fevers, wound erythema, and abdominal pain, and therefore the decision was made to return to the operating room for reexploration of a presumed infected hematoma. A large amount of clot was evacuated along the liver edge without evidence of persistent hemorrhage. Intraoperative cultures of the evacuated clot

TABLE 2. Donor morbidity[a]

Patients	Complication
7	Wound problems (seroma or infection)
5	Biloma (4 requiring percutaneous drainage)
4	Neuropraxia (all resolved)
4	Localized area of alopecia
2	Pleural effusion (requiring thoracentesis)
1	Pulmonary edema
1	Portal vein thrombosis (reoperation)
1	Postoperative hematoma (reoperation)

[a] Morbidity rate 39% (20/51 patients with 25 complications).

The majority of complications were mild and self-limited; however, two donors required reoperation for portal vein thrombosis and evacuation of a perihepatic hematoma, respectively. No donor deaths were encountered.

were negative. The patient was discharged on postoperative day 28 and returned to full-time work 4 months after surgery.

Liver Regeneration and Function

Liver regeneration was measured at 1 week and 1, 3, 6, and 12 months postoperatively and calculated using helical CT scan (Fig. 1). Forty-three donors had complete data for statistical analysis. Donor residual liver volume was 49.4±5.7% of the original donor TLV with an overall regeneration of 83.4±9.0% by 1 year. The increase in liver volume from baseline to 1 week was 1.5±1.2% per day ($P<0.0001$), and from 1 week to 1 month was 0.4±0.3% per day ($P<0.0001$ vs. previous visit). Beyond these time points, the rate of liver regeneration was less but still statistically significant (1–3 months 0.08±0.11% per day, $P<0.001$; 3–6 months 0.06±0.06% per day, $P<0.0001$; and 6–12 months 0.02±0.04% per day, $P<0.01$). Female donors had significantly slower liver regrowth when compared with males at 12 months (79.8±9.3% vs. 85.6±8.2%, $P<0.01$) (Table 3) (Figure 2). No effect of age, body mass index, operative time, estimated blood loss, presence of postoperative complications, or perioperative liver function tests on liver regeneration was observed (Table 4). Only one donor had complete restoration of his liver volume during this time period; however, all had normal liver function tests, and none had long-term complications.

Postoperative liver function tests LFT are shown in Figure 3. Total bilirubin peaked on postoperative day 2 whereas enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) peaked on postoperative day 1. All liver function tests normalized by postoperative day 7.

TABLE 3. Donor remnant regeneration

Day	Sex	n	Percent regeneration	Percent regeneration/day from prior visit	*P*
0	Female	16	51.0±5.1		
	Male	27	48.5±5.8		
7	Female	16	59.8±7.4	1.13±1.20	<0.01
	Male	27	61.5±7.4	1.66±1.17	<0.0001
30	Female	15	69.0±6.8	0.38±0.45	<0.01
	Male	27	71.0+8.6	0.34+0.25	<0.0001
90	Female	14	72.9+7.3	0.07+0.10	<0.05
	Male	23	75.9+7.0	0.09+0.12	<0.01
180	Female	15	78.3+9.0	0.06+0.06	<0.01
	Male	22	81.2+9.6	0.06+0.06	<0.01
365	Female	11	79.8+9.3	0.02+0.02	<0.01
	Male	18	85.6+8.2	0.02+0.04	<0.05, <0.01*

Male remnant volume was 48.5% of total liver volume. Statistically significant growth was seen throughout the year and was statistically significantly different from females at 12 months (*$P <$ 01 vs. females). Female remnant volume was 51% of total liver volume. Similar to males, each time point was statistically different from the previous one.

DISCUSSION

The ethical debate that surrounds LDALT continues since there have been reported deaths in the donor population (*4*, *5*, *17*). To minimize donor morbidity and mortality, standardized program guidelines are being developed. To further this goal, accurate reporting of surgical outcome and all complications encountered helps to ensure proper informed consent of prospective donors. To date, attempts to develop a live-liver donor national database have not been successful because of economic and political reasons.

The reported morbidity rate associated with donor right hepatectomy has varied greatly (*6–9*, *18*). Some of this discrepancy is explained by nonstandardized definitions of what constitutes a complication. In our center, all unexpected and untoward events were recorded because any complication in the live donors is significant. Approximately 40% of the donors in this series experienced at least one complication. Fortunately, most of these adverse events were minor and self-limited; however, eight patients required additional invasive procedures including surgery. Severe hypophosphatemia was a universal event among donors and may have contributed to some of the observed complications (*14*).

Multislice CTA or magnetic resonance angiography are being used as noninvasive methods for evaluating liver vas-

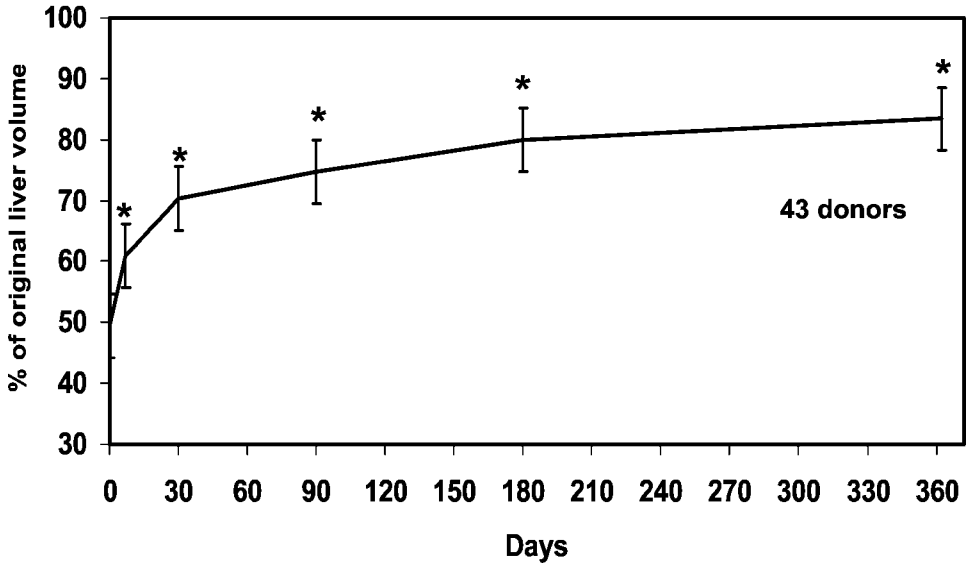

FIGURE 1. Overall donor remnant liver regeneration. Forty-three donors with complete data were included in the statistical evaluation. All time points are statistically different when compared with previous visit ($P<0.01$).

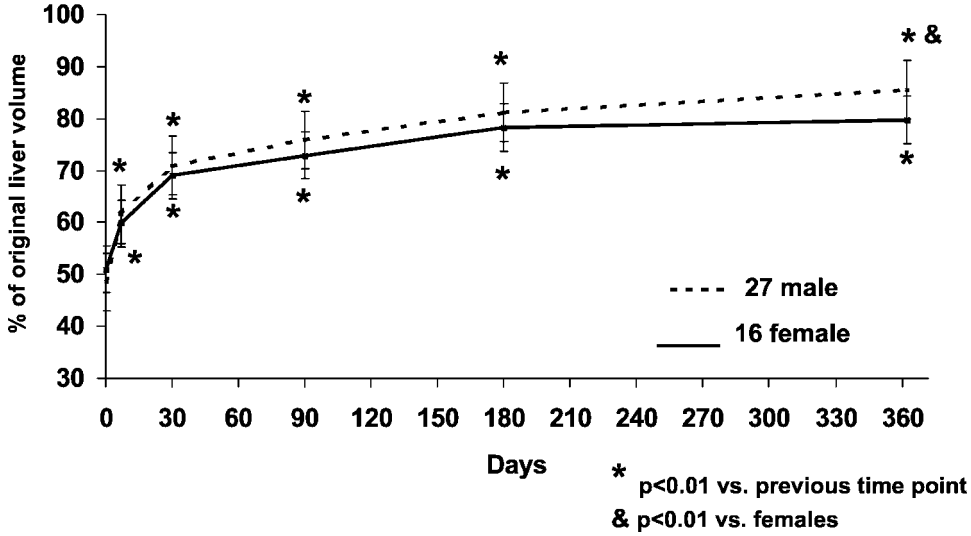

FIGURE 2. Donor remnant liver regeneration by gender. Twenty-seven males and 16 females had complete data for evaluation. Differences in liver regeneration between sexes reached statistical significance 12 months postresection.

TABLE 4. Donor characteristics

51 right-lobe donors	Min	Max	Mean	Standard deviation
Age	18	55	36	±9.7
Body mass index	19.3	34.9	26.5	±3.5
CT total LV (mL)	1,153	2,838	1,845	±350
CT right-lobe LV (mL)	637	1,816	1,025	±223
Actual right-lobe graft weight (g)	575	1,450	935	±189
Donor remnant volume (%)	35.1	62.5	49.1	±5.9
Operating room time (hr)	3.0	8.67	6.25	±1.1
Estimated blood loss (mL)	50	4,500	835	±762
Autologous blood use (U)	0	2	0.65	±0.77
Hospital length of stay (days)	6	28	8.3	±3.1

LV, liver volume

cular anatomy (*19*, *20*). CTA is also a useful technique for estimating right-lobe graft volume and donor residual left-lobe volume. In our experience, CTA significantly overestimated AGW by 8.7% ($P<0.0001$). With recent improvements in three-dimensional CTA technology, we have been able to demonstrate that the original projected "virtual" resection plane on the surface of the liver to the right of the middle hepatic vein should be curved to match with the bifurcation of the portal vein. Therefore, a straight virtual resection plane in a line between the gallbladder fossa and suprahepatic vena cava includes a small portion of the caudate lobe that is not included in the graft.

Normal liver regeneration is a complicated process dependent upon the activation of more than 100 genes and the involvement of numerous growth factors, cytokines, and transcriptional factors (*21–24*). Numerous studies have addressed the extent of liver regeneration after partial hepatectomy for benign and malignant tumors, but few have characterized hepatic regeneration in the healthy live donor (*25–28*).

The mechanisms controlling liver regeneration are still poorly understood. Recent animal studies suggest that the endothelium is a key modulator in regenerating liver mass. Greene et al. (*29*) demonstrated that the endothelial cell is involved in the regulation of regenerating adult liver mass and suggest that the regulation of angiogenesis controls the regenerative process. After partial hepatectomy, massive hepatocyte proliferation is observed to begin immediately and peaks 48 hours postoperatively. Endothelial cell proliferation lags behind the hepatocyte, peaking at 4 days and returning to normal levels after regeneration is complete. The endothelial cell may represent the "physiologic brake" that stops the hepatic regenerative process because endothelial proliferation decreased, whereas endothelial apoptosis increased on postoperative day 8 as the regenerating liver reached its preoperative mass (*29*).

Human studies investigating hepatic regeneration in the live-liver donor have typically involved left lateral segment grafts transplanted into children. These donors have rarely been followed with serial imaging studies beyond several weeks or months. In a small series of four patients, Kawasaki et al. (*11*) reported slower growth of the DRV when compared with recipient regeneration. Similar to the current study, two of these patients had 1-year follow-up, and both demonstrated steady growth throughout the first postoperative year.

Nakagami et al. (*10*) evaluated liver regeneration in 37 live-liver donors after formal left or left lateral segment hepatectomy. The authors reported complete hepatic regeneration by postoperative day 28; however, magnetic resonance imagery (MRI) volumetric studies were not performed serially in the same individuals after donation. The patients were separated by the type of surgical procedure they had and then further subdivided into three groups undergoing MRI on either postoperative day 14, 21, or 28 (*10*). Thus, the extrapolation of this composite data does not necessarily support the conclusion that all donors in the study had completed liver regeneration. In addition, the pattern of liver restoration observed after left-lobe donation may not reflect what is occurring with right-lobe liver donation. Similarly, Marcos et al. (*12*) reported that live-liver donors who pro-

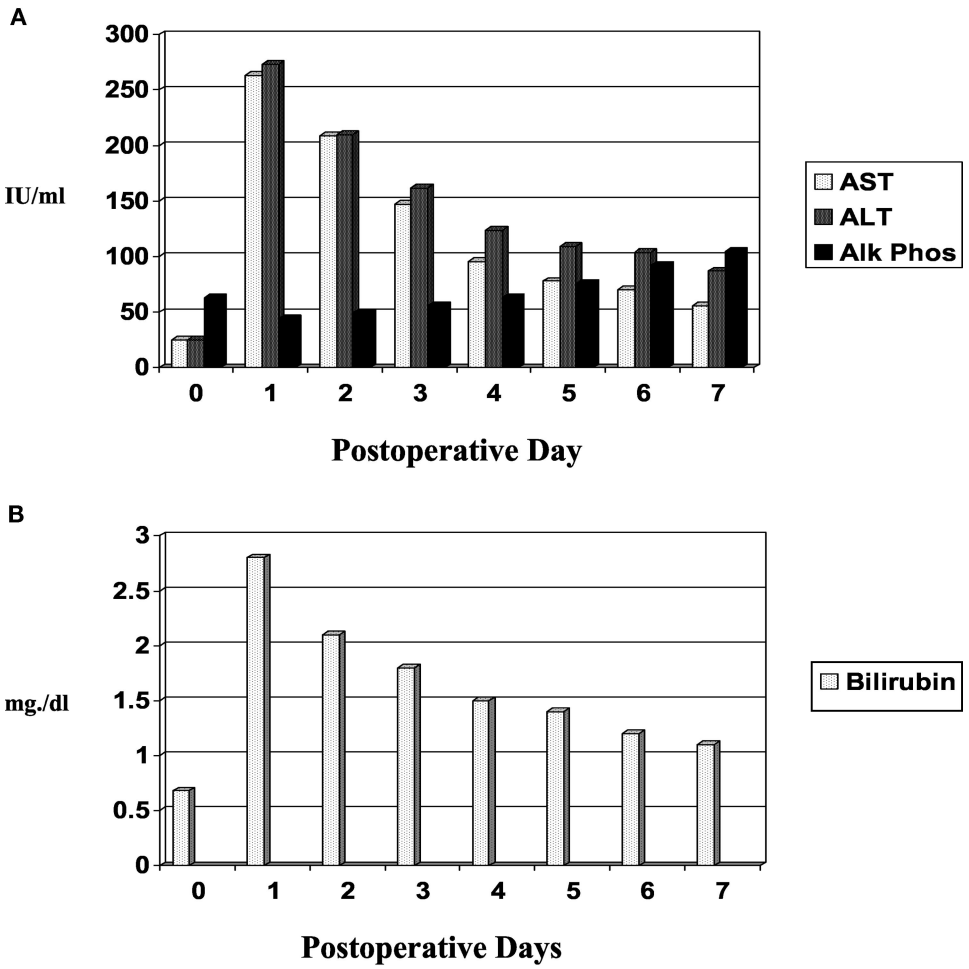

FIGURE 3. Postoperative liver function tests. (A) Enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) peaked during the first postoperative day and returned to normal by postoperative day 7. Alkaline phosphatase (Alk Phos) increased gradually during this time period. (B) Total bilirubin also peaked on postoperative day 1 and normalized rapidly.

vided right-lobe grafts had near total liver regeneration within 1 week of surgery.

The results of these studies differ from the present report in that liver regeneration was observed to continue throughout the first postoperative year. Only one donor achieved complete restoration of their liver volume within 1 year of surgery. Fortunately, all donors achieved normal hepatic synthetic function within 1 week of surgery. The clinical significance of the observation that liver regeneration is a relatively protracted process is unclear. Liver function normalizes rapidly after liver donation and well before regeneration is completed. There does not appear to be any untoward effect on the donor as the result of not achieving complete liver regeneration within 1 year of surgery. Our current recommendation is that donors abstain from alcohol ingestion or oral contraceptives agents while liver regeneration is occurring. Most donors reported being back to a "normal" life style and health within 3 months of donation. All but one donor reported that they would consider donation again if possible.

The mechanisms controlling live regeneration are poorly understood. Previous reports have suggested a clear stimulatory effect of estrogen (*30*, *31*). Therefore, the finding in the present study that females had significantly lower rates of liver regeneration compared with males is curious. Additional studies to elucidate the mechanisms affecting this apparent sex difference in liver regeneration are warranted. In addition, because statistically significant liver growth was observed between 6 and 12 months after resection in all donors, future studies should evaluate liver regeneration in the healthy donor beyond 1 year to determine when liver growth plateaus.

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GRAFT SURVIVAL FOLLOWING LIVING-DONOR RENAL TRANSPLANTATION: A COMPARISON OF TACROLIMUS AND CYCLOSPORINE MICROEMULSION WITH MYCOPHENOLATE MOFETIL AND STEROIDS

SUPHAMAI BUNNAPRADIST,[1,2] ADARSH DASWANI,[1] AND STEVEN K. TAKEMOTO[3,4]

Background. **Registry databases offer the statistical power to analyze differences in graft survival rates that may not be detected in randomized clinical trials. This study analyses 2-year graft survival using tacrolimus (tac) or cyclosporine (CsA) with mycophenolate mofetil (MMF) and steroids.**

Methods. **Data reported to the United Network for Organ Sharing Renal Transplant Registry for living-donor kidney patients receiving a transplant during 1998 to 1999 were included. The primary end point was graft survival after adjustment for confounding variables. A Cox model multivariate analysis was used to adjust for potential confounding factors.**

Results. **Patients receiving CsA-MMF (n=4,686) and tac-MMF (n=2,393) were included. Unadjusted all-cause 2-year graft survival rate was significantly higher with CsA-MMF than tac-MMF (94.3% vs. 92.2%, *P*=0.0006). After adjustment for potential confounding factors, risk of graft failure at 2 years was significantly higher in patients receiving tac-MMF versus CsA-MMF for both all-cause graft failure (hazards ratio [HR] 1.28, 95% confidence interval [CI] 1.09–1.49, *P*=0.002) and death-censored graft failure (HR 1.25, 95% CI 1.05–1.49, *P*=0.013). Other independent risk factors for graft failure were recipient or donor age greater than 55 years, female sex, pretransplant blood transfusions, one or two haplotype mismatches compared with zero haplotype mismatch, and panel reactive antibody (PRA) greater than 30%.**

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[1] Multiorgan Transplant Program, Cedars-Sinai Medical Center, Los Angeles, CA.
[2] David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA.
[3] Dumont Transplant Program and Immunogenetics Center, UCLA School of Medicine, Los Angeles, CA.
[4] Address correspondence to: Steven K. Takemoto, Adjunct Associate Professor, UCLA Immunogenetics Center, 1000 Veteran Avenue Room 1-542, Los Angeles, CA 90095-1652. E-mail: stakemoto@mednet.ucla.edu.

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