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ORIGINAL ARTICLE

Functional Elements Associated With Hepatic Regeneration in Living Donors After Right Hepatic Lobectomy

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We quantified the rates of hepatic regeneration and functional recovery for 6 months after right hepatic lobectomy in living donors for liver transplantation. Twelve donors were studied pre-donation (baseline); 8 were retested at a mean ± SD of 11±3 days after donation (T1), 10 were retested at a mean of 91±9 days after donation (T2), and 10 were retested at a mean of 185±17 days after donation (T3). Liver and spleen volumes were measured with computed tomography (CT) and single-photon emission computed tomography (SPECT). Hepatic metabolism was assessed with caffeine and erythromycin, and hepatic blood flow (HBF) was assessed with cholates, galactose, and the perfused hepatic mass (PHM) by SPECT. The regeneration rates (mL kg^{-1} of body weight day^{-1}) by CT were 0.60±0.22 mL from the baseline to T1, 0.05±0.02 mL from T1 to T2, and 0.01±0.01 from T2 to T3; by SPECT they were 0.54±0.20, 0.04±0.01, and 0.01±0.02, respectively. At T3, the liver volumes were 84%±7% of the baseline according to CT and 92%±13% of the baseline according to SPECT. Changes in the hepatic metabolism did not achieve statistical significance. At T1, the unadjusted clearance ratios with respect to the baseline were 0.75±0.07 for intravenous cholate ($P<0.001$), 0.88±0.15 for galactose ($P=0.07$), 0.84±0.08 for PHM ($P=0.002$), and 0.83±0.19 for the estimated HBF ($P=0.06$). At T1, these ratios adjusted per liter of liver were up to 50% greater than the baseline values, suggesting recruitment of HBF by the regenerating liver. Increased cholate shunt, increased spleen volume, and decreased platelet count, were consistent with an altered portal circulation. In conclusion, initial hepatic regeneration is rapid, accounts for nearly two-thirds of total regeneration, and is associated with increases in HBF and cholate uptake. Right lobe donation alters the portal circulation of living donors, but the long-term clinical consequences, if there are any, are unknown. ***Liver Transpl 19:292–304, 2013***. © **2013 AASLD.**

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Donor safety and outcomes are the chief concerns of programs performing living donor liver transplantation.[1,2] For adult recipients, a right lobe graft may be preferred to a left lobe graft because of the larger hepatic mass and the anatomic orientation of vascular and biliary structures. For donors, one result of donating a right lobe graft is a relatively small remnant of residual liver from which their liver mass can be regenerated. Even though hepatic regeneration permits donors to tolerate these resections, typically uneventfully, transient hepatic impairment is common, and hepatic failure, although rare, has been described.[1-3]

In animal models, hepatic regeneration after the resection of an otherwise normal liver is rapid and

usually complete within a few weeks.[4,5] In these models, survival is linked to the rate and completeness of regeneration and the restoration of hepatic function.

Less is known about hepatic regeneration, hepatic function, and clinical outcomes in humans. Humar et al.[6] measured liver volumes by computed tomography (CT) 3 months after donation and found that the donor liver volume was 78.6% of the ideal, whereas the recipient liver volume was 103.9% of the ideal. Nadalin et al.[7] measured the volumes of donor remnants by magnetic resonance imaging (MRI) and found that the remnant volumes were 39% of the baseline immediately after resection, increased to 77% by 3 months, and were 83% of the baseline 1 year after donation. Pomfret et al.[8] performed CT studies at the baseline and 1 week and 1, 3, 6, and 12 months after donation. By 1 year, the liver volume was 83.3% of the baseline, and female donors had significantly less regeneration than male donors (79.8% versus 85.6%, $P=0.01$). These studies suggest that the regeneration of donor remnants is incomplete.

Some studies have also evaluated the impact of donation on hepatic function. Nadalin et al.[7] studied the galactose elimination capacity (GEC) and found that the unadjusted GEC had declined 50% by day 10 but returned to the baseline at subsequent time points. The GEC adjusted for the remnant liver volume declined by less than 25% by day 10, was greater than the baseline at days 90 and 180, and returned to the baseline by day 360. Jochum et al.[9] had results similar to those of Nadalin et al.: GEC, expressed per kilogram of body weight, was 50% lower than the baseline value at day 10 and was nearly at the baseline by day 90. Jochum et al. also observed that the indocyanine green half-life increased, and the lidocaine half-life was not significantly altered. Neither study measured a broad array of liver functions, nor did they examine the relationships of function and regeneration.

In this study, we measured multiple hepatic functions, the hepatic blood flow (HBF), and the total liver and perfused liver volumes, and we related these results to the regeneration of the remnant left lobe during the first 6 months after right lobe donation.

PATIENTS AND METHODS

Patients

Donors were approached for participation in this study only after they had undergone a full evaluation for living donor liver transplantation, they had been approved by the selection committee for liver transplantation, and the date of the operation had been scheduled. Donors were recruited from 2 Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) clinical centers: the University of Colorado Denver and the University of California San Francisco.

The protocol was approved by the institutional review boards at the participating institutions, and all

Abbreviations: Δt, time interval; ΔV, change in the hepatic volume between consecutive time points; A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; CT, computed tomography; EBT, erythromycin breath test; GEC, galactose elimination capacity; HBF, hepatic blood flow; PHM, perfused hepatic mass; SPECT, single-photon emission computed tomography; T0, day of donation; T1, T2 and T3, post-donation study periods; t_T, time at study period T; t_{T-1}, time at study period T−1; Vpredonation, predonation liver volume; V_t, liver volume at time t; V_T, liver volume at study period T; V_{T-1}, liver volume at study period T−1

This article is publication 20 from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study, which is registered with ClinicalTrials.gov (NCT00096733).

In addition to the institutions affiliated with the authors, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study includes Northwestern University (Chicago, IL), the University of California Los Angeles (Los Angeles, CA), Columbia University Health Sciences, NY, NY, University of Virginia, Charlottesville, VA, and Virginia Commonwealth University (Richmond, VA).

Gregory T. Everson and Claus U. Niemann were the principal investigators at the 2 clinical centers at the University of Colorado and the University of California San Francisco, respectively. John C. Hoefs and Norah Milne were responsible for the analyses of single-photon emission computed tomography liver-spleen scans. Kim M. Olthoff participated in the preparation of the manuscript. Robert Dupuis analyzed the erythromycin breath tests, and Shannon Lauriski analyzed the cholate clearances and shunt and the caffeine and galactose samples. Andrea Herman was the study coordinator in Colorado. Brenda W. Gillespie and Nathan P. Goodrich performed the statistical analyses. James E. Everhart was the project officer from National Institute of Diabetes and Digestive and Kidney Diseases.

Gregory T. Everson has intellectual property rights related to the filing (by the University of Colorado Denver) of US patent application 60/647,689 (Methods for Diagnosis and Intervention of Hepatic Disorders) on January 26, 2005 and International Application PCT/US2006/003132 as published under the Patent Cooperation Treaty, World Intellectual Property Organization, International Patent Classification A61K 49/00 (2006.01), International Publication Number WO 2006/081521 A2 on August 3, 2006. Everson also has an equity interest in HepQuant LLC. The other authors have no financial relationships to disclose.

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subjects provided written informed consent for both the main A2ALL study and this A2ALL-approved ancillary study.

Procedures, Test Compounds, and Analytical Methods

Participants maintained a caffeine-free, grapefruit juice-free, and alcohol-free diet for 3 days and were studied in the morning after an overnight fast at the general clinical research centers of the participating centers. An indwelling, intravenous 20-gauge catheter was placed for administering test compounds and sampling blood. Patients were supine during the study and minimized their activity.

The hepatic metabolism was quantified with erythromycin[10] and caffeine[11] as the test compounds.

Erythromycin Breath Test (EBT)

Three microcuries of [^{14}C-*N*-methyl]-erythromycin [product 02410806 (investigational new drug 31,760), Metabolic Solutions, Inc., Nashua, NH] was administered intravenously with a bolus injection, which was followed by a normal saline flush (10 mL). Breath samples for the measurement of $^{14}CO_2$ generated from the hepatic metabolism of erythromycin were collected at the baseline and 20 minutes after dose administration with a T-tube apparatus, a capture solution, and an indicator dye.[12] $^{14}CO_2$ was quantified by radioscintigraphy, and the percentage of erythromycin metabolized per hour was determined.

Caffeine Elimination Rate and Clearance

Caffeine [300 mg; product 0072-5 (investigational new drug 65,175), Ruger Chemical Co., Irvington, NJ] was administered orally, and its hepatic metabolism was determined from the clearance measured via high-performance liquid chromatography of saliva samples obtained 2, 4, 8, and 12 hours after dosing. The distribution volume and the elimination rate were determined by a linear regression of the $\log_e$ concentration versus time, and the clearance was the product of the distribution volume and the elimination rate.

The hepatic circulation was quantified with test compounds via flow-dependent, high first-pass hepatic extraction (galactose,[13] cholates,[14-17] and ^{99m}Tc-cis-sulfur colloid[15-18]).

GEC

Galactose [30 g of low-endotoxin D-galactose; product G-105-1 (investigational new drug 65107), Pfanstiehl Laboratories, Inc., Waukegan, IL] in 100 mL of sterile water was administered intravenously over the course of 5 minutes. Blood samples were obtained at the baseline and 20, 40, 60, and 80 minutes after dosing, and the galactose concentration was quantified by spectrophotometry with a standardized lactose/D-galactose kit (catalog number 176 303, Boehringer Mannheim). GEC is the slope from the linear regression of the concentration versus the time.

Cholate Clearances and Shunt

Dual isotopes of cholate were simultaneously administered in an anionic form in bicarbonate solutions: one orally and the other intravenously.[14-17] The oral solution contained 40 mg of 2,2,4,4-^{2}H cholate [product D-2452 (studied under investigational new drug 65123), CDN Isotopes, Inc., Quebec, Canada] plus 600 mg of $NaHCO_3$ in apple or grape juice. The intravenous solution contained 20 mg of 24-^{13}C cholate [product C-3448 (studied under investigational new drug 65121), CDN Isotopes] dissolved in 5 mL of United States Pharmacopeia–grade $NaHCO_3$ (1 mEq/mL; Baxter HealthCare, Tarrytown, NY). This solution was mixed with 5 mL of United States Pharmacopeia–grade human serum albumin (25%; NDC 0026-0692-16, Bayer HealthCare, Tarrytown, NY) and was administered via the antecubital vein over the course of 1 minute. Blood samples were obtained at the baseline and 5, 20, 45, 60, and 90 minutes after dosing,[14] and cholate isotopes were quantified by liquid chromatography–mass spectrometry. The cholate oral clearance and the cholate clearance after intravenous administration were calculated from the dose (40 mg for oral administration and 20 mg for intravenous administration) divided by the area under the concentration-time curves for each isotope (milligrams per minute per milliliter) and normalized for the body weight (kilograms), and the cholate shunt was the ratio of clearances for intravenously and orally administered isotopes. The estimated HBF was calculated with the following equation:

$$\text{HBF} = (\text{Cholate clearance after intravenous administration})/[(1-(\text{Shunt}/100)) \times (1-(\text{Hematocrit }\%/100))]$$

An example of dual cholate clearance studies for one donor before and after donation is shown in Fig. 1.

Single-Photon Emission Computed Tomography (SPECT) Liver-Spleen Scans

After the completion of blood sampling for the galactose and cholate tests, patients ingested a standard meal and 375 mL of Ensure (Abbott Laboratories, Abbott Park, IL) 30 minutes before the intravenous administration of 5 to 6 mCi of ^{99m}Tc-cis-sulfur colloid with a particle size of 2 to 12 μm (CIS-US, Inc., Bedford, MA) for SPECT.[15-18] SPECT studies were performed at the 2 clinical sites, and the data were transferred to the University of California Irvine for processing (J.C.H. and N.M.). The perfused hepatic mass (PHM), which was calculated from these images, was used to quantify the relative distribution of sulfur

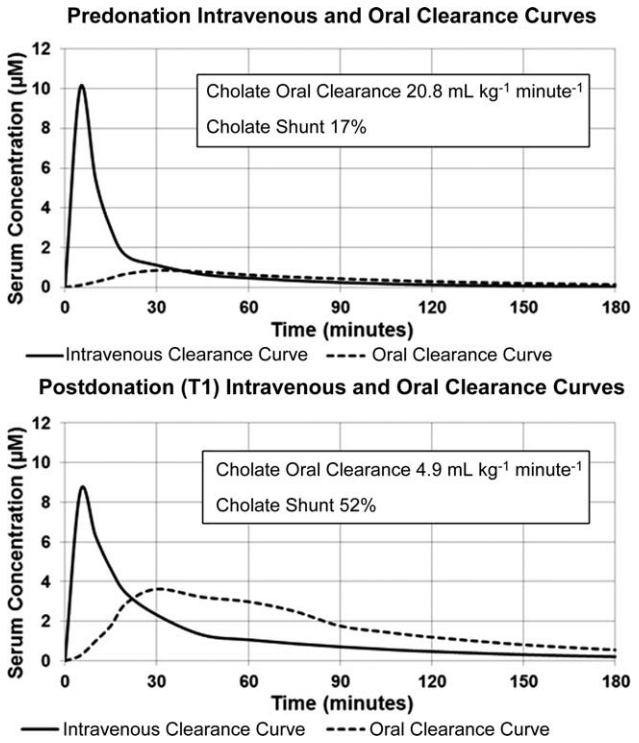

Figure 1. Cholate clearance before and after donation. This figure displays clearance curves for intravenously and orally administered cholate isotopes in a single donor at the baseline, before donation (top panel), and at T1 after donation (bottom panel). The increase in the systemic concentrations of orally administered [2,2,4,4-D]-cholate reflects the altered portal circulation and reduced hepatocyte mass after resection.

colloid between the liver, spleen and bone marrow. The liver and spleen volumes were also determined.[16-20]

The organ volumes and the rates of hepatic regeneration were measured with both CT and SPECT liver-spleen scans.

Volumes From CT/MRI

CT studies and SPECT liver-spleen scans were performed on different days. Liver and spleen volumes were determined with the standard CT software algorithms used by the radiology departments at the participating clinical sites.

Volumes From SPECT

The liver and spleen volumes were also calculated from the SPECT reconstruction of images with the Hoefs method.[16-20] Each volume was derived from the total count in the liver or spleen from regions of interest around the summarized transaxial image and a representative organ concentration from a single transaxial slice through the division of the total hepatic or splenic count by the representative concentration.

The hepatic regeneration rates were defined as $\Delta V/\Delta t$ via both CT and SPECT, where ΔV is the change in the hepatic volume between consecutive time points and Δt is the time interval. The baseline volume was the liver volume measured before donation. The remnant liver volume on the day of donation [time 0 (T0)] was determined from baseline CT via the subtraction of the estimated right lobe graft volume from the total liver volume. For SPECT, we assumed the same proportionate size of the remnant with respect to the baseline that was estimated with CT. Regeneration rates were determined for each postdonation follow-up interval.

Clearance tests were expressed with respect to the body size (per kilogram) or liver size (per liter of liver). Changes in hepatic metabolism (microsomal function) were estimated from serial changes in caffeine clearance (cytochrome P450 1A2) and EBT results (cytochrome P450 3A4). Changes in total HBF were estimated from serial changes in GEC, the clearance of intravenously administered 24-^{13}C cholate, and SPECT liver-spleen scans. Alterations of the portal circulation were assessed through changes from the baseline in the clearance of orally administered 2,2,4,4-^{2}H cholate, the cholate shunt, the PHM from SPECT liver-spleen scans, the platelet count, and the spleen volume.

Statistical Analysis

Results are expressed as means, standard deviations, and ranges. Differences between baseline and postdonation results at T1, T2, and T3 and differences between post-donation time points were compared with 2-sided paired *t* tests. To test the relationship between platelet counts and spleen size, we used both linear regression and mixed model regression with subjects as random effects. Statistical analyses were performed at the data coordinating center for A2ALL (University of Michigan) with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Twelve donors were studied at the baseline; 8 were retested at a mean of 11±3 days after surgery (T1), 10 were retested at a mean of 91±9 days after surgery (T2), and 10 were retested at a mean of 185±17 days after surgery (T3). The mean age was 38 years (range=21–54 years), the body mass index was 25.2±2.8 kg/m^2, the male/female sex ratio was 4/8, and 10 donors were white.

Standard Laboratory Tests

Table 1 displays the changes in routine laboratory tests over time after donation. All laboratory values were normal at the baseline. At T1, the bilirubin, prothrombin time international normalized ratio, and alanine aminotransferase values were higher than the baseline values, and the albumin value was lower. By T2, these tests were trending toward the baseline, and at T3, all had returned to the baseline values.

Total Liver Volume by CT Versus Perfused Liver Volume by SPECT

Volumes by CT are larger than those measured by SPECT. Using data from all time points, a linear regression through the origin of CT and SPECT volumes

TABLE 1. Laboratory Values Before and After Donation

	Before Donation (Baseline)	After Donation T1	After Donation T2	After Donation T3
Bilirubin (mg/dL)	0.78±0.22 (n=12)	1.34±0.75 (*P*=0.047, n=9)	0.66±0.15 (*P*=0.002, n=9)	0.77±0.34 (*P*=0.92, n=7)
INR	1.03±0.05 (n=12)	1.22±0.16 (*P*=0.004, n=9)	1.08±0.08 (*P*=0.12, n=10)	1.06±0.07 (*P*=0.35, n=8)
Albumin (g/dL)	3.74±0.51 (n=12)	3.22±0.38 (*P*=0.047, n=9)	3.57±0.44 (*P*=0.66, n=9)	3.69±0.47 (*P*=0.15, n=7)
Alanine aminotransferase (IU/mL)	22±5.80 (n=12)	91±70.61 (*P*=0.02, n=9)	31±11.62 (*P*=0.047, n=9)	25±12.94 (*P*=0.85, n=7)

NOTE: The data are presented as means and standard deviations. *P* values were derived from 2-sided paired *t* tests comparing postdonation and predonation values. Tests were based on postdonation sample sizes; this ensured data at both time points INR, international normalized ratio for prothrombin time.

indicated that liver volumes by CT/MRI were approximately 22% larger (slope=1.22, r=0.93, P<0.001) and spleen volumes were 4% larger (slope=1.04, r=0.95, P<0.001) in comparison with SPECT volumes. The ratios of the perfused liver volume (by SPECT) to the total liver volume (by CT) were constant during regeneration (0.84–0.86), although they were slightly greater than the ratio at the baseline (0.78).

Regeneration Rates

The liver volumes at each time point (milliliters and milliliters/kilogram), the reconstitution of the baseline volume ($V_T/V_{predonation}$, where V_T is the liver volume at study period T and $V_{predonation}$ is the predonation liver volume), and the rates of regeneration (milliliters per kilogram per day) are given in Table 2. The relative changes in these parameters during regeneration were similar with CT and SPECT. The total liver volumes by CT at each time point (T0-T3) with respect to the predonation volumes are shown for each donor in Fig. 2A.

There were at least 2 phases of regeneration: an early rapid phase during the first 2 weeks and a slower later phase after the first 2 weeks. According to CT, the regeneration rates (mL kg^{-1} of body weight day^{-1}) were 0.60±0.22 from T0 to T1, 0.05±0.02 from T1 to T2, and 0.01±0.01 from T2 to T3 (Table 2). According to SPECT, the regeneration rates were: 0.54±0.20 from T0 to T1, 0.04±0.01 from T1 to T2, and 0.01±0.02 from T2 to T3 (Table 2).

Approximately two-thirds of total hepatic regeneration occurred within the first 2 weeks after donation, and there was minimal regeneration after 3 months. At T3, approximately 6 months after donation, the liver volumes were 84%±7% of the baseline according to CT and 92%±13% of the baseline according to SPECT (Table 2).

Hepatic Metabolism

Changes in hepatic metabolism from the predonation baseline are shown in Table 3. The total clearances of caffeine and erythromycin were slightly lower than the baseline at T1 and were slightly greater than the baseline at T2 and T3. After adjustments for the liver volume, the clearances of caffeine and erythromycin were increased above the baseline at T1, and this increase persisted through T2 and T3. However, none of these changes in the metabolism were statistically significant.

HBF

Total unadjusted clearances of intravenously administered galactose, cholate, and ^{99m}Tc-cis-sulfur-colloid (PMN by SPECT) and the calculated HBFs are displayed in Table 4. These tests reflect the total blood flow to the remnant. At T1, the clearance of galactose (GEC) was 0.88±0.15 of the predonation baseline (*P*=0.07), the cholate clearance was 0.75±0.07 of the baseline (*P*<0.001), PHM was 0.84±0.08 of the baseline (*P*=0.002), and HBF had decreased to 0.83±0.19 of the baseline (*P*=0.06). Thus, by 3 very different methods (GEC, dual cholate clearance, and SPECT), we demonstrated consistent and moderate decreases in total clearances and HBF at T1 without adjustments for the liver volume.

In contrast, when the clearances were adjusted for the liver volume and expressed per liter of liver, they were increased at T1 (Table 4). The clearances per liter of liver for galactose, cholate, and ^{99m}Tc-cis-sulfur colloid (relative change in HBF) were all increased above the baseline. These findings suggest that the early rapid phase of regeneration is associated with enhanced blood flow per unit of the regenerating liver.

Orally administered cholate is delivered to the portal circulation after its absorption from the intestine: changes in the clearance of orally administered cholate reflect changes in clearance from the portal circulation. Like the clearance of intravenous cholate, the total clearance of orally administered cholate was decreased at T1 (Table 5), and this reflected the reduced hepatic mass. However, unlike the clearance of intravenous cholate, the clearance of orally administered cholate per liter of liver did not increase above the baseline at T1. The selective increase in the

TABLE 2. Hepatic Regeneration: Liver Volumes Before and After Donation

		After Donation			*P* Value		
	Before Donation (Baseline)	T0 (Estimated)*	T1	T2	T3	T0 Versus T1	T1 Versus T2	T2 Versus T3
CT								
Liver volume (mL)	1525.9±341.9 (n=10)	478.3±123.0 (n=10)	840.9±145.7 (n=8)	1151.4±209.2 (n=10)	1282.2±286.6 (n=10)	<0.001 (n=8)	<0.001 (n=8)	0.009 (n=10)
Liver volume (mL/kg)	20.9±2.4 (n=10)	6.5±1.0 (n=10)	12.0±1.7 (n=8)	16.2±1.4 (n=10)	17.5±2.0 (n=10)	<0.001 (n=8)	<0.001 (n=8)	0.01 (n=10)
$V_t/V_{predonation}$	1.0	0.31±0.03 (n=10)	0.59±0.09 (n=8)	0.78±0.07 (n=10)	0.84±0.07 (n=10)	<0.001 (n=8)	<0.001 (n=8)	0.02 (n=10)
Regeneration rate (mL kg^{-1} day^{-1})†			0.60±0.22 (n=8)	0.05±0.02 (n=8)	0.01±0.01 (n=10)		<0.001 (n=8)	0.007 (n=8)
SPECT								
Liver volume (mL)	1197.1±253.6 (n=10)	376.2±95.4 (n=10)	710.4±105.02 (n=7)	963.5±143.7 (n=10)	1084.7±187.6 (n=10)	<0.001 (n=7)	<0.001 (n=7)	0.03 (n=10)
Liver volume (mL/kg)	16.4±1.5 (n=10)	5.1±0.8 (n=10)	10.3±1.1 (n=7)	13.6±0.8 (n=10)	14.9±2.0 (n=10)	<0.001 (n=7)	<0.001 (n=7)	0.04 (n=10)
$V_t/V_{predonation}$	1.0	0.31±0.03 (n=10)	0.64±0.08 (n=7)	0.82±0.10 (n=10)	0.92±0.13 (n=10)	<0.001 (n=7)	<0.001 (n=7)	0.03 (n=10)
Regeneration rate (mL kg^{-1} day^{-1})†			0.54±0.20 (n=7)	0.04±0.01 (n=7)	0.01±0.02 (n=10)		<0.001 (n=7)	0.03 (n=7)

NOTE: The data are presented as means and standard deviations. *P* values were derived from 2-sided paired *t* tests comparing values at adjacent time points.

*For CT, the T0 volume was estimated from predonation CT scans via the subtraction of the right lobe volume from the total liver volume. For SPECT, the T0 volume was assumed to be proportionate to the predonation volume estimated by CT. Liver and spleen volumes are displayed both unadjusted and adjusted per kg body weight.

†The regeneration rate was calculated for each interval as follows:

Regeneration rate=$(V_T-V_{T-1})/(t_T-t_{T-1})$ where V_T and V_{T-1} are measured in milliliters and t_T and t_{T-1} are measured in days. The study periods were T0, T1, T2, and T3 post-donation.

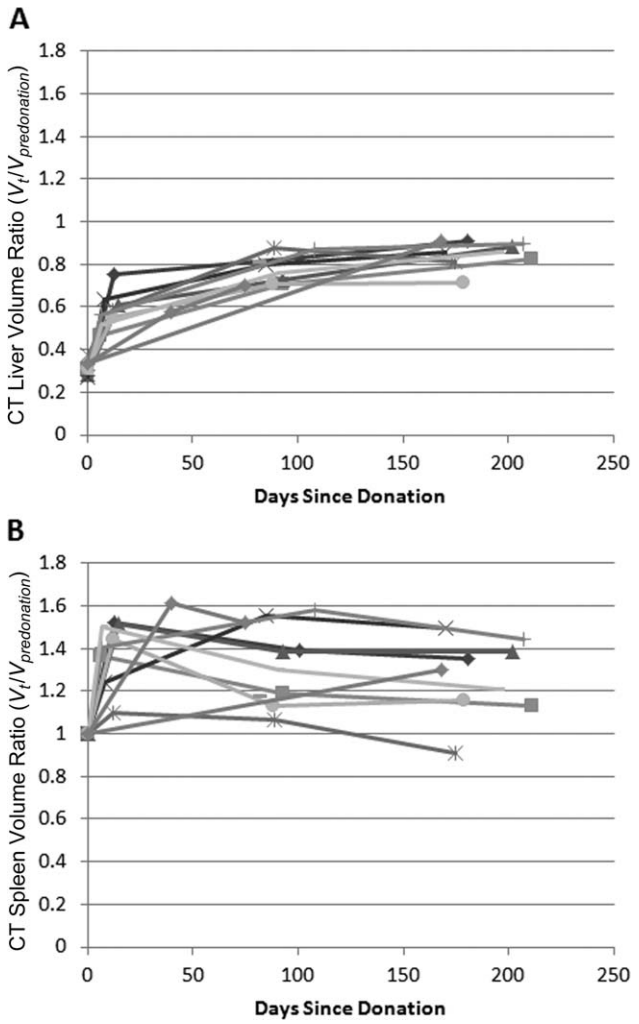

Figure 2. Liver and spleen volume ratios (with respect to the baseline before donation) by the time since donation. (A) Liver volumes with respect to the volume of the liver at the baseline before donation are shown for each donor (n=10). (B) Spleen volumes with respect to the volume of the spleen at the baseline before donation are shown for each donor (n=10).

clearance of intravenously administered cholate per liter of liver is consistent with the selective enhancement of hepatic arterial flow during the early phase of regeneration.

First-Pass Uptake of Cholate

We estimated the first-pass uptake of cholate from the fraction of the oral dose escaping hepatic extraction (corrected for the administered dose of cholate and normalized to the liver volume). At T1, during the period of rapid regeneration, we found a significant increase in the cholate uptake (21±5 mg/L of liver at the baseline versus 31±9 mg/L of liver at T1, P=0.02). The cholate uptake at T2 (25±4, P=0.03) and T3 (24±6, P=0.06) approached the baseline values.

Alteration of the Portal Circulation

Several of our test results suggest that the portal circulation is altered after right lobe donation (Table 5). At T1, the total clearance of orally administered cholate decreased (P<0.001), the cholate shunt increased (P=0.03), and the platelet count decreased (P=0.07). These changes persisted at T2 but, except for the platelet count, trended toward normal by T3.

Paralleling the changes in the platelet count, the spleen volumes by both CT and SPECT increased by T1. The spleen volumes did not increase further, declined slightly, but remained above the baseline values throughout the study period (Fig. 2B and Table 5). By T3, 6 months after donation, the CT spleen volume remained at 127%±17% of the baseline (P<0.001), and the SPECT spleen volume remained at approximately 150% of the baseline (P=0.02). The platelet count at T1 was 14% lower than the baseline, and it remained decreased through T3 (Table 5). The platelet count was inversely related to the spleen volume (Fig. 3). This relationship was significant when it was unadjusted (P<0.001) or adjusted (P=0.002) for subject effects with a mixed model.

DISCUSSION

This prospective study examined longitudinal changes in multiple hepatic functions after the donation of the right hepatic lobe by living donors as well as functional changes uniquely related to the regeneration of the left lobe remnant. Ten of the 12 donors that we studied had an uncomplicated postoperative course as indicated by standard laboratory tests and a lack of clinical complications. As for the 2 donors with complications, one had a grade 2 urinary tract infection, and the other had a grade 1 pleural effusion and a grade 2 wound infection; all occurred in the first month after donation. Thus, our results for hepatic imaging, volume determination, and function testing can likely be applied to other donors undergoing right hepatic lobectomy with an uncomplicated or modestly complicated course.

We observed differences in liver volumes related to the differences in CT and SPECT imaging. CT images include all structures within the region of interest, including vascular, connective tissue, and biliary structures. SPECT images are based on the phagocytosis of ^{99m}Tc-cis-sulfur colloid by the reticuloendothelial system and exclude nonparenchymal structures. The 22% lower volume measured by SPECT likely reflects its selectivity for parenchyma and PHM.

The rates of regeneration varied with the time after hepatic lobectomy. After lobectomy, the residual left lobe remnant was 31% of the baseline hepatic volume according to CT/MRI. In the first 2 weeks after donation, the hepatic volume nearly doubled, and the regeneration rate was 0.60 mL day^{-1} kg^{-1} of body weight by CT/MRI and 0.54 mL day^{-1} kg^{-1} of body weight by SPECT. Regeneration slowed dramatically after the first 2 weeks. During the following period of

TABLE 3. Hepatic Metabolism Before and After Donation

		After Donation			*P* Value		
	Before Donation (Baseline)*	T1	T2	T3	Baseline Versus T1	Baseline Versus T2	Baseline Versus T3
Total clearance							
Caffeine	n=11	n=7	n=9	n=7	n=7	n=9	n=7
Elimination rate ($hour^{-1}$)	0.119±0.076	0.096±0.083	0.128±0.058	0.141±0.089	0.73	0.99	0.48
Clearance (mL $minute^{-1}$ kg^{-1} of body weight)	1.54±0.90	1.41±1.21	1.78±1.14	1.75±1.32	0.98	0.72	0.76
EBT	n=10	n=5	n=8	n=8	n=5	n=8	n=8
% metabolized ($hour^{-1}$)	2.96±1.12	2.37±0.95	2.54±1.26	2.67±1.28	0.14	0.12	0.16
% metabolized ($hour^{-1}$ kg^{-1} of body weight)	0.04±0.02	0.03±0.01	0.04±0.02	0.04±0.02	0.14	0.22	0.17
Clearance per liter of liver							
Caffeine	n=11	n=7	n=9	n=7	n=7	n=9	n=7
Clearance by CT (mL $minute^{-1}$ L^{-1} of liver)	55±35	76±56	79±34	75±39	0.29	0.15	0.31
Clearance by SPECT (mL $minute^{-1}$ L^{-1} of liver)	70±38	91±70	96±44	88±47	0.34	0.15	0.44
EBT	n=10	n=5	n=8	n=8	n=5	n=8	n=8
% metabolized by CT ($hour^{-1}$ L^{-1} of liver)	2.03±1.10	2.97±1.35	2.28±1.36	2.24±1.49	0.19	0.76	0.89
% metabolized by SPECT ($hour^{-1}$ L^{-1} of liver)	2.55±1.28	3.36±1.39	2.68±1.60	2.56±1.48	0.44	0.98	0.72

NOTE: The data are presented as means and standard deviations. *P* values were derived from 2-sided paired *t* tests comparing postdonation and predonation (baseline) values.

*For comparison with postdonation T1 values, the following predonation means are presented for the 7 patients who had both predonation and T1 values for caffeine: caffeine elimination rate, 0.107±0.031 $hour^{-1}$; clearance 1.40±0.52 mL $minute^{-1}$ kg^{-1} of body weight; and clearance adjusted for liver volume by CT, 51±11 mL $minute^{-1}$ L^{-1} of liver. For the 5 patients with paired EBT tests before donation and at T1, the predonation total EBT was 3.22%±1.45% $hour^{-1}$, and EBT adjusted for liver volume by CT was 2.37%±1.43% $hour^{-1}$ L^{-1} of liver.

TABLE 4. HBF Parameters

	Before Donation (Baseline)	After Donation			*P* Value		
		T1	T2	T3	Baseline Versus T1	Baseline Versus T2	Baseline Versus T3
Total clearance	n=11	n=8	n=10	n=10	n=7	n=9	n=9
GEC	6.46±1.14	5.42±0.87	6.62±1.42	6.96±1.34	0.08	0.23	0.02
(mg minute^{-1} kg^{-1} of body weight)							
Cholate (intravenous) (mL minute^{-1} kg^{-1} of body weight)	5.68±2.08	4.06±1.32	4.80±1.53	4.70±1.90	0.003	0.41	0.32
HBF	13.2±6.6	10.4±5.1	11.9±4.9	11.0±4.4	0.04	0.78	0.39
(mL minute^{-1} kg^{-1} of body weight)							
PHM (from ^{99m}Tc-cis-sulfur-colloid)	104±4	87±5	95±6	97±6	0.002	0.001	0.003
	(n=12)	(n=7)	(n=10)	(n=10)	(n=7)	(n=10)	(n=10)
Clearance per liter of liver							
GEC by CT (mg minute^{-1} L^{-1} of liver)	303±54	455±60	408±73	403±91	0.003	0.002	0.001
	(n=11)	(n=8)	(n=10)	(n=10)	(n=7)	(n=9)	(n=9)
GEC by SPECT (mg minute^{-1} L^{-1} of liver)	386±76	524±71	487±97	468±76	0.04	0.005	0.003
	(n=11)	(n=7)	(n=10)	(n=10)	(n=6)	(n=9)	(n=9)
Cholate (intravenous) by CT (mL minute^{-1} L^{-1} of liver)	272±110	348±135	292±77	270±99	0.02	0.56	0.89
	(n=11)	(n=8)	(n=10)	(n=10)	(n=7)	(n=9)	(n=9)
Cholate (intravenous) by SPECT (mL minute^{-1} L^{-1} of liver)	340±130	372±117	352±105	313±106	0.11	0.73	0.56
	(n=11)	(n=7)	(n=10)	(n=10)	(n=6)	(n=9)	(n=9)
Total HBF by CT (mL minute^{-1} L^{-1} of liver)*	633±341	904±522	726±262	630±237	0.048	0.45	0.87
	(n=11)	(n=8)	(n=10)	(n=10)	(n=7)	(n=9)	(n=9)
Total HBF by SPECT (mL minute^{-1} L^{-1} of liver)*	794±418	866±273	874±340	728±253	0.19	0.58	0.61
	(n=11)	(n=7)	(n=10)	(n=10)	(n=6)	(n=9)	(n=9)
Change in HBF estimated by serial SPECT	n=12	n=7	n=10	n=10	n=7	n=10	n=10
PHM ratio to baseline	1	0.84±0.08	0.91±0.06	0.93±0.06	0.001	<0.001	0.003
Liver volume ratio to baseline	1	0.64±0.08	0.82±0.10	0.92±0.13	<0.001	<0.001	0.09
Relative change in HBF	1	1.33±0.20	1.13±0.18	1.03±0.16	0.005	0.05	0.61

NOTE: The data are presented as means and standard deviations. For the measures with baseline values, *P* values were derived from 2-sided paired *t* tests comparing predonation and (baseline) values. For the ratios compared with baseline values, *P* values were derived from 1-sample *t* tests comparing the means of the individual ratios and 1.0 (the null mean value).

*The total HBF was calculated as follows:

HBF=(Total Cholate clearance after intravenous administration)/[(1−(Shunt fraction %/100)) × (1−(Hematocrit %/100))]

TABLE 5. Measures Reflecting Changes in the Portal Circulation Before and After Donation

	Before Donation (Baseline)	T1	T2	T3	*P* Value: Baseline Versus T1	*P* Value: Baseline Versus T2	*P* Value: Baseline Versus T3
Cholate clearance (oral) (mL minute^{-1} kg^{-1} body weight)	25.6±7.0 (n=12)	12.3±5.5 (n=8)	16.3±4.7 (n=10)	23.5±15.9 (n=10)	<0.001 (n=8)	<0.001 (n=10)	0.59 (n=10)
Cholate shunt (%)	22±11 (n=11)	37±14 (n=8)	30±10 (n=10)	24±11 (n=10)	0.03 (n=7)	0.048 (n=9)	0.36 (n=9)
Platelet count (μL^{-})	232±63 (n=12)	200±94 (n=9)	196±64 (n=10)	193±44 (n=8)	0.07 (n=9)	<0.001 (n=10)	0.01 (n=8)
CT							
Spleen volume (mL/kg)	3.0±1.2 (n=12)	4.3±2.0 (n=8)	4.0±1.6 (n=10)	3.8±1.4 (n=10)	0.002 (n=8)	<0.001 (n=10)	<0.001 (n=10)
$V_T/V_{predonation}$	1.0	1.39±0.15 (n=8)	1.33±0.19 (n=10)	1.27±0.17 (n=10)	<0.001 (n=8)	<0.001 (n=10)	<0.001 (n=10)
SPECT							
Spleen volume (mL/kg)	2.4±1.1 (n=12)	3.6±1.7 (n=7)	3.9±2.3 (n=10)	3.5±1.8 (n=10)	0.05 (n=7)	0.03 (n=10)	0.02 (n=10)
$V_T/V_{predonation}$	1.0	1.58±0.52 (n=7)	1.58±0.65 (n=10)	1.50±0.52 (n=10)	0.03 (n=7)	0.02 (n=10)	0.01 (n=10)

NOTE: The data are presented as means and standard deviations. *P* values were derived from 2-sided paired *t* tests comparing postdonation and predonation (baseline) values.

approximately 3 months, the regeneration rate was only 0.05 mL day^{-1} kg^{-1} of body weight by CT/MRI and 0.04 mL day^{-1} kg^{-1} of body weight by SPECT. The regeneration rate was even slower between 3 (T2) and 6 months (T3). In agreement with other studies,[6-9] hepatic regeneration in the donors was incomplete. Six months after donation, the donors achieved only 84% (CT/MRI) to 92% (SPECT) of their baseline hepatic volumes. The dramatic differences in the regeneration rates between the time intervals suggests that factors regulating hepatic growth and, ultimately, the final liver volume must vary considerably between the early and later phases of regeneration.

The early rapid phase of hepatic regeneration, from the baseline to T1, was associated primarily with 2 functional changes: an enhancement of HBF per gram of hepatic tissue and an increase in the hepatic uptake of cholate. Naturally, the total HBF must decrease with the removal of 60% of hepatic tissue, but the liver compensates by increasing local flow. The HBF per liter of liver was assessed by 3 independent measurements, which indicated up to a 50% increase in tissue blood flow. Thus, the blood flow per liter of tissue increased, and this helped to preserve blood flow–dependent hepatic function and partially compensate for the decrease in the total hepatic mass.

In contrast to the increase in the hepatic flow per liter of liver, the clearance of orally administered cholate per liter of liver, a marker of portal inflow, did not change. Taken together, these observations suggest that the enhancement of HBF is likely related to the selective recruitment of oxygen-rich hepatic arterial inflow. The importance of arterial perfusion in hepatic regeneration was emphasized recently in a rat model of ischemic injury.[21] In that model, hepatic arterial perfusion determined not only the extent of hepatic necrosis but also the formation of vascularized sinusoidal channels and parenchymal recovery.

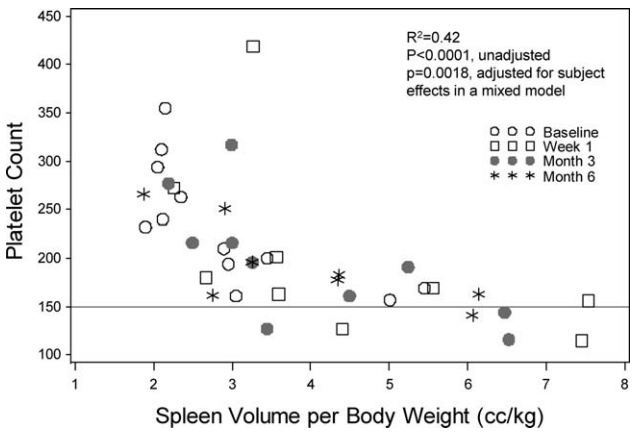

Figure 3. Platelet counts and spleen volumes per kilogram of body weight before and after donation. The relationship between the platelet count and the spleen volume is shown, with the cutoff for a normal platelet count at 150 μL^{-1}. The results for studies performed at the baseline and at T1, T2, and T3 after donation are indicated by separate markers. There was an inverse relationship between the platelet count and the spleen volume.

Another unique finding of our study was the selective enhancement of the hepatic uptake of orally administered cholate during early rapid hepatic regeneration. In animal models, activation of the primary nuclear bile acid receptor (farnesoid X receptor) by the hepatic flux of bile acids accelerates regeneration and inhibits genes of metabolism.[22-24] Thus, it is interesting that we measured a specific increase in the hepatic uptake of cholate during the early rapid phase of hepatic regeneration. We speculate that enhanced cholate uptake during the early phase of regeneration in living donors supports a role for bile acids in the regulation of human hepatic regeneration.

We did not observe statistically significant changes in the clearance or metabolism of 2 substrates of the cytochrome P450 system, caffeine and erythromycin. The immediate effect of hepatic resection is a reduction in the total hepatic metabolic capacity.[25] Our results indicated that 11±3 days after donation, the hepatic metabolic capacity had returned to the baseline, and the metabolism of both caffeine and erythromycin per liter of liver had increased; this was consistent with compensatory up-regulation of hepatic cytochrome P450 enzymes. A study examining the acute phase response of cytochrome P450 enzymes after living donor liver transplantation found an early reduction at days 3 to 4 in EBT with a return to nearly the baseline around day 10.[26] Nonetheless, in the first several days after donation, it is likely that donors have a reduced total metabolic capacity due to the loss of hepatocyte mass and the immediate regenerative process.[22-25] A clinical point worth emphasizing is that the dosing of medications cleared by hepatic metabolism should be adjusted downward to avoid excessive accumulation and toxicity during the first 1 to 2 weeks after donor hepatectomy.

An important observation of our study with potential clinical implications is the evidence pointing to an alteration of the portal circulation. Cholate shunt is a real-time measure of events in the portal circulation. There was an initial perturbation of the portal circulation with increased cholate shunt, which then trended toward normal by T2 and was at or near the baseline by T3. Other findings indicated a persistently altered portal circulation. The spleen volume increased by T1, trended downward by T2 and T3, but remained significantly above the baseline at T3. The increase in the spleen size was associated with a decreased platelet count; indeed, we found a significant inverse correlation between the platelet count and the spleen volume.

Others have also noted a relationship between the platelet count and the spleen size after living donation.[25,27,28] In these studies, a reduction in the platelet count was associated with normal or elevated levels of thrombopoeitin.[29] These findings and our results are consistent with hypersplenism from the persistence of an altered portal circulation and portal hypertension and suggest that long-term follow-up of donors and evaluations for manifestations of an altered portal circulation or portal hypertension may be warranted.

We conclude that there are at least 2 phases of hepatic regeneration. The early rapid phase of regeneration lasts for 2 weeks, accounts for two-thirds of total regeneration, and is associated with the recruitment of hepatic arterial inflow and enhanced uptake of bile acids. Right hepatic lobectomy alters the portal circulation; some of the changes are reversed, but others persist. Although the clinical implications of these findings are unknown, further long-term studies of the portal circulation of donors may be warranted.

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