Published in final edited form as:
Liver Transpl. 2013 March ; 19(3): 292–304. doi:10.1002/lt.23592.

Functional Elements Associated with Hepatic Regeneration in Living Donors after Right Hepatic Lobectomy[1,,2]

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Abstract

We quantified rates of hepatic regeneration and functional recovery for 6 months after right hepatic lobectomy in living donors for liver transplantation.

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[1]This is publication number 20 from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL Study Group). A2ALL was registered with clinicaltrials .gov (NCT00096733).

[2]**Financial Support:** This study was supported by the National Institute of Diabetes, Digestive & Kidney Diseases, National Institutes of Health, Bethesda, MD (NIDDK grant numbers: U01-DK62536, U01-DK62444, U01-DK62467, U01-DK62483, U01-DK62484, U01-DK62494, U01-DK62496, U01-DK62498, U01-DK62505, U01-DK62531) and University of California – Irvine, Irvine, CA (contract 38643).

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Conflicts of Interest G. T. Everson has equity interest in HepQuant LLC.

Authors with no financial relationships to disclose are: J. Hoefs, C. Niemann, K. Olthoff, R. Dupuis, S. Lauriski, A. Herman, N. Milne, B. Gillespie, N. Goodrich, J. Everhart.

Contributions of Authors: Gregory T. Everson and Claus U. Niemann were principal investigators at the two clinical centers at the University of Colorado and University of California San Francisco, respectively. John C. Hoefs and Norah Milne were responsible for the analyses of SPECT liver-spleen scans. Kim Olthoff participated in preparation of the manuscript. Robert Dupuis analyzed the erythromycin breath tests and Shannon Lauriski analyzed the cholate clearances and shunt and caffeine and galactose samples. Andrea Herman was study coordinator at Colorado. Brenda Gillespie and Nathan Goodrich performed the statistical analyses. James Everhart was the project officer from NIDDK, NIH.

Twelve donors were studied at baseline; eight retested at (mean±SD) 11±3 days (T1), 10 at 91±9 days (T2), and 10 at 185±17 days (T3) after donation. Liver and spleen volumes were measured by computed tomography (CT) and single photon emission computed tomography (SPECT). Hepatic metabolism was assessed from caffeine and erythromycin, and hepatic blood flow from cholates, galactose, and perfused hepatic mass (PHM, by SPECT).

Regeneration rates (mL liver per kg body weight per day) were 0.60±0.22 from baseline to T1, 0.05±0.02 from T1 to T2, 0.01±0.01 from T2 to T3 by CT, 0.54±0.20, 0.04±0.01 and 0.01±0.02 by SPECT. At T3, liver volume was 84±7% of baseline by CT and 92±13% by SPECT. Changes in hepatic metabolism did not achieve statistical significance. At T1, unadjusted clearance ratios relative to baseline were 0.75±0.07 for intravenous cholate (p=0.0001), 0.88±0.15 for galactose (p=0.0681), 0.84±0.08 (p=0.002) for PHM, and 0.83±0.19 (p=0.056) for estimated hepatic blood flow. These ratios approached 1.00 by T3. At T1, ratios adjusted per L liver were 20%-50% greater than baseline and trended toward baseline by T3. Several findings were consistent with alteration of the portal circulation: increased cholate shunt, increased spleen volume, decreased platelet count, and decreased clearance of orally-administered cholate.

During the first 2 weeks after donation, hepatic regeneration is rapid and accounts for nearly two-thirds of total regeneration. Increases in hepatic blood flow and uptake of cholate characterize the early phase of regeneration. Right lobe donation alters the portal circulation of living donors, but long-term clinical consequences, if any, are unknown.

Keywords

cholate; SPECT liver-spleen scan; erythromycin; caffeine; galactose

Donor safety and outcome are the chief concerns of programs performing living donor liver transplantation (1,2). For adult recipients, a right lobe graft may be preferred over left lobe grafts due to the larger hepatic mass and anatomic orientation of vascular and biliary structures. For donors, a consequence of donating the right lobe graft is a relatively small remnant of residual liver from which to regenerate their liver mass. 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 resection of an otherwise normal liver is rapid, and usually complete within a few weeks (4,5). In these models, survival is linked to rate and completeness of regeneration and restoration of hepatic function.

Less is known about hepatic regeneration, hepatic function, and clinical outcomes in humans. Humar and colleagues measured liver volumes by computed tomography (CT) at 3 months post-donation and found that donor liver volume was 78.6% of ideal, whereas recipient liver volume was 103.9% of ideal (6). Nadalin measured the volumes of donor remnants by magnetic resonance imaging (MRI) and found that remnant volumes were 39% of baseline immediately after resection, increased to 77% by 3 months, and were 83% of baseline at 1 year after donation (7). Pomfreit and colleagues performed CT studies at baseline and 1 week and 1, 3, 6, and 12 months post-donation (8). By 1 year, liver volume was 83.3% of baseline, and female donors had significantly less regeneration compared with male donors (79.8 vs. 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 studied galactose elimination capacity (GEC) and found that unadjusted GEC had declined 50% by day 10, but had returned to baseline at subsequent time points (7). GEC adjusted for

volume of remnant liver declined by less than 25% by day 10, was increased above baseline at days 90 and 180, and returned to baseline by day 360. Jochum (9) had results similar to Nadalin – GEC, expressed per kg body weight, was 50% lower than baseline at day 10 and nearly at baseline by day 90. Jochum also observed that indocyanine green (ICG) half-life increased and lidocaine half-life was not significantly altered (9). Neither study measured a broad array of liver functions nor did they examine the relationships of function to regeneration.

In our study, we measured multiple hepatic functions, hepatic blood flow, total liver and perfused liver volumes, and related these results to 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, were approved by the Selection Committee for liver transplantation, and the date of the operation was scheduled. Donors were recruited from two Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) clinical centers – University of Colorado, Denver and University of California, San Francisco.

The protocol was approved by the Institutional Review Boards at the participating institutions, and all 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 in the General Clinical Research Centers (GCRC) of the participating centers. An indwelling intravenous 20-gauge catheter was placed for administration of test compounds and sampling blood. Patients were supine during the study and minimized their activity.

Hepatic metabolism was quantified using erythromycin (10) and caffeine (11) as test compounds.

Erythromycin breath test (EBT)—Three μCi of [^{14}C-N-methyl] erythromycin (Metabolic Solutions Inc, Nashua, NH, product #: 02410806, IND: 31,760) was administered intravenously with a bolus injection followed by a 10 ml normal saline flush. Breath samples for measurement of $^{14}CO_2$ generated from the hepatic metabolism of erythromycin were collected at baseline and 20 minutes after dose administration using a T-tube apparatus, capture solution, and indicator dye (12). $^{14}CO_2$ was quantified by radioscintigraphy and percentage of erythromycin metabolized per hour determined.

Caffeine elimination rate (Caff k_{elim}) and clearance (Caff Cl)—Caffeine, 300 mg (Ruger Chemical Co., Irvington, NJ, product number 0072-5, IND 65,175), was administered orally and its hepatic metabolism determined from clearance measured by high-performance liquid chromatography (HPLC) of saliva samples obtained at 2, 4, 8, and 12 hours after dosing. Volume of distribution (V_d) and k_{elim} were determined by linear regression of $\log_e$ concentration versus time and Cl was the product of V_d multiplied by k_{elim}.

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

Galactose elimination capacity (GEC)—Galactose, 30 g of low endotoxin D-galactose (Pfanstiehl Laboratories, Inc., Waukegan, IL, product number G-105-1, IND 65107), in 100 mL sterile water was administered intravenously over 5 minutes. Blood samples were obtained at baseline and 20, 40, 60, and 80 minutes after dosing and galactose concentration quantified by spectrophotometry using a standardized kit (Lactose/D-galactose kit, Boehringer Mannheim Cat. No. 176 303). GEC is the slope from the linear regression of concentration versus time.

Cholate clearances (CA Cl) and shunt (CA shunt)—Dual isotopes of cholate were simultaneously administered in 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 (CDN Isotopes Inc. Quebec Canada, product # D-2452, studied under IND 65123) plus 600 mg $NaHCO_3$ in apple or grape juice. The intravenous solution contained 20 mg 24-^{13}C cholate (CDN Isotopes Inc. Quebec Canada, product # C-3448, studied under IND 65121) dissolved in 5 mL of USP grade $NaHCO_3$, 1meq/mL (Baxter HealthCare, Tarrytown, NY). This solution was mixed with 5 mL of USP grade 25% human serum albumin (Bayer HealthCare Tarrytown, NY 10591 NDC# 0026-0692-16) and administered via antecubital vein over 1 minute. Blood samples were obtained at baseline and at 5, 20, 45, 60, and 90 minutes after dosing (14) and cholate isotopes quantified by LC/MS. CA Cl_{oral} and CA Cl_{iv} were calculated from dose (40 mg oral or 20 mg intravenous) divided by area under the concentration versus time curves for each isotope (mg*min/mL) and normalized for body weight (kg), and CA shunt was the ratio of clearances of the intravenously to orally-administered isotopes. Estimated hepatic blood flow was calculated from the equation, CA Cliv/((1-shunt/100)*(1-hematocrit)). An example of a pair of studies from one donor of dual cholate clearance studies prior to and after donation is shown in Figure 1.

SPECT liver-spleen scan—After completion of blood sampling for the galactose and cholate tests, patients ingested a standard meal and 375 ml Ensure (Abbott Laboratories, Abbott Park, IL) at 30 minutes prior to intravenous administration of 5 to 6 mCi of ^{99m}Tc-cis-sulfur colloid (2 to 12 micron particle size, CIS-US, Inc., Bedford, MA) for SPECT (15-18). SPECT studies were performed at the two clinical sites and data transferred to UC Irvine for processing (JCH, NM). Perfused hepatic mass (PHM) calculated from these images quantified the relative distribution of sulfur colloid between liver, spleen and bone marrow. Volumes of liver and spleen were also determined (16-20).

Organ volumes and rates of hepatic regeneration were measured by both CT and SPECT liver-spleen scan.

Volumes from CT/MRI—CT studies and SPECT liver-spleen scan were performed on different days. Liver and spleen volumes were determined from the standard CT software algorithms used by the Radiology Departments at participating clinical sites.

Volumes from SPECT—Liver and spleen volumes were also calculated from the SPECT reconstruction of images using the method of Hoefs (16-20). Volume was derived from total counts in liver and spleen from regions of interest around the summarized transaxial image, a representative organ concentration from a single transaxial slice, and dividing the total hepatic or splenic counts by a representative concentration.

Hepatic regeneration rates were defined by $\Delta V/\Delta t$, from both CT and SPECT, where ΔV was the change in hepatic volume between consecutive time points and Δt the time interval. Baseline (B) volume was the liver volume measured prior to donation. Remnant liver volume on the day of donation (T0) was determined from baseline CT by subtracting the estimated right lobe graft from total liver. For SPECT, we assumed the same proportionate size of remnant relative to baseline as was estimated from CT. Regeneration rates were determined for the intervals from T0 to T1, T1 to T2, and T2 to T3.

Clearance tests were expressed relative to body size (per kg) or liver size (per L liver). Changes in hepatic metabolism (microsomal function) were estimated from the serial changes in caffeine clearance (CYP1A2) and the erythromycin breath test (CYP3A4). Changes in total hepatic blood flow were estimated from the serial changes in galactose elimination capacity, clearance of intravenously-administered 24-^{13}C cholate, and SPECT liver-spleen scan. Alteration of the portal circulation was assessed by the changes from baseline in clearance of orally-administered 2,2,4,4-^{2}H cholate, cholate shunt, PHM from SPECT liver spleen scan, platelet count, and spleen volume.

Statistical Analyses

Results are expressed as means, standard deviations, and ranges. Differences between baseline and post-donation results at T1, T2, and T3, and differences between post-baseline time points, were compared using 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) using SAS release 9.2 (SAS Institute, Cary, NC).

RESULTS

Twelve donors were studied at baseline (B); eight were retested at 11±3 days (T1), ten at 91±9 days (T2), and ten at 185±17 (T3) days after surgery. The mean age was 38 years (range 21 to 54 years), body mass index (BMI) 25.2±2.8, sex 4M:8F, and 10 were white.

Standard Laboratory Tests

Table 1 displays the changes in routine laboratory tests over time after donation. All laboratory values were normal at baseline. At T1, bilirubin, INR, and ALT were higher and albumin lower than baseline values. By T2, these tests were trending toward baseline and at T3, all had returned to baseline values.

Total Liver versus Perfused Liver Volume

Volumes by CT are larger than those measured by SPECT. Linear regression through the origin of CT versus SPECT volumes, using data from all time points, indicated that liver volumes by CT/MRI were approximately 22% larger (slope 1.22, $r = 0.93$, $p<0.0001$) and spleen volumes 4% larger when compared with SPECT (slope 1.04, $r = 0.95$, $p<0.0001$). Ratios of perfused liver volume (by SPECT) to total liver volume (by CT) were constant during regeneration (0.84 to 0.86), although slightly greater than the ratio at baseline (0.78).

Regeneration Rates

Liver volumes at each time point (mL and mL/kg), reconstitution of baseline volume ($V_t/V_{pre\text{-}donation}$), and rates of regeneration (mL kg^{-1} d^{-1}) are given in Table 2. The relative changes in these parameters during regeneration were similar between CT and SPECT. Total liver volumes by CT at each time point (T0 through T3), relative to pre-donation volumes, are shown for each donor in Figure 2, Panel A.

There were at least two phases of regeneration – a rapid early phase during the first 2 weeks and a slower later phase after the first 2 weeks. Based on CT, regeneration rates were 0.60±0.22 mL $kg^{-1}d^{-1}$ from T0 to T1, 0.05±0.02 mL $kg^{-1}d^{-1}$ from T1 to T2, and 0.01±0.01 mL $kg^{-1}d^{-1}$ from T2 to T3 (Table 2). Based on SPECT, regeneration rates were similar: 0.54±0.20 mL$kg^{-1}d^{-1}$ from T0 to T1, 0.04±0.01 mL $kg^{-1}d^{-1}$ from T1 to T2, and 0.01±0.02 mL $kg^{-1}d^{-1}$ 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, liver volumes were 84±7% of baseline by CT and 92±13% of baseline by SPECT (Table 2).

Hepatic Metabolism

Changes in hepatic metabolism from pre-donation baseline are shown in Table 3. Total clearances of caffeine and erythromycin were slightly lower than baseline at T1; and slightly greater than baseline by T2 and T3. After adjusting for liver volume, clearances of caffeine and erythromycin were increased above baseline at T1, and this increase persisted through T2 and T3. However, none of these changes in metabolism were statistically significant.

Hepatic Blood Flow

Total clearances of galactose, intravenous cholate, and SPECT, and calculated total hepatic blood flow are displayed in Table 4. These tests reflect the total blood flow to the remnant. At T1, total clearance of galactose (GEC) was 0.88±0.15 of pre-donation baseline (p=0.0681), cholate after intravenous administration (CA Cl_{iv}) 0.75±0.07 of baseline (p=0.0001), and ^{99m}Tc-cis-sulfur colloid (SPECT) 0.84±0.08 of baseline (p=0.002). Total hepatic blood flow had decreased to 0.83±0.19 of baseline (p=0.056). Thus, by three very different methods (GEC, dual cholate clearance, and SPECT) we demonstrated, unadjusted for liver volume, a consistent moderate decrease in total clearance and hepatic blood flow at T1.

Although the total clearances of flow-dependent compounds were reduced at T1, clearances adjusted for liver volume, expressed per L liver, were increased at T1 (Table 4). Clearances per L liver of galactose, intravenous cholate, and ^{99m}Tc-cis-sulfur colloid (estimated change in HBF) were all increased above baseline. These findings suggest that the early rapid phase of regeneration is associated with enhanced blood flow per unit of 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 intravenous cholate, total clearance of orally-administered cholate is decreased at T1, reflecting the reduced hepatic mass. But, unlike intravenous cholate, clearance per L liver of orally-administered cholate did not increase above baseline at T1 (Table 5). The selective increase in clearance per L liver of intravenously-administered cholate, is consistent with selective enhancement of hepatic arterial flow during the early phase of regeneration.

First Pass Uptake of Cholate

We estimated 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 liver volume. At T1, during the period of rapid regeneration, we found a significant increase in cholate uptake (B vs. T1, mg/L liver: 21±5 vs. 31±9, p=0.017). Cholate uptake at T2 (25±4, p=0.034) and T3 (24±6, p=0.058) approached baseline values.

Alteration of the Portal Circulation

Several of our test results suggested that the portal circulation is altered after right lobe donation (Table 5). At T1, the total clearance of orally-administered cholate decreased (p=0.0006), cholate shunt increased (p=0.03), and platelet count decreased (p=0.07). These changes persisted at T2, but, except for platelet count, trended toward normal by T3.

Paralleling the changes in platelet count, spleen volumes by both CT and SPECT increased by T1. Spleen volume did not increase further, declined slightly, but remained above baseline throughout (Figure 2, Panel B and Table 5). By T3, 6 months after donation, CT spleen volume remained at 127±17% of baseline (p=0.0009) and SPECT spleen volume remained at 150% of baseline (p=0.015). Platelet count at T1 was 14% lower than baseline and remained decreased through T3 (Table 5). Platelet count was inversely related to spleen volume (Figure 3). This relationship was significant both unadjusted (p=0.0001) or adjusted (p=0.0018) for subject effects with a mixed model.

DISCUSSION

This prospective study examined the longitudinal changes in multiple hepatic functions after donation of the right hepatic lobe by living donors, and uniquely related functional changes to the regeneration of the left lobe remnant. Ten of the 12 donors we studied had an uncomplicated post-operative course as indicated by standard laboratory tests and lack of clinical complications. For the two 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 in the first month post-donation. Thus, our results of hepatic imaging, volume determinations, and function testing may likely apply to other donors undergoing a right hepatic lobectomy with an uncomplicated or modestly complicated course.

We observed differences in liver volumes related to the differences in imaging between CT and SPECT. CT images include all structures within the region of interest, including vascular, connective tissue, and biliary structures. SPECT images are based on 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 the perfused hepatic mass.

Rates of regeneration varied with time following hepatic lobectomy. After lobectomy, the residual left lobe remnant was 31% of baseline hepatic volume by CT/MRI. In the first 2 weeks post-donation, hepatic volume nearly doubled, and regeneration rate was 0.60 mL d^{-1} kg^{-1} body weight by CT/MRI and 0.54 mL d^{-1} kg^{-1} body weight by SPECT. Regeneration slowed dramatically after the first 2 weeks. During the following approximate 3 months, regeneration was only 0.05 mL d^{-1} kg^{-1} body weight by CT/MRI and 0.04 mL d^{-1} kg^{-1} body weight by SPECT. Regeneration rate was even slower between 3 (T2) and 6 months (T3). Consistent with other studies (6-9), hepatic regeneration in donors was incomplete. At 6 months post-donation, donors achieved only 84% (CT/MRI) to 92% (SPECT) of their baseline hepatic volume. The dramatic differences in regeneration rates between time intervals suggests that factors regulating hepatic growth and, ultimately, final liver volume must vary considerably between the early and later phases of regeneration.

The rapid early phase of rapid hepatic regeneration, from baseline to T1, was associated primarily with two functional changes – enhancement of hepatic blood flow per gram of hepatic tissue and increase in the hepatic uptake of cholate. Naturally, the total hepatic blood flow must decrease with removal of 60% of hepatic tissue, but the liver compensates by increasing local flow. Hepatic blood flow per L liver was assessed by three independent measurements that indicated a ~30% to 50% increase in tissue blood flow. Thus, the blood

flow per L tissue increased helping to preserve blood flow dependent hepatic function and partially compensate for the decrease in total hepatic mass.

In contrast to the increase in hepatic flow per L liver, the clearance of orally-administered cholate per L liver, a marker of portal inflow, did not change. Taken together, these observations suggest that the enhancement of hepatic blood flow is likely related to 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 the latter model, hepatic arterial perfusion determined not only the extent of hepatic necrosis but also the formation of vascularized sinusoidal channels and parenchymal recovery.

Another unique finding of our study was selective enhancement of 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 (FXR), by the hepatic flux of bile acids accelerates regeneration and inhibits genes of metabolism (22-24). Thus, it is of interest that we measured a specific increase in 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 two substrates of the cytochrome P450 system, caffeine and erythromycin. The immediate effect of hepatic resection is reduction in total hepatic metabolic capacity (25). Our results indicated that by 11±3 days post-donation, hepatic metabolic capacity had returned toward baseline and the metabolism of both caffeine and erythromycin per L liver had increased – consistent with compensatory up-regulation of hepatic cytochrome P450 enzymes. A study examining the acute phase response of cytochrome P450 enzymes after LDLT found early reduction at day 3-4 in EBT with a return to near baseline around day 10 (26). Nonetheless, in the first several days post-donation, it is likely that donors have a reduced total metabolic capacity due to loss of hepatocyte mass and the immediate regenerative process (22-25). A clinical point worth emphasizing is that 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 was 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 portal circulation with increased cholate shunt which then trended toward normal by T2 and was at or near baseline by T3. Other findings indicated a persistently altered portal circulation. Spleen volume increased by T1, trended downward by T2 and T3, but remained significantly above baseline at T3. The increase in spleen size was associated with decreased platelet count – indeed we found a significant inverse correlation of platelet count to spleen volume.

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

We conclude that there are at least two 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 recruitment of hepatic arterial inflow and enhanced uptake of bile acids. Right hepatic lobectomy alters the portal circulation, some of the changes reverse 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.

Acknowledgments

The authors wish to acknowledge the contributions of our co-investigators, study coordinators, and staff at each of the participating institutions: Jennifer DeSanto RN, Rita Lerner, Michelle Jaramillo at University of Colorado Denver, Aurora, CO; Jenifer Twiford, RN at University of California San Francisco, San Francisco, CA, Dulce MacLeod, RN at University of California San Francisco, San Francisco, CA; Carrie Nielsen at University of North Carolina, Chapel Hill, NC; Peg Hill-Callahan, Katherine Baisden, and Terese Howell at University of Michigan, Ann Arbor, MI; Jay H. Hoofnagle and Leonard Seeff at National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition, Bethesda, MD; and, members of the Data and Safety Monitoring Board for A2ALL.

Financial Disclosures: G. T. Everson has intellectual property rights related to the University of Colorado Denver filing of US Patent Application No. 60/647,689, “Methods for Diagnosis and Intervention of Hepatic Disorders”, 26 January 2005, and International Application Number 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, 3 August 2006 (03.08.2006).

Biography

The following individuals were instrumental in the planning, conduct and/or care of patients enrolled in this study at each of the participating institutions as follows:

Columbia University Health Sciences, New York, NY (DK62483): PI Jean C. Emond, M.D.; Co-PI, Robert S. Brown Jr, M.D., M.P.H.; study coordinators, Scott Heese, B.A., and Jonah S. Zaretsky, B.A.

Northwestern University, Chicago, IL (DK62467): PI Michael M. I. Abecassis, M.D., M.B.A.; Co-PI Laura M. Kulik, M.D.; study coordinator, Patrice Al-Saden, R.N., C.C.R.C.

University of Pennsylvania Health System, Philadelphia, PA (DK62494): PI Abraham Shaked, M.D., Ph.D.; Co-PI Kim M. Olthoff, M.D.; study coordinators, Brian Conboy, P.A., M.B.A., and Mary Shaw, R.N., B.B.A.

University of Colorado Health Sciences Center, Denver, CO (DK62536): PI Gregory T. Everson, M.D.; Co-PI Igal Kam, M.D.; study coordinators, Carlos Garcia, B.S., and Anastasia Krajec, R.N.

University of California Los Angeles, Los Angeles, CA (DK62496):PI Johnny C. Hong, M.D.; Co-PI Ronald W. Busuttil, M.D., Ph.D.; study coordinator, Janet Mooney, R.N., B.S.N.

University of California San Francisco, San Francisco, CA (DK62444): PI Chris E. Freise, M.D., F.A.C.S.; Co-PI Norah A. Terrault, M.D.; study coordinator, Dulce MacLeod, R.N.

University of Michigan Medical Center, Ann Arbor, MI (DK62498): PI Robert M. Merion, M.D.; data coordinating center staff, Anna S. F. Lok, M.D., Akinlolu O. Ojo, M.D., Ph.D., Brenda W. Gillespie, Ph.D., Margaret Hill-Callahan, B.S., L.S.W., Terese Howell, B.S., A.C.R.P., Lisa Holloway, B. S., A.C.R.P., Monique Lowe, B.S., Abby Smith, B.A., and Abby Brithinee, B.A.

University of North Carolina, Chapel Hill, NC (DK62505): PI Paul H. Hayashi, M.D., M.P.H.; study coordinator, Tracy Russell, M.A.

University of Virginia (DK62484): PI Carl L. Berg, M.D.; study coordinator, Jaye Davis, R.N.

Medical College of Virginia Hospitals, Virginia Commonwealth University, Richmond, VA (DK62531): PI Robert A. Fisher, M.D., F.A.C.S.; Co-PI R. Todd Stravitz, M.D.; study coordinators, April Ashworth, R.N., and Andrea Lassiter, B.S.

Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD: James E. Everhart, M.D.,M.P.H., Averell Sherker, M.D., and Jay H. Hoofnagle, M.D.

Heather Van Doren, MFA, a senior medical editor with Arbor Research Collaborative for Health, provided editorial assistance on this manuscript.

List of Abbreviations

A2ALL	Adult-to-Adult Living Donor Liver Transplantation Cohort Study
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
Cl	clearance
EBT	erythromycin breath test
GCRC	General Clinical Research Center
GEC	galactose elimination capacity
IND	Investigational New Drug
INR	prothrombin time international normalized ratio
$\mathbf{k_{elim}}$	elimination rate constant
LC/MS	liquid chromatography–mass spectrometry
LDLT	living donor liver transplantation
PHM	perfused hepatic mass
QLFTs	quantitative liver function tests
SD	standard deviation
SPECT	single photon emission computed tomography

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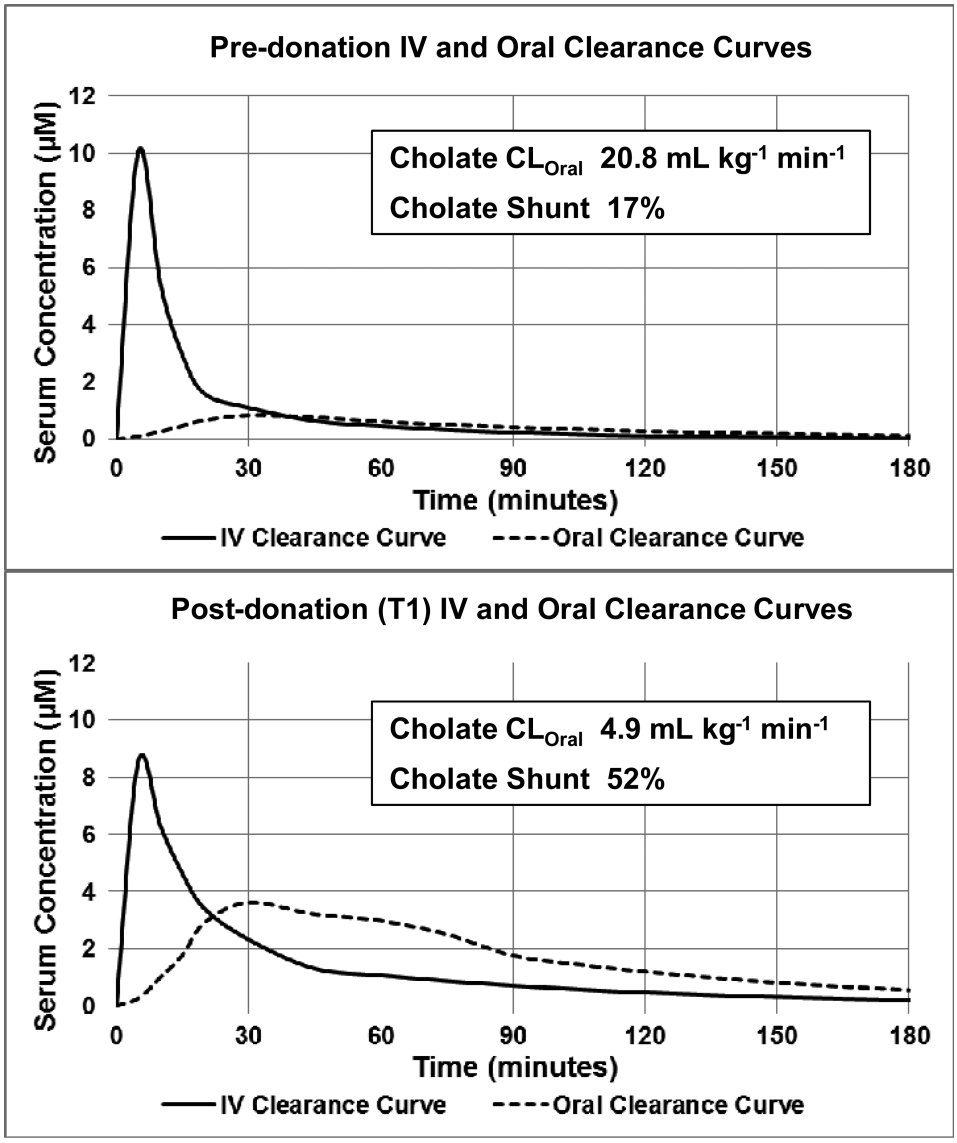

Figure 1. Example of clearances of cholates before and after donation

This figure displays the clearance curves for intravenously- (solid line) and orally-(dashed line) administered cholate isotopes in a single donor at baseline, prior to donation (upper Panel) and at T1 after donation (lower Panel). The increase in systemic concentrations of the orally-administered [2,2,4,4-D] cholate reflects the altered portal circulation and reduced hepatocyte mass after resection.

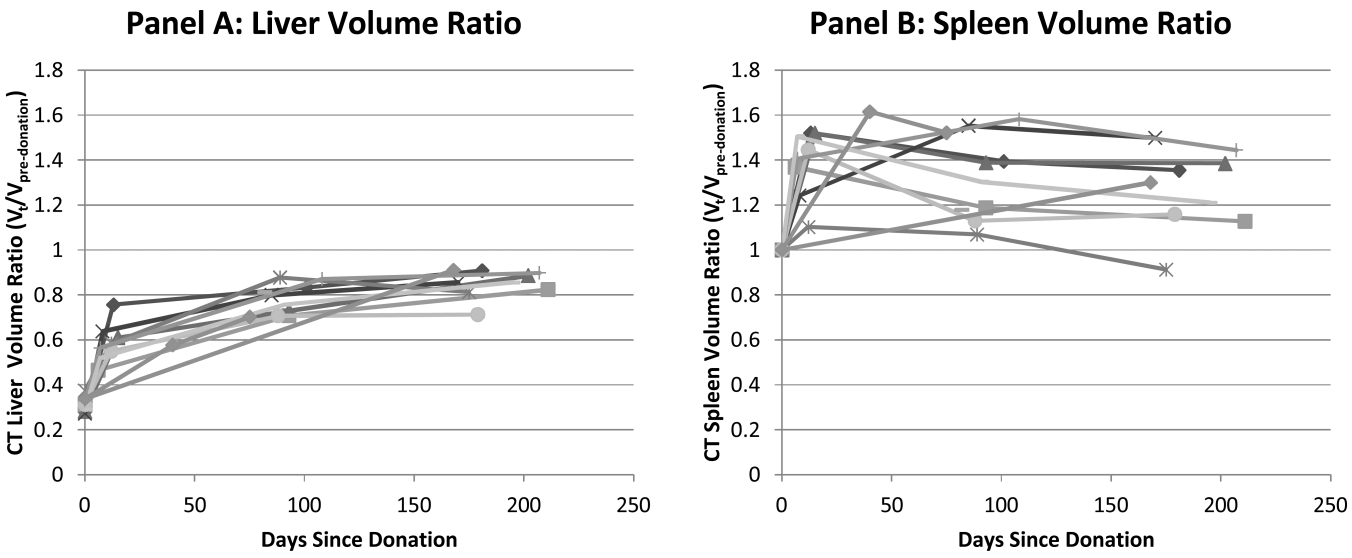

Figure 2. Liver and spleen volume ratios (compared with baseline pre-donation) by time since donation

Panel A. Liver volumes relative to the volume of the liver at baseline prior to donation are shown for each donor (n=10). Panel B. Spleen volumes relative to the volume of the spleen at baseline prior to donation are shown for each donor (n=10).

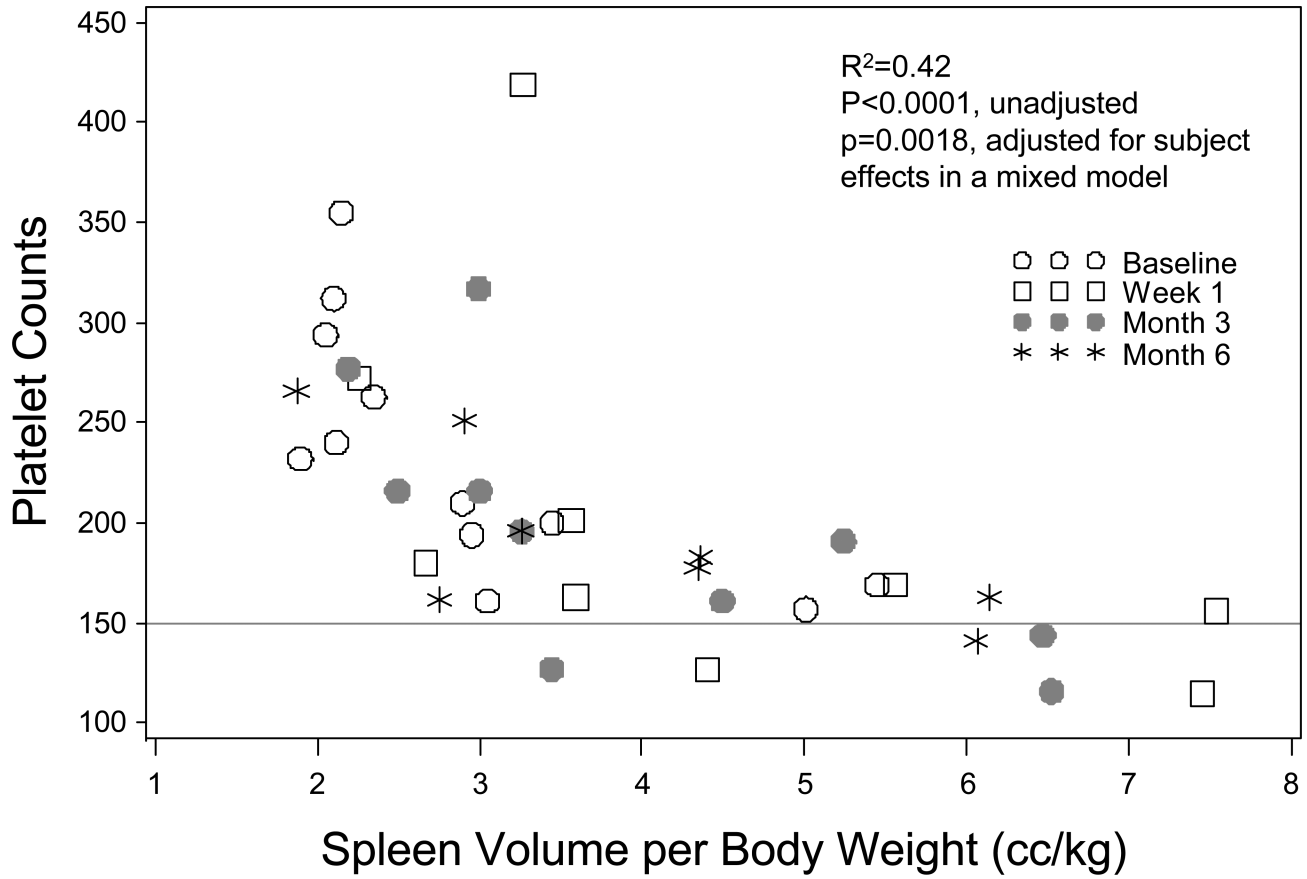

Figure 3. Platelet count and spleen volume per kg body weight before and after donation

The relationship of platelet count to spleen volume is shown with the cutoff for normal platelet count at 150 μL^{-1}. Results for studies performed at baseline, and at T1, T2, and T3 after donation are indicated by separate markers. In general, regardless of study period, there was an inverse relationship of platelet count to spleen volume.

Table 1

Laboratory values before and after donation

Mean (Standard Deviation), p-value*, n				
	Pre-donation (B)	Post-donation		
		T1	T2	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=0.921 n=7
INR	1.03 (0.05) n=12	1.22 (0.16) p=0.004 n=9	1.08 (0.08) p=0.122 n=10	1.06 (0.07) p=0.351 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=0.662 n=9	3.69 (0.47) p=0.148 n=7
ALT (IU/mL)	22 (5.80) n=12	91 (70.61) p=0.018 n=9	31 (11.62) p=0.047 n=9	25 (12.94) p=0.846 n=7

Tests are based on post-donation sample sizes, which assured data at both time points.

*P-values are from two-sided paired t-tests comparing post-donation with pre-donation values.

Table 2

Hepatic regeneration: Liver volumes (V) before and after donation

	Mean (standard deviation)					p-values*		
	Pre-donation (B)	Post-donation				T0 vs. T1	T1 vs. T2	T2 vs. T3
		T0 (estimated)**	T1	T2	T3			
By 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)	<0.0001 (n=8)	0.0005 (n=8)	0. 0094 (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)	<0.0001 (n=8)	0.0002 (n=8)	0.0149 (n=10)
$V_t/V_{pre\text{-}donation}$	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)	0.0001 (n=8)	0.0003 (n=8)	0.0175 (n=10)
Regeneration rate (mL kg^{-1} d^{-1})*			0.60 (0.22) (n=8)	0.05 (0.02) (n=8)	0.01 (0.01) (n=10)		0.0002 (n=8)	0.0069 (n=8)
By 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)	<0.0001 (n=7)	0.0002 (n=7)	0.0277 (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)	0.0002 (n=7)	<0.0 001(n=7)	0.0372 (n=10)
$V_t/V_{pre\text{-}donation}$	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)	0.0001 (n=7)	<0.0001 (n=7)	0.0343 (n=10)
Regeneration rate (mL kg^{-1} d^{-1})			0.54 (0.20) (n=7)	0.04 (0.01) (n=7)	0.01 (0.02) (n=10)		0.0007 (n=7)	0.0326 (n=7)

* P-values are from two-sided paired t-tests comparing values at adjacent time points.

** For CT, T0 CT volume was estimated from pre-donation CT scans by subtracting right lobe from total liver volume. For SPECT T0, volume was assumed to be proportionate to pre-donation volume as estimated by CT.

*** Regeneration rate was calculated for each interval from $(V_T - V_{T-1})/(t_T - t_{T-1})$, where V is liver volume in mL, T is the study period (T0, T1, T2, or T3), and t is time in days.

Table 3

Hepatic metabolism before and after donation

	Mean (standard deviation)				p-values*		
	Pre- donation** (B)	Post-donation			B vs. T1	B vs. T2	B vs. T3
		T1	T2	T3			
Total clearance							
Caffeine	n=11	n=7	n=9	n=7	n=7	n=9	n=7
Elimination rate constant (k_{elim}) (h^{-1})	.119 (.076)	.096 (.083)	.128 (.058)	.141 (.089)	0.7348	0.9860	0.4812
Clearance (Cl) (mL min^{-1} kg^{-1} body weight)	1.54 (0.90)	1.41 (1.21)	1.78 (1.14)	1.75 (1.32)	0.9822	0.7198	0.7592
Erythromycin breath test (EBT)	n=10	n=5	n=8	n=8	n=5	n=8	n=8
% metabolized (per hour)	2.96 (1.12)	2.37 (0.95)	2.54 (1.26)	2.67 (1.28)	0.1358	0.1156	0.1586
% metabolized (per hour kg^{-1} body weight)	0.04 (0.02)	0.03 (0.01)	0.04 (0.02)	0.04 (0.02)	0.1393	0.2219	0.1748
Clearance per liter liver							
Caffeine	n=11	n=7	n=9	n=7	n=7	n=9	n=7
Clearance (mL min^{-1} L^{-1} liver by CT)	55 (35)	76 (56)	79 (34)	75 (39)	0.2900	0.1494	0.3056
Clearance (mL min^{-1} L^{-1} liver by SPECT)	70 (38)	91 (70)	96 (44)	88 (47)	0.3419	0.1474	0.4445
EBT	n=10	n=5	n=8	n=8	n=5	n=8	n=8
% metabolized (per hour L^{-1} liver by CT)	2.03 (1.10)	2.97 (1.35)	2.28 (1.36)	2.24 (1.49)	0.1945	0.7642	0.8938
% metabolized (per hour L^{-1} liver by SPECT)	2.55 (1.28)	3.36 (1.39)	2.68 (1.60)	2.56 (1.48)	0.4446	0.9849	0.7164

*P-values are from two-sided paired t-tests comparing post-donation to pre-donation (baseline) values.

**For comparison with post-donation T1 values, the following pre-donation mean (SD) are given for the seven patients who had both pre-donation and T1 values for caffeine: caffeine k_{elim}, 0.107 (0.031), Cl/body weight 1.40 (0.52), and Cl/liver volume by CT 51 (11). For the five patients with paired EBT tests at pre-donation and T1, the pre-donation EBT total was 3.22 (1.45) and EBT adjusted for liver volume by CT was 2.37 (1.43).

Table 4

Parameters of hepatic blood flow (HBF)

	Mean (standard deviation)				p-values*		
	Pre-donation (B)	Post-donation			B vs. T1	B vs. T2	B vs. T3
		T1	T2	T3			
Total clearance	n=11	n=8	n=10	n=10	n=7	n=9	n=9
GEC ** **(mg/min per kg body weight)**	6.46 (1.14)	5.42 (0.87)	6.62 (1.42)	6.96 (1.34)	0.0801	0.2311	0.0238
CA Cl_{iv} total *** **(mL/min per kg body weight)**	5.68 (2.08)	4.06 (1.32)	4.80 (1.53)	4.70 (1.90)	0.0032	0.4070	0.3168
HBF (mL/min per kg body weight)	13.2 (6.6)	10.4 (5.1)	11.9 (4.9)	11.0 (4.4)	0.0358	0.7790	0.3902
Perfused hepatic mass (PHM)	104 (4) n=12	87 (5) n=7	95 (6) n=10	97 (6) n=10	0.0021 n=7	0.0011 n=10	0.0032 n=10
Clearance per liter liver by CT and SPECT ***							
GEC ** **(mg/min per L liver by CT)**	303 (54) n=11	455 (60) n=8	408 (73) n=10	403 (91) n=10	0.0031 n=7	0.0015 n=9	0.0010 n=9
GEC ** **(mg/min per L liver by SPECT)**	386 (76) n=11	524 (71) n=7	487 (97) n=10	468 (76) n=10	0.0385 n=6	0.0046 n=9	0.0034 n=9
CA Cl_{iv} total **** **(mL/min per L liver by CT)**	272 (110) n=11	348(135) n=8	292 (77) n=10	270 (99) n=10	0.0192 n=7	0.5628 n=9	0.8916 n=9
CA Cl_{iv} total **** **(mL/min per L liver by SPECT)**	340 (130) n=11	372 (117) n=7	352 (105) n=10	313 (106) n=10	0.1073 n=6	0.7349 n=9	0.5616 n=9
Total HBF (mL/min per L liver ***** **by CT)**	633 (341) n=11	904 (522) n=8	726 (262) n=10	630 (237) n=10	0.0479 n=7	0.4518 n=9	0.8716 n=9
Total HBF (mL/min per L liver ***** **by SPECT)**	794 (418) n=11	866 (273) n=7	874 (340) n=10	728 (253) n=10	0.1908 n=6	0.5799 n=9	0.6118 n=9
Change in HBF estimated by serial SPECT	n=12	n=7	n=10	n=10	n=7	n=10	n=10
Perfused hepatic mass (PHM) ratio to baseline	1	0.84 (0.08)	0.91 (0.06)	0.93 (0.06)	0.0016	0.0008	0.0032
Liver volume ratio to baseline	1	0.64 (0.08)	0.82 (0.10)	0.92 (0.13)	<0.0001	0.0004	0.0852
Relative change in HBF	1	1.33 (0.20)	1.13 (0.18)	1.03 (0.16)	0.0047	0.0535	0.6084

* P-values are from two-sided paired t-tests comparing post-donation with pre-donation (baseline) values for measures with baseline values. For the ratios compared with baseline, p-values are from one-sample t-tests comparing the means of the individual ratios with 1.0, the null mean value.

** GEC = Galactose elimination capacity

*** SPECT = single photon emission computed tomography

**** CA Cl_{iv} = cholate clearance after intravenous administration

***** Total HBF calculated as: CA Cl_{iv}/((1-shunt fraction%/100)(1-hematocrit))

Liver Transpl. Author manuscript; available in PMC 2014 March 01.

Table 5

Measures reflecting changes in the portal circulation before and after donation

	Mean (standard deviation)				p-value*		
	Pre-donation (B)	**T1**	**T2**	**T3**	**B vs. T1**	**B vs. T2**	**B vs. T3**
CA ** **Cl_{oral} (mL kg-1 min-1)**	25.6 (7.0) n=12	12.3 (5.5) n=8	16.3 (4.7) n=10	23.5 (15.9) n=10	0.0006 n=8	0.0009 n=10	0.5924 n=10
Cholate shunt (%)	22 (11) n=11	37 (14) n=8	30 (10) n=10	24 (11) n=10	0.0266 n=7	0.0479 n=9	0.3617 n=9
Platelet count (μL-1)	232 (63) n=12	200 (94) n=9	196 (64) n=10	193 (44) n=8	0.0739 n=9	0.0003 n=10	0.0100 n=8
by 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	0.0022 n=8	0.0004 n=10	0.0003 n=10
$V_t/V_{pre\text{-}donation}$	1.0	1.39 (0.15) n=8	1.33 (0.19) n=10	1.27 (0.17) n=10	0.0002 n=8	0.0003 n=10	0.0009 n=10
by 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	0.0513 n=7	0.0309 n=10	0.0227 n=10
$V_t/V_{pre\text{-}donation}$	1.0	1.58 (0.52) n=7	1.58 (0.65) n=10	1.50 (0.52) n=10	0.0259 n=7	0.0199 n=10	0.0145 n=10

* P-values are from two-sided paired t-tests comparing post-donation to pre-donation (baseline) values.

** CA = cholate