Volumetric and Functional Recovery of the Liver After Right Hepatectomy for Living Donation

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Our objective was to study the kinetics of recovery of the liver volume and liver function after right hepatectomy (RH) for living donation, comparing conventional and quantitative liver function tests, i.e., galactose elimination capacity (GEC). A total of 27 donors underwent RH averaging 61% of the whole liver volume. The conventional and quantitative liver function tests, as well as magnetic resonance imaging volumetric studies, were performed preoperatively at postoperative day (POD) 10, 90, 180, and 360. Mean residual volume increased by 88% within 10 days from RH and thereafter did not show any significant variation. After 1 year, only 83% of the original volume was reached. GEC per milliliter of liver volume expressed in percent of initial value (GEC/mL) showed a decrease of 25% at POD10, an increase up to 125% at POD 180, and returned to normal values at POD 360. Liver biochemistries, International Normalized Ratio (INR), and bilirubin returned to normal in 10 days. Cholinesterase showed a similar course like GEC. In conclusion, within 10 days of 61% loss of its initial volume, the liver is capable of regenerating a volume necessary to its function, although it corresponds to only 74% of the initial one. It takes only 10 days to normalize liver biochemistries, while cholinesterase and albumin recover over 90 days. However, a direct measure of the cytosolic liver function obtained by GEC shows that functional recovery occurs much more gradually than the recovery of volume and liver biochemistries. (*Liver Transpl 2004;10: 1024–1029.*)

Liver regeneration is a fascinating process that introduces the feasibility of performing living donor liver transplantation.

Studies of liver regeneration performed in animals after major hepatectomy showed that the regenerative process is completed in a week.[1,2] Living liver donors are unique "patients" since they are absolutely healthy and have normal liver function before surgery. It is imperative that living donors return to this state of good health and normal liver function in a reasonably fast time frame. The first reports on liver regeneration in living donors undergoing right hepatectomy (RH) used computed tomography scans to measure the change in liver volume at 1 to 2 weeks after the hepatectomy.[3–5] These reports showed that the residual volume increases dramatically in the first 7–10 days after surgery, but the liver does not return to its initial volume entirely. Computed tomography volumetric examination up to 1 year after RH demonstrates that only an average of 85% of the initial volume is regenerated,[6–8] while bilirubin and liver biochemistries normalized within 2 weeks after the surgery.[7] These findings provided evidence for a rapid donor recovery.

On the other hand, several reports are now available showing that donors do not return to preoperative functional status for an average of 3 months after the operation, and some donors require as long as 6 months.[7,9–12] It appears that, despite early postoperative normalization of the conventionally checked laboratory parameters and the increase in residual volume, the period of partial insufficiency, reflected by this prolonged "recovery" phase of the donor, is much longer than just a few weeks. In other words, the liver appears to function normally because the liver biochemistries are normal, but in reality its functional reserve is constantly active and thus the return to baseline function is more protracted.

The aim of our study was to evaluate the kinetics of recovery of liver volume and of liver function after RH in healthy adult living liver donors. We compared conventional and quantitative tests of liver function, i.e., galactose elimination capacity (GEC) test. This test is based on the phosphorylation of a fixed dose of galac-

Abbreviations: RH, right hepatectomy; GEC, galactose elimination capacity; POD postoperative day; body weight (bw).

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tose by the enzyme Galactokinase, and it quantitatively reproduces the cytosolic capacity of the liver correlated to the hepatic cellular mass.[13]

Patients and Methods

A total of 27 adult right liver donor (segments 5-8) candidates underwent standard preoperative evaluation following the protocol of the University of Essen.[14,15] All donors provided informed consent before enrollment in the study.

The volumetric and quantitative liver function tests were performed preoperatively, at postoperative day (POD) 10, 90, 180, and 360.

Volumetry

The volume of the liver was measured by magnetic resonance imaging with 1.5 T scanner (Magnetom Sonata; Siemens, Erlangen, Germany) equipped with high-performance gradients characterized by an amplitude of 40 mT/m and a slew rate of 240 mT/m/ms. Hepatic volumes were determined by manually tracing the contours of the whole liver and of the right liver alone (segments 5-8) on the axial T1-weighted postcontrast images (2D Flash Fatsat, repetition time/echo time 114/2.0 ms, flip 60 degree, 10 mm sections, 256 × 256 matrix). Each section encompassed 10 mm thickness, and the areas of each section were added to derive the liver volume.

Volumes are expressed as: a) percent of the initial total donor liver volume; and b) percent of the residual donor liver volume immediately after RH.

Quantitative Liver Function Test: GEC

Galactose (25% D-Galactose; Pharmaceutical Inst., University of Essen, Essen, Germany) was infused at a dose of .5 g/kg/body weight (bw), at initial preoperative test, at POD 90, 180, and 360. At POD 10, a smaller dose of .33 g/kg/bw was administered to prevent galactose overload within the reduced size of the liver.

To obtain pharmacokinetic data, 23 blood samples were taken at 24 hours (baseline = 0 and 3, 6, 10, 15, 20, 25, 30, 35, 40, 50, 60, 80, 100, 120, 180, 240, 300, and 360 minutes and after 10, 14, and 24 hours) after intravenous infusion of galactose.

Serum samples were treated with .33 mol/lit percloric acid and centrifuged at 2,400 g. The supernatant was analyzed using the Enzymatic Test Kit Galactose (Fa. Roche Diagnostics GmbH, Mannheim, Germany), which is based on the following chemical reaction: galactose + NAD^+ + galactose dehydrogenase = galactono-lacton + NADH + H^+. NADH content was photometrically measured using a spectral photometer at 340 nm (PM6; Fa Zeiss, Jena, Germany). The extinctions were calculated to mg%.

After plotting concentrations (mg%) versus time of blood taking (minutes), the linear part of the curve, beginning at about 15–20 minutes, was used to determine the time when the concentration was zero. The GEC was calculated using the following formula:

$$(\text{Infusion dose [g] galactose} - \text{galactose in urine [g]}) / (\text{time at concentration zero} + 7 \text{ [i.e., infusion time, corrected if longer]}) \times 1{,}000/\text{kg BW}$$

The results were expressed as mg/kg/minute. Additionally GEC was also correlated to each milliliter of liver volume and expressed as mg/kg/minute/mL.

Conventional Liver Function Parameters

Aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase (GGT), alkaline phosphatase, bilirubin, cholinesterase, albumin, and coagulation parameters with INR were obtained preoperatively, every day post operatively until discharge, and at each time point chosen for the study.

Results

From January 2001 to May 2002, 27 donors were enrolled in the study which consisted of 16 males and 11 females with a mean age of 33.5 ± 11 years.

All donors underwent an RH consisting of segments 5, 6, 7, 8. The mean baseline total liver volume of these donors was 1,540 ± 285 mL and the mean right liver volume was 936 ± 180 mL for an average resection of 61%. The mean residual liver volume was 603 ± 127 mL. The average operative time was 390 ± 78 minutes and no donor underwent blood transfusion prior to or after the surgery. Neither albumin nor total parenteral nutrition were given to the donors post operatively, and oral intake was restarted in all donors within 72 hours after the surgery. The incidence of complication was 22%: 4 donors had a bile leak from the resection surface and were successfully treated with conservative management; 3 patients had a wound infection. No patients required reoperation and the average hospital stay was 16 ± 4 days.

Volumetry

Within the first 10 PODs the residual volume increased from 39% ± 3% of initial liver volume to 74% ± 12% at POD 10. In the following 12 months the residual liver grew only another 5% to reach an average 83% ± 12% of the initial volume at day POD 360 (Fig. 1A). The regeneration of the residual volume was also studied as a percentage increase with the baseline volume of

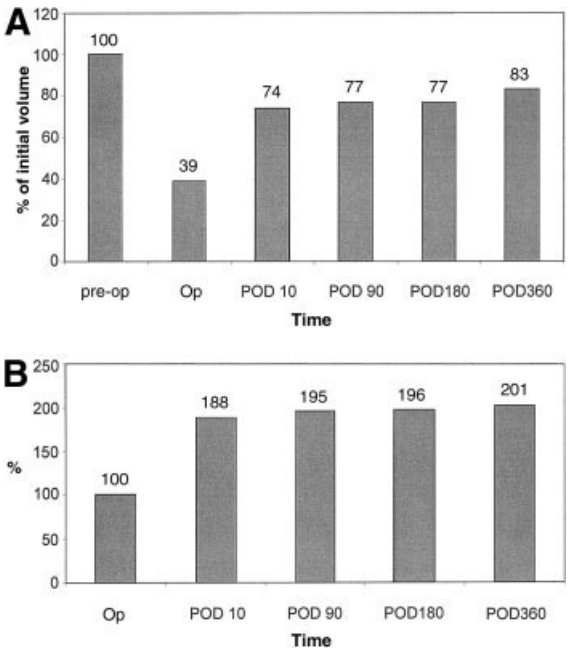

Figure 1. Kinetics of regeneration of liver volume expressed as percent of initial liver volume (A) and as percent of residual liver volume (B). POD, postoperative day.

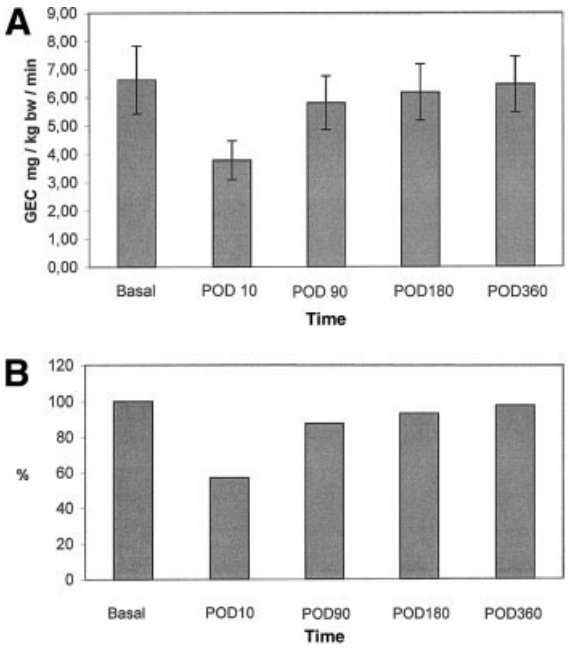

Figure 2. Kinetics of recovery galactose elimination capacity (GEC) expressed as mg/kg bw/minute (A) and as percent of initial basal value (B). POD, postoperative day.

the residual liver set at 100% at POD 0. As shown in Fig. 1B, an average increase of 88 and 101% was observed at POD 10 and POD 360, respectively. This indicates that almost all of the volume recuperation occurs during the first 10 days after surgery.

Galactose Elimination Capacity

The mean preoperative GEC-value was 6.63 mg/kg bw/minute. It decreased to 57% of the initial value, to 3.78 mg/kg bw/minute at POD 10 and then increased progressively reaching 5.8 mg/kg bw/minute at POD 90 (87%), 6.17 mg/kg bw/minute at POD 180 (93%), and 6.45 at POD 360 (97%) (Fig. 2A and B).

The kinetics of regeneration of cytosolic liver function was also studied in relation to the mL of liver volume and expressed in percent of initial value (GEC/mL). It showed a decrease of 25% at POD 10, an increase up to 125% at POD 180, and returned to normal values at POD 360 (Fig. 3).

Conventional Laboratory Parameters

Liver biochemistries (aspartate aminotransferase, alanine aminotransferase), INR, and bilirubin returned toward normal values within 10 days of the RH. Interestingly, only cholinesterase had a similar trend to the one observed for GEC (see Fig. 4). At POD 10, when the values of the liver biochemistries had already almost normalized, the average drop in the serum cholinesterase was 59%, and it returned to the initial preoperative values only 6 months later.

Discussion

Since its clinical introduction in 1989, living donor liver transplantation is now routinely performed in Asi-

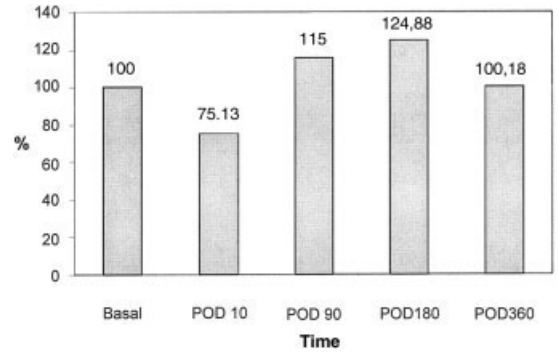

Figure 3. Kinetics of recovery of galactose elimination capacity (GEC) related to milliliter of liver volume. POD, postoperative day.

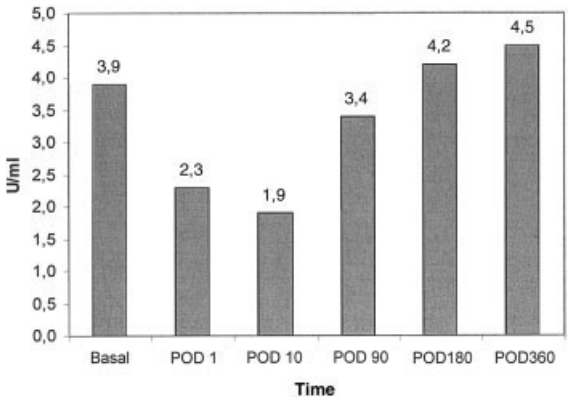

Figure 4. Kinetics of Cholinesterase values.

atic countries without cadaveric organ donation[16] and also in many centers in the western world.[15] Many concerns have been raised regarding the immediate and short-term risk of complications for the donor, particularly since right lobe living donor liver transplantation was introduced.[17,18] It has been reported that the donor operation carries a mortality risk of less than 1% and a complication rate varying between 12 and 40%.[19–21] However, live organ donation depends on the rapid restoration of the donor's health. The full recovery of the donor from the surgery and his/her return to work have been the focus of several studies.[7,9–11,22,23]

The prevailing idea is that after RH, the residual liver of the donor will grow back to its original volume and that its function recovers rapidly as reflected by normalization of the transaminases, bilirubin, and coagulation parameters. Both phenomena have been described to occur within 2 or 3 weeks of the surgery.[4,8]

In reality, we have little knowledge of the impact of a major liver resection on the hepatic function of a healthy person. The need for a better understanding of the functional recovery of the donor was recently highlighted by the American Society of Transplant Surgeons (ASTS) (Press release April 25 2003 ASTS.ORG living donor update. Cfm).

The results of the analysis of liver biochemistries, bilirubin, and the liver volume as determined by serial magnetic resonance imagings confirm previous observations. Within 2 weeks of the RH, the liver biochemistries return to normal and the liver regenerates most of its volume.[4–8] Up to 1 year after surgery, no further significant alteration of the liver biochemistries and bilirubin is observed.

The Lahey clinic group found that no donor recuperated 100% of the initial liver volume, and most of the increase in volume occurred within 1 week to 10 days of the hepatectomy.[6] In our study, 20% of the initial hepatic mass is never recuperated, and on average, the liver grows back to only 80% of its initial volume. Whether the tremendous increase in residual liver volume that occurs in the first 10 post operative days and the permanent 20% deficit in volume have a consequence on the hepatic function can not be detected by analyzing the values of liver biochemistries and bilirubin. Certainly, liver biochemistries and bilirubin do not reflect the real clinical conditions of the donors who may require several weeks to return to normal self.

In our study, GEC was used as a quantitative test of the cytosolic capacity of the liver correlated to the hepatic cellular mass.[13] Since the donor suffers a great loss of liver mass, it appears that GEC is the most appropriate quantitative test to monitor hepatic function from early postoperative period to full recovery. Moreover, GEC has been proven to be an appropriate test to measure hepatic function and a predictor of survival in conditions of hepatic mass loss such as cirrhosis.[24]

A greater than 40% decrement from baseline GEC was observed at 10 days after RH, and this deficit persisted for up to 3 months after the hepatectomy. Normal GEC values were obtained only at 6 months after hepatectomy and were confirmed at the 1 year control.

It appears that there is a clear discrepancy between the recovery of liver volume, the normalization of liver biochemistries and bilirubin, and measurement of hepatic function by GEC. The impression that hepatic function has fully recuperated once the liver biochemistries have returned to normal and the liver volume has grown is misleading. In reality, hepatic function lags behind and takes much longer to return to the preoperative values. GEC also reflects more precisely the real clinical recovery of the donors, who despite normal biochemistries need weeks to return to normal functional status.

Of importance is the finding that at the 1 year control, GEC has returned to the preoperative levels. In fact, the donor can be assured that full hepatic function without any permanent deficit will occur even when the liver volume at the end of the regeneration process does not match the preoperative volume.

The full recovery of hepatic function is confirmed also by analyzing the recuperation of GEC in relation to the actual liver mass as measured at each time point. In fact after setting the immediate postoperative GEC value at 100%, an interesting phenomenon is observed: in the first 10 days after RH, GEC values drop by 25 to

75%. By 3 months, however, the GEC value rises to 115%, and at 6 months to 125%. At 1 year, the value returns to normal (100%). It can then be concluded that the hepatic function does totally recover even when studied in relation to actual hepatic mass and not only in relation to the preoperatively obtained values. Of interest is the temporary increase above the preoperative values of the GEC, detected at 3 and 6 months after the hepatectomy when all other parameters have already returned to normal. The explanation for this temporary GEC increase cannot be given with the data that we have collected. It could be speculated that the increase in GEC of the liver is connected to an enhanced activity of the hepatocytes correlated to matrix synthesis and histology rearrangement after regeneration as proposed by Michalopoulos and DeFrances.[1]

The last observation is that of the conventional liver function parameters taken in consideration, only cholinesterase showed a trend similar to the GEC. In fact, it did not reach the preoperative values at POD 10, and only at POD 90 was a trend towards normalcy detected.

Our study provides an important new insight into liver regeneration in living donors: recovery of hepatocellular function substantially lags behind recovery of the liver volume. The impairment of liver function demonstrated by GEC was not evident by examination of routine liver biochemistries alone. However, the gradual recovery of hepatic function is consistent with the time course of patients' return to their preoperative functional status. Instead, GEC provides a direct measure of hepatic function and specifically expresses hepatic function in relation to hepatic mass.

It is also important to stress that the normal liver biochemistries, bilirubin, and coagulation parameters detected soon after surgery do not reflect normal liver functioning. As already pointed out by Tygstrup, "an injured organ often appears to function normally because the reserve is more or less constantly in action, and the injury is only detected if the functional capacity is tested."[13]

The result of our study confirms that despite early normalization of the liver biochemistries and the fast volume increase, the period of partial hepatic insufficiency after an RH can last as long as 3 months. It is this functional partial insufficiency more than the liver biochemistries and the volume that correlates with the subjective clinical recovery of the donors. Any means of accelerating the recovery of the donor should then reflect its efficacy on a direct liver function test, e.g., the GEC.

References

1. Michalopoulos GK, DeFrances MC. Liver regeneration. Science 1997;276:60–66.
2. Court FG, Wemyss-Holden SA, Dennison AR, Maddern GJ. The mystery of liver regeneration. Br J Surg 2002;89:1089–1095.
3. Chen MF, Hwang TL, Hung CF. Human liver regeneration after major hepatectomy. A study of liver volume by computed tomography. Ann Surg 1991;213:227–229.
4. Marcos A, Fisher RA, Ham JM, Shiffman ML, Sanyal AJ, Luketic VA, et al. Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. Transplantation 2000;69:1375–1379.
5. Pomfret EA, Pomposelli JJ, Lewis WD, Gordon FD, Burns DL, Lally A, et al. Live donor adult liver transplantation using right lobe grafts: donor evaluation and surgical outcome. Arch Surg 2001;136:425–433.
6. Pomfret EA, Pomposelli JJ, Gordon FD, Erbay N, Lyn Price L, Lewis WD, Jenkins RL. Liver regeneration and surgical outcome in donors of right-lobe liver grafts. Transplantation 2003;76:5–10.
7. Pascher A, Sauer IM, Walter M, Lopez-Haeninnen E, Theruvath T, Spinelli A, et al. Donor evaluation, donor risks, donor outcome, and donor quality of life in adult-to-adult living donor liver transplantation. Liver Transpl 2002;8:829–837.
8. Olthoff KM. Hepatic regeneration in living donor liver transplantation. Liv Transpl 2003;(S2):S35–S41.
9. Karliova M, Malago M, Valentin-Gamazo C, Reimer J, Treichel U, Franke GH, et al. Living-related liver transplantation from the view of the donor: a 1-year follow-up survey. Transplantation 2002;73:1799–1804.
10. Diaz GC, Renz JF, Mudge C, Roberts JP, Ascher NL, Emond JC, Rosenthal P. Donor health assessment after living-donor liver transplantation. Ann Surg 2002;236:120–126.
11. Kim-Schluger L, Florman SS, Schiano T, O'Rourke M, Gagliardi R, Drooker M, et al. Quality of life after lobectomy for adult liver transplantation. Transplantation 2002;73:1593–1597.
12. Trotter JF, Talamantes M, McClure M, Wachs M, Bak T, Trouillot T, et al. Right hepatic lobe donation for living donor liver transplantation: impact on donor quality of life. Liver Transpl 2001;7:485–493.
13. Tygstrup N. Determination of the hepatic elimination capacity of galactose by single injection. Scand J Lab Invest 1966; 92(suppl 18):118–125.
14. Testa G, Malago M, Broelsch CE. Living-donor liver transplantation in adults. Langenbecks Arch Surg. 1999;384:536–543.
15. Malagó M, Testa G, Frilling A, Nadalin S, Valentin-Gamazo C, Paul A, et al. Right living donor liver transplantation: an option for adult patients: single institution experience with 74 patients. Ann Surg 2003;238:853–863.
16. Wilson A, Calvert RJ, Geoghegan H. Plasma cholinesterase activity in liver disease: its value as a diagnostic test of liver function compared with flocculation tests and plasma protein determinations. J Clin Invest 1952;31:815–823.
17. Chen CL, Fan ST, Lee SG, Makuuchi M, Tanaka K. Living-donor liver transplantation: 12 years of experience in Asia. Transplantation 2003;75(3 suppl):S6–S11.
18. Brown RS, Jr, Russo MW, Lai M, Shiffman ML, Richardson MC, Everhart JE, Hoofnagle JH. A survey of liver transplanta-

tion from living adult donors in the United States. N Engl J Med 2003;348:818–825.
19. Lo CM. Complications and long-term outcome of living liver donors: survey of 1508 cases in five Asian centers. Transplantation 2003;75(3 suppl):S12–S15.
20. Broelsch CE, Testa G, Alexandrou A, Malago M. Living related liver transplantation: medical and social aspects of a controversial therapy. Gut 2002;50:143–145.
21. Broelsch CE, Frilling A, Testa G, Cicinnati V, Nadalin S, Paul A, Malago M. Early and late complications in the recipient of an adult living donor liver. Liver Transpl 2003;9(10 suppl 2):S50–S53.
22. Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, et al. Operative morbidity of living liver donors in Japan. Lancet 2003;362:687–690.
23. Beavers KL, Sandler RS, Shrestha R. Donor morbidity associated with right lobectomy for living donor liver transplantation to adult recipients: a systematic review. Liver Transpl 2002;8:110–117.
24. Salerno F, Borroni G, Moser P, Sangiovanni A, Almasio P, Budillon G, et al. Prognostic value of the galactose test in predicting survival of patients with cirrhosis evaluated for liver transplantation. A prospective multicenter Italian study. AISF Group for the Study of Liver Transplantation. Associazione Italiana per lo Studio del Fegato. J Hepatol 1996;25:474–480.