World Journal of Surgery

Published Online: 18 November 2005

World J Surg (2005) 29: 1658–1666
DOI: 10.1007/s00268-005-0101-2

Liver Regeneration and Splenic Enlargement in Donors after Living-Donor Liver Transplantation

Salleh Ibrahim, MBBS Sing, FRCS Glas, Chao-Long Chen, MD, Chih-Chi Wang, MD, Shih-Ho Wang, MD, Chih-Che Lin, MD, Yeuh-Wei Liu, MD, Chin-Hsiang Yang, MD, Chee-Chien Yong, MD, Allan Concejero, MD, Yu-Fan Cheng, MD

Department of Liver Transplant and Surgery and Diagnostic Radiology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, 123 Ta-Pei Rd, Niao-Sung, Kaohsiung, Taiwan R.O.C

Abstract

Liver regeneration after donor hepactectomy offers a unique insight into the process of liver regeneration in normal livers. As the liver restores itself, concurrent splenic enlargement occurs. There are many theories about why this phenomenon takes place: some investigators have proposed a relative portal hypertension that leads to splenic congestion or, perhaps, the presence of a common growth factor that induces both the liver and spleen to enlarge. Between the months of June 2001 and May 2004, 112 live donor liver transplants (LDLTs) were performed in Chang Gung Memorial Hospital, Kaohsiung, Taiwan. The total number of donor hepatectomies performed during this period was 113, however, because one of the cases required dual donors. Of our 113 donors, we eventually analyzed the data of 109; 4 patients were lost to follow-up 6 months later and were excluded from our study. The average age of our donor population was 32.32 ± 8.48 years. The mean liver volume at donation was noted to be 1207.72 ± 219.95 cm^3, and 6 months later, it was 1027.18 ± 202.41 cm^3. Expressed as a percentage of the original volume, the mean liver volume 6 months after hepatectomy was 90.70% ± 12.47% in this series. For right graft donors, mean liver volume after 6 months was 89.68% ± 12.37% of the original liver volume, whereas that for left graft donors was 91.99% ± 12.6%. Only 26 of the 109 (23.85%) donors were able to achieve full regeneration 6 months post-donation. Notably, liver function profiles of all donors were normal when measured 6 months after operation. The average splenic volume at donation as measured by computed tomography (CT) volumetry was 159 ± 58 cm^3, and the splenic volume 6 months post-donation was 213 ± 85 cm^3. There was a mean increment in splenic volume of 35% ± 28% 6 months after donation. The blood profiles of the donors were monitored; particular attention was given to platelet levels and liver function tests, and these were found to be within normal limits 6 months after operation. Of note, splenic enlargement was significantly greater among right-sided donors than their left-sided counterparts. Greater splenic enlargement was also observed in those donors who achieved full liver regeneration at their evaluation 6 months postoperatively than in those who did not. Although original liver volume was not re-established in most patients 6 months after liver donation, there seemed to have been no untoward effects to the donor. The factors that affect liver regeneration are complex and myriad. Although there is splenic enlargement at 6 months post-donation in donors of LDLT, there are no untoward effects of this enlargement.

Correspondence to: Chao-Long Chen, MD, Department of Liver Transplant and Surgery and Diagnostic Radiology, Chang Gung Memorial Hospital, Kaohsiung Medical Center, 123 Ta-Pei Rd, Niao-Sung, Kaohsiung, Taiwan R.O.C. e-mail: clchen@adm.cgmh.org.tw

The exceptional ability of the liver to regenerate after liver resection makes donor hepactectomy in living donor liver transplants exceptionally unique. This has

always been a point of great interest to both the transplant surgeon and the donor involved. The question most frequently asked by donors relates to the rate of liver regeneration that can be expected post-donation.[1]

Several authors have studied liver regeneration following hepactectomy, but this has always been in diseased livers, for which the underlying disorder may affect liver regeneration.[2,3] The model that came closest to studying liver regeneration in normal livers, to date, was in the field of traumatic liver surgery. However, operations were conducted in an emergent circumstance, and patients were unstable and severely ill.[4] Living donor hepactectomy offers an exclusive insight into liver regeneration in normal livers, for which much is still unknown.[5–8]

In the same way, there have been publications concerning the rate of liver regeneration after living donor liver transplantation.[9,10] Complete and prompt liver regeneration does occur in both the donor and the recipient. In fact, some studies have suggested that complete liver regeneration occurs within a matter of weeks after the donation.[11] Here, we attempt to delineate liver regeneration 6 months after donation, and we also try to ascertain any possible factors that could influence this process.

It has been well documented that splenic enlargement occurs in the postoperative period following major hepatic resection.[12,13] The postulations behind this phenomenon include relative portal hypertension causing splenic congestion and/or an elevation in the levels of a common growth factor for both the liver and the spleen.[14] There have been reports of splenic enlargement leading to dangerous hypersplenism in the postoperative period.[13] Experimental evidence, however, suggested that splenic factors suppress liver regeneration after hepactectomy.[15–17]

Like the liver, the spleen possesses the ability to regenerate itself, as seen after partial splenectomy and auto-transplantation after trauma.[18,19] Nevertheless, splenic regeneration is not as efficient as that of the liver.[14] The prior publications, however, reported only abnormal livers for which major hepatectomies were undertaken. The possibility of underlying disease, such as cirrhosis, may play an important role in causing splenic enlargement and thus act as a confounding factor.

Our study involving donor hepatectomies provides an excellent opportunity to examine splenic changes after liver resection in the normal liver and their effect on the donor. We studied the spleen size of all of our donors, who were to undergo a donor hepatectomy, prior to donation and 6 months after donation. From the preoperative study, we were able to document splenic enlargement and also to look for factors that could affect its occurrence.

MATERIALS AND METHODS

Between the months of June 2001 and May 2004, 112 LDLTs were performed in Chang Gung Memorial Hospital, Kaoshiung Medical Center, Taiwan. There were, however, a total of 113 donor hepactectomies carried out, as one of the LDLTs (case 116) was in fact a dual donor. The processes involved in preoperative evaluation and donor selection have been described in our earlier publication.[20] Briefly, the preoperative radiological evaluation of choice in our institution is computed tomographic angiography (CTA), which investigates liver vasculature, its volume, and also reveals the presence of any subclinical pathology. Multiple-detector computed tomography (CT) machines that allow high-speed, high-resolution helical scanning and image processing with three-dimensional multiplanar reconstruction are used to produce images of superior quality. Computed tomography volumetry is calculated from 10-mm cut slices, and this gives an accurate volume with an error of ± 10%. The splenic volume was also measure at donation and 6 months post-donation.

Regarding anesthetic management and graft procurement methods, we employed the same methods that have been previously published.[21] Worth mentioning again, though, it is our routine practice to take a sliver of liver for biopsy during graft harvesting to analyze the level of fatty change while also looking for the presence of any incidental microscopic liver parenchymal disease.

Postoperatively, all donors are monitored with a daily blood profile that includes a complete blood count and a liver function test. The donors are subsequently discharged when they have completely recovered. They then undergo a repeat CT volumetry test 6 months later, together with a blood profile that includes a complete blood count and liver and renal function test.

Regarding liver regeneration, we looked retrospectively at the demographics of the donors, and analyzed their basic epidemiology, intraoperative data, liver volume 6 months after hepactectomy, and blood profiles before donation and 6 months later. We also looked at the level of fatty change of the liver at donation to evaluate if there was any correlation with subsequent liver volume 6 months later.

The splenic size increment was calculated from the following formula:

$$\frac{\text{Spleen size } (\text{cm}^3) \text{ at 6 months} - \text{Spleen size at donation}}{\text{Spleen size at donation}} \times 100\%$$

We analyzed splenic volume changes against several factors. These include percentage restoration of liver volume, fatty change of the liver, type of graft, and donor gender

Statistical Analysis

All values were expressed as mean ± standard deviation. The *t*-test was used for comparing right-lobed and left-lobed graft liver regeneration, as well as for comparison between the sexes. The Kruskal-Wallis test was used for comparing the groups of donors according to their level of fatty change.

The *t*-test was also used to compare data involving splenic volume, operative parameters, and blood investigations among the groups of patients. Finally, the *t*-test was used for comparing liver and spleen volume before and after donation. The findings of other statistical tests are indicated in the respective sections of the *Results*. In all cases, a P value < 0.05 was considered significant. Statistical analyses were performed with the SPSS computer software (SPSS for Windows, SPSS Inc., Chicago, IL)

RESULTS

Although there were 113 donor hepactectomies, 4 of them had to be excluded from both analyses, and a fifth was excluded on the basis of splenic enlargement. Three donors did not return for follow-up evaluation 6 months after operation because they were not living in Taiwan; they underwent postoperative evaluation in their native countries. The fourth donor who was excluded had only ultrasound investigation performed, and not CTA, because he reported a history of allergy to radiological contrast after the pre-donation investigations. The last donor, who was excluded for splenic enlargement, had undergone a splenectomy prior to his donation due to previous trauma. Consequently, the records of 109 patients were evaluated for liver regeneration, with a follow-up rate of 97.2%, and 108 donors were analyzed for splenic enlargement.

Liver Regeneration

The average age of donors was 32.32 ± 8.48 years. There were 63 women and 46 men donors. The basic operative parameters are shown in Table 1.

All donors showed normal liver vasculature with CTA and had normal blood profiles at their 6-month follow-up. The average liver volume at donation was 1207.72 ± 219.95 cm^3 and the average liver volume 6 months after donation was 1087.18 ± 202.41 cm^3. There was a significant reduction in liver volume overall in donors 6 months post-donation ($P < 0.001$). Only 26 donors were able to achieve at least complete liver regeneration 6 months later. Of these 26 donors, 11 were left-lobed donors and 15 were right-lobed donors.

The overall mean liver volume 6 months after hepatectomy in this series is 90.70% ± 12.47% of the original liver volume. The liver volume 6 months later for patients who underwent right-lobed graft procurement was 89.68% ± 12.37% of the original liver volume, whereas that of the left-lobed grafts was 91.99% ± 12.6%. This was not statistically significant ($P = 0.529$).

The mean liver volume at 6 months in female donors was 89.52% ± 11.24% of their original liver volume at donation, whereas that of their male counterparts was 92.32% ± 13.9%. This difference was not statistically significant ($P = 0.345$).

The 6-month liver volume was also compared between three groups of patients and were divided according to the degree of fatty change measured during mandatory liver biopsy at donation. Group 1 ($n = 75$) comprised donors with no fatty change, group 2 ($n = 26$) comprised donors with 5% fatty change, and group 3 ($n = 8$) comprised donors with 10% fatty change. The change in mean liver volume postoperatively for groups 1, 2, and 3 was 90.20% ± 11.19%, 93.55% ± 15.09%, and 86.86% ± 14.58%, respectively. There were no significant statistical differences found between these three groups ($P = 0.537$).

Splenic Enlargement

The average donor age was 32.32 ± 8.48 years with the average donor body weight being 62.92 ± 12.33 kg. There were 48 left lobe graft donors and 60 right lobe graft donors. Among the 108 donors, there were 63 female and 45 male donors.

Average splenic volume at donation measured by CTA was noted to be 159 ± 58 cm^3, whereas the average splenic volume 6 months post-donation was 213 ± 85 cm^3. There was a statistically significant increment in

Table 1.
Right lobe graft versus left lobe graft

Parameters	Right graft	Left graft	*P* Value
Blood loss (ml)	**122.58 ± 85.51**	**83.70 ± 77.27**	**0.0001**
Mean CVP (cm H_2O)	8.5 ± 1.75	7.83 ± 1.52	0.085
Duration of operation (min)	**867.31 ± 104.24**	**757.74 ± 131.43**	**0.0001**
Transection time (min)	163.11 ± 36.38	146.03 ± 195.38	0.513
Peak AST (U/l)	332.39 ± 156.22	299.14 ± 160.88	0.277
Peak ALT (U/l)	332.53 ± 176.52	327.20 ± 185.79	0.958
Peak TB mg%	**3.68 ± 1.74**	**1.74 ± 1.01**	**0.0001**
Peak creatinine mg%	0.72 ± 0.19	0.75 ± 0.20	0.545
Complication rate	5%	2.1%	
Mean increment in splenic size (%)	**46 ± 27**	**22 ± 24**	**0.0001**
Liver volume 6 months post-donation (expressed as % of the original liver volume)	90 ± 12	92 ± 13	0.529

CVP: central venous pressure; AST: aspartate aminotransferase; ALT: alanine transferase; TB: total bilirubin.
Significance are highlighted in bold.

splenic volume in donors 6 months post-donation ($P < 0.001$) with a mean increment of splenic size of 35% ± 28% at 6 months following donation. The blood profiles of all 108 patients proved to be normal at this time; we looked particularly at platelet levels and tests of liver function. The mean platelet value of donors at donation was 29/10,000/mm^3 (normal range 15–40/10,000/mm^3), whereas at 6 months the mean platelet value was 31.5/10,000/mm^3. There was no statistical significance difference in platelet levels pre-donation and 6 months post-donation ($P = 0.245$). In all donors the portal vein and splenic vein were patent at the 6 months post-donation CTA. The liver was also normal and there were no radiological evidence of portal hypertension.

Splenic Enlargement among Right and Left Lobe Donors

The mean graft weight obtained in right lobe donors was 702.3 ± 146.5 g, which was significantly greater ($P < 0.0001$) as compared to mean graft weight in left lobe donors, which was 283.1 ± 9 g. The mean increment in splenic size of right graft donors was 46% ± 27% and that of left graft donors was 22% ± 24%. Splenic enlargement is more substantial among right-sided donors as compared to left-sided donors, and this difference was found to be statistically significant ($P < 0.0001$). There was also significantly higher blood loss in right lobe hepatectomies than left lobe donors. Similarly, the operative time was much longer in right lobe grafts as compared to left lobe grafts (Table 1).

Splenic Enlargement in Male and Female Right and Left Lobe Donors

We compared the splenic enlargement in male right and left lobe donors to that in female right and left lobe donors. The mean splenic enlargement among male right lobe donors ($n = 29$) was 52% ± 30%, and that among female right lobe donors ($n = 31$) was 40% ± 23%. There was no statistically significant differences between these two groups of donors ($P = 0.245$). Splenic enlargement among male left lobe donors ($n = 15$) was 18% ± 30%, whereas that in female left lobe donors ($n = 33$) it was 24% ± 21%. Again, there was no statistically significant difference between the two groups ($P = 0.345$).

Splenic Enlargement in Donors with Full Liver Regeneration (Group 1) as Compared to Those with Less than Full Liver Regeneration (Group 2)

We divided the donors into two groups: group 1 ($n = 26$), which comprised donors who attained at least 100% of their original liver volume at 6 months, and group 2 ($n = 82$), which consisted of donors who did not attain full regeneration. In group 1 there were 12 female donors and 14 male donors, and in group 2 there were 52 female donors and 30 male donors. In group 1 there were 15 right lobe donors and 11 left lobe donors; in group 2 there were 45 right lobe donors and 37 left lobe donors. The mean increment of splenic volume for group 1 patients was 47% ± 35% and that of group 2 was 32% ± 24 %. This was statistically significant ($P < 0.025$), revealing that splenic enlargement was more marked in donors who

Table 2.
Group 1 compared to group 2

Parameters	Group 1 (n = 26) (donors with full liver regeneration at 6 months)	Group 2 (n = 82)(donors with less than full liver regeneration at 6 months)	P Value
Age (years)	30.84 ± 7.19	32.82 ± 8.96	0.188
Sex	14M/12F	30M/52F	
Type of graft	15 right lobe/11 left lobe	45 right lobe/37 left lobe	
No of donors with steatosis	11 of 26 donors	23 of 82 donors	
Body weight (kg)	62.55 ± 12.82	63.08 ± 12.37	0.873
Duration of operation (minutes)	852.23 ± 144.31	816 ± 83 ± 124.76	0.700
Blood loss (ml)	116.35 ± 102.94	99.75 ± 77.01	0.509
Mean CVP	8.27 ± 2.02	8.19 ± 1.58	0.739
Transection time (minutes)	142.88 ± 43.13	160.12 ± 152.43	0.563
Peak AST (U/l)	304.69 ± 130.90	319.38 ± 168.14	0.642
Peak ALT (U/l)	357.35 ± 187.20	319.45 ± 180.43	0.533
Peak TB (U/l)	2.61 ± 1.64	2.82 ± 1.77	0.382
Peak creatinine (mg%)	0.79 ± 0.23	0.76 ± 0.19	0.299
Graft weight (gm)	482.49 ± 244.55	530.16 ± 242.39	0.277
Complications (%)	3.8%	3.7%	
Mean increment in splenic size	**47% ± 35%**	**32% ± 24%**	**0.025**

Significant values are highlighted in bold.

achieved full regeneration 6 months postoperatively. In terms of complications, in group 1 there was one donor (LDLT no. 116) who had a biloma that required percutaneous drainage and antibiotics. In group 2 there were three donors who had complications. One donor (LDLT no. 80) had late intestinal obstruction that resolved with conservative management. Another donor (LDLT no. 130) had a bile leak that was treated conservatively. The last donor (LDLT no 173) in group 2 underwent re-laparotomy for postoperative bleeding. All three of these patients are well to date. There were no differences in terms of donor age, donor body weight, blood loss, peak aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine level between the two groups (Table 2).

Factors Affecting Splenic Enlargement

We assessed the effects of various factors on splenic enlargement using multiple regression analysis. The variables considered in the regression analysis included age, gender, graft weight, side of grafts, and liver volume attained at 6 months post-donation. We found that right side donors ($P < 0.0001$) and donors with full liver regeneration ($P < 0.014$) also had greater splenic enlargement. There was no association with the other factors examined.

Correlation between Graft Weight and Liver Regeneration as well as Splenic Enlargement

Graft weight was correlated with the percentage of original liver volume attained at 6 months (Spearman correlation coefficient, $r = -0.195$, $P = 0.038$) and percentage enlargement of the spleen ($r = 0.341$, $P = 0.0002$).

DISCUSSION

One of the great advantages of living donor liver transplantation as compared to living related kidney transplantation is the exclusively unique ability of the liver to regenerate itself in the donor after hepactectomy.[9] Unfortunately, the process of regeneration is a complex one, and it is still poorly understood. There have been many studies that analyzed regeneration of the liver after resection, but these have been done in diseased livers, and their results cannot be extrapolated to include living donor hepactectomy.[3] The closest human model for the study of liver regeneration in presumably normal liver is in liver resection for benign disease.[4]

Animal models have shown that liver regeneration is seemingly controlled by vessel endothelial cells. Greene *et al.*[22] demonstrated that the endothelial cells are involved in the regulation of the regenerating adult liver, and they suggested that angiogenesis controls the regenerative process. After partial hepactectomy, massive hepatocyte proliferation is observed to begin immediately, peaking at 48 hours postoperatively. Endothelial cells, on the other hand, lag behind, and peak only 4 days after the operation proper.[22]

In our series, the mean liver volume as measured 6 months after hepatectomy was 90.70% ± 12.47% of the

original liver volume. This percentage was significantly lower when compared to pre-donation volumes overall in all donors, but this reduction in volume did not lead to any ill effects; all donors had normal liver function. This is in accordance with other previously published series.[1,9,10] However, with a margin of error of ± 10% in CT volumetry, the volume difference between pre-donation and 6 months post-donation can reflect this margin of error rather than a true difference. The difference in the volume of liver regeneration measured at 6 months between right-lobed and left-lobed grafts was not statistically significant. Nakagami *et al.*[1] suggested that the patterns of liver regeneration after right-lobed graft procurements and left lateral segmentectomies were different, with liver regeneration stopping after the liver achieves some 75%–90% of its original volume. He suggested that the liver would reach its full regenerative potential only after at least one month, with some requiring even up to a year. In another series, the liver volume measured at one year was 83.3% ± 9% of the original volume,[10] less than in our series. We observed that although full liver regeneration was not attained with most donors, the liver functions of these patients remained within normal limits as measured by biochemical tests. Only 26 donors achieved full (or more) regeneration of their livers 6 months after surgery. There is a possibility that the liver stops regenerating once there is sufficient liver mass to cope with metabolism of the body. Some authors believe that the liver will enter into a slower pace of regeneration once it reaches an adequate hepatocyte mass to support normal metabolism.[1,6,7,8] Long-term studies would be required to perceive if the liver volume of all donors could reach original values, while at the same time investigating the possible presence of any factors that affect the rate of regeneration. This would be useful both for candidates involved in liver donation as well as for patients undergoing other forms of hepatic surgery.

The difference in liver volume regeneration between the female and male donors was not found to be statistically significant when measured at 6 months, and we found this to be curious, knowing that estrogen induces liver regeneration.[23,24] This emphasizes the fact that liver regeneration is multifactorial in nature, not affected by a single factor but by many different physiological and anatomical ones that together, form a web of complex relationships. There is a correlation between amount of resected tissue (that is graft weight) and liver volume attained at 6 months, and this implies that the trigger for liver regeneration may be the amount of liver tissue removed.

When we analyzed the liver volume between the three different groups of donors segregated according to their different levels of fatty change of their livers, we again found no statistically significant differences. However, group 3 (10% fatty change) had a slightly lower liver volume measured at 6 months compared to the average in the whole series (86.86% versus 90.70%). Although this was not statistically significant, it should alert us to a possibility that fatty changes in the liver could impair liver regeneration. A possible reason for not reaching statistical significance could be the small sample size (group 3 having only 8 donors). However, the liver volume achieved by this group was evidently sufficient to support normal metabolism, as the liver function profiles were normal and these patient remain clinically well.

It has been noted for a long time that there is splenic enlargement in patients who undergo liver resection.[12,13] Akimaru *et al.*[13] showed that there was splenic enlargement with resultant hypersplenism after major hepactectomy. This enlargement was most marked in patients with liver cirrhosis in whom hypersplenism can be detrimental. It has also been demonstrated that after hepactectomy the spleen enlarges as the liver regenerates. Ando *et al.* showed that the spleen enlarges as much as 155% ± 40% within 14 days after hepactectomy.[14] The conventional wisdom states that the spleen enlarges as a consequence of relative portal hypertension, and that the enlargement is simply a reflection of splenic engorgement.[25] These studies were performed in patients with cirrhosis, and the underlying liver parenchymal disease could in itself affect splenic enlargement.

It has also been assumed that the liver functions, including regenerative capacity, are remotely controlled by splanchnic organs, including the spleen.[26] In animal studies, Ueda *et al.*[26] found that transforming growth factor-beta 1 released from the spleen worked as an inhibitor of hepatocyte proliferation and that removal of the spleen enhances liver regeneration during the early regenerative phase of liver proliferation. In another animal study, Kaido[27] found that there was increased secretion of hepatocyte growth factor activator inhibitor 1,2 (HAI-1,2) by the spleen in cirrhotic rats, a substance that may impair liver regeneration.

Charters *et al.*[28] showed that the uptake of ^{3}H-thymidine in the spleens of rats after a hepactectomy involving 70% of the liver increased markedly, and peaked at 72 hours after hepactectomy. This time course is mirrored almost exactly in the uptake of thymidine by the hepatocytes.[20] This observation of increments of DNA synthetic activity of both the spleen and liver following hepactectomy give great evidence that these organs respond to

the same growth factors, which may include the likes of hepatocyte growth factor, epidermal growth factor, transforming growth factor-a, or perhaps a combination of these factors.[29–31] However, in humans the relationship between the splenic enlargement post-hepatectomy is rather complex and controversial. On the one hand, Ando *et al.*[14] recently, found that the increment in splenic volume correlated well with the increment in remnant liver volume and suggested the presence of a common growth factor. Sato *et al.*,[32] on the other hand, suggested that the percent increase in liver volume was inversely related to the spleen volume. Both of the above studies were done in diseased liver with underlying parenchymal disease.

In this series of healthy donors, we discovered the following findings:

There is statistical significant splenic enlargement among healthy donors six month post-donation of liver

The enlargement in patients obtaining full liver regeneration was larger than in those who do not attain full liver regeneration. This was a factor found to be significant in both univariate analysis and multiple regression analysis. Also proved with both univariate and multiple regression analysis, splenic enlargement is most marked in donors of right lobe grafts and there is no differences between males and females.

Similiarly, there was a strong correlation between the amount of resected tissue (graft weight) and the size of splenic enlargement; again, gender was not a factor.

Although there is splenic enlargement, the platelet level in the donors before and six months post-donation were not significantly different.

We found that those donors who achieved complete regeneration of their original liver volume had a higher increment of splenic volume than those donors who did not. This favors the hypothesis that both organs are stimulated by the same growth factor, and in some donors, this process seems to be more active, leading to greater enlargement in both the spleen and liver. The liver and the spleen both belong to the reticuloendothelial system, and it makes sense that they would respond similarly to the same growth factors.[14]

There was a greater increment in splenic size in right lobe donors as compared to left lobe donors 6 months post-donation. A possible explanation is that, after right lobe graft procurement, a smaller liver remnant is left behind than after left lobe graft procurement. This in turn will lead to greater relative portal hypertension in right lobe donors, which may translate to greater splenic congestion and enlargement. Moreover, there was a greater increment in splenic volume in donors who had donated a greater hepatic mass (graft weight), another finding that gives credence to this theory. To prove this relationship, we have to measure the portal flow (as a reflection of portal pressure) in donors before and after donation to see if there is an increment in flow. Unfortunately, we do not routinely measure the portal flow in these donors post-donation, so this is something to be considered for future studies.

When we compared splenic enlargement between male right lobe and female right lobe donors, there were no differences; the findings were similar in left lobe donors. The gender of the donor seems not to have any influence on the degree of splenic enlargement.

Because this is a retrospective analysis, there could be other confounding factors not examined in this series. One possible confounding factor could be the change in the donor's body weight before donation and 6 months after. Unfortunately, we have not recorded the donor's body weight 6 months post-donation and so could not analyze this factor. Nonetheless, the donor's body weight at donation seems not to be a factor in either liver volume or splenic enlargement at 6 months post-donation.

In our series of healthy donors, although there were increases in splenic volume, they did not result in any harmful effects. The platelet levels and liver function test at 6 months were normal, and all donors remain healthy, with no untoward effects. At the last CTA, all the donors' portal and splenic vein were patent. Another series reported low platelet levels in some of their donors. Because the donors remained clinically asymptomatic, the investigators could offer no explanation for this.[19]

In conclusion, liver regeneration is a highly complex process in humans. Many factors play a part in the physiological regeneration of the liver. We found that in the great majority of donors the liver did not reach its original volume within 6 months after donation. In our series, there were no significant correlations between type of graft, gender, or level of fatty change in the liver volume 6 months after transplant. However, there does seem to be a lower regenerative capacity in donors with higher fatty changes. Although the liver function tests have been normal and there are no problems in these donors, long-term follow-up regarding liver volume may provide further insight into the long-term effects of donation.

There is also splenic enlargement in donors of living-donor liver transplantation 6 months post-donation. This splenic enlargement, fortunately, has not led to any deleterious effect to the donors. However, whether the spleen ultimately regresses to its original size requires long-term study. Enlargement of the spleen could be due to splenic engorgement secondary to relative portal

hypertension and the presence of a common growth factor that influences both the spleen and the liver. Whether splenic enlargement leads to long-term consequences in healthy donors requires further study and long-term follow-up.

ACKNOWLEDGEMENTS

This work is supported in part by program project grant NHRI-EX 93-228SP from the National Health Research Institutes, Taiwan.

REFERENCES

1. Nakagami M, Morimoto T, Itoh K, *et al.* Patterns of restoration of remnant liver volume after graft harvesting in donors for living related liver transplantation. Transplant Proc 1998;30:195–199.
2. Nagasue N, Yukaya N, Ogawa Y, et al. Human liver regeneration after major hepatic resection. Ann Surg 1987;206:30.
3. Tanaka W, Yamanaka N, Oriyama T, *et al.* Multivariate analysis of liver regenerative capacity after hepactectomy in humans. J Hepatobil Pancreat Surg 1997;4:78–82.
4. Yamanaka N, Okamoto E, Kawamura E, *et al.* Dynamics of normal and injured liver human liver regeneration after hepactectomy as assessed on the basis of computed tomography and liver function. Hepatology 1993;18:79–85.
5. Bucher NH. Experimental aspects of hepatic regeneration. N Engl J Med 1967;277:686.
6. Fausto N.. Liver regeneration: from laboratory to clinic. Liver Transplant. 2001;7:835.
7. Court FG, Wemyss-Holden SA, Dennison AR, *et al.* The mystery of liver regeneration. Br J Surg 2002;89:1089.
8. Olthoff KM.. Molecular pathways of regeneration and repair after liver transplantation. World J Surg 2002;26:831.
9. Marcos A, Fischer RA, Ham JM, *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.
10. Pomfret EA, Pomposelli JJ, Gordon FD, *et al.* Liver regeneration and surgical outcome in donors of right lobe liver grafts. Transplantation 2003;76:5–10.
11. Kawasaki S, Makuuchi M, Matsunami H, *et al.* Living related liver transplantation in adults. Ann Surg 1998;227–269.
12. Zollinger RM, Zollinger RM Jr. Left hepatic lobectomy. In Zollinger RM, Zollinger RM Jr, (editors), Atlas of Surgical Operations, 4th edition, New York, Macmillian, 1990; 172.
13. Akimaru K, Onda M, Tajiri T, *et al.* Hypersplenism induced by hepatectomy. Hepato-Gastroenterology 2001;48:1170–1175.
14. Ando H, Nagino M, Arai T, *et al.* Changes in splenic volume during liver regeneration. World J Surg 2004;28:977–981.
15. Tanaka W, Yamanaka N, Oriyama T. Multivariate analysis of liver regenerative capacity after hepactectomy in humans. J Hepatobiliary Pancreatic Surg 1997;4:78–82.
16. Miyagawa S, Kawasaki S, Noike T, *et al.* Liver regeneration after extended right hemihepactectomy in patients with hilar or diffuse bile duct carcinoma. Hepatogastroenterology 1999;46:364–368.
17. Nagino M, Ando M, Kamiya J, *et al.* Liver regeneration after major hepactectomy for biliary cancer. Br J Surg 2001;88:1084–1091.
18. Jacob HS, Macdonald RA, Jandl JH. Regulation of spleen growth and sequestering function. J Clin Invest 1963;42:1476–1490.
19. Tavassoli M. Limitation of splenic growth as studied by heterotopic splenic implants. Blood 1975;46:631–635.
20. Chen YS, Cheng YF, De Villa VH, *et al.* Evaluation of living liver donors. Transplantation 2003;75(Suppl 3):S16–S19.
21. Chen CL, Chen YS, De Villa VH, *et al.* Minimal blood loss living donor hepatectomy. Transplantation 2000;69:2580–2586.
22. Greene AK, Wiener S, Puder M, *et al.* Endothelial directed hepatic regeneration after partial hepactectomy. Ann Surg 2002;236:530–534.
23. Francavilla A, Polimeno L, Dileo A, *et al.* The effect of estrogen and tamoxifen on hepatocyte proliferation *in vivo* and in vitro. Hepatology 1989;9–614.
24. Chiu J, Lin L, Chi W, *et al.* Estrogen therapy for hepactectomy with poor liver function? Med Hypotheses 2002;58:516.
25. Nagasue N, Yukaya H, Ogawa Y, *et al.* Portal pressure following partial to extensive hepatic resection in patients with and without cirrhosis of the liver. Ann Chir Gynecol 1983;72:18–22.
26. Ueda S, Yamanoi A, Hishikawa Y, *et al.* Transforming growth factor beta-1 released from the spleen exerts a growth inhibitory effect on liver regeneration in rats. Lab Invest 2003;83:1595–1603.
27. Kaido T, Oe H, Yoshikawa A, *et al.* Expressions of molecules associated with hepatocyte growth factor activation after hepatectomy in liver cirrhosis. Hepato-Gastroenterology 2004;51:547–551.
28. Charters AC, Oakes DD, Froechlich JP. Effect of hepatectomy on mitotic activity in rat spleen. J Surg Res 1980;29:331–337.
29. Rosenkranz E, Charters AC, Orloff MJ. Regeneration in rat liver injured by carbon tetrachloride. Surg Forum 1975;26:411–412.
30. Tomiya T, Tani M, Yamada S, *et al.* Serum hepatocyte growth factor levels in hepactomised and nonhepacto-

mised surgical patients. Gastroenterology 1992;103:1621–1624.
31. Nishizaki T, Takenaka K, Yoshizumi T, *et al.* Alteration in levels of human hepatocyte growth factor following hepactectomy. J Am Coll Surg 1995;181:6–10.
32. Sato K, Tanaka M, Tanikawa K. The effect of spleen volume on liver regeneration after hepatectomy—a clinical study of liver and spleen volumes by computed tomography. Hepatogastroenterology 1995;42:961–965.