Remnant liver regeneration and spleen volume changes after living liver donation: influence of the middle hepatic vein


Abstract: Background and objectives: Graft harvest with or without the middle hepatic vein (MHV) affects venous return and function of the remaining liver. The aims of this study are to compare the remnant liver volume and spleen changes in the donors of different types of graft harvest and to evaluate the influence of resection with or without the MHV on the remnant liver volume regeneration, spleen volume change and serum total bilirubin. Patients and methods: A total of 165 donors were grouped according to the type of graft harvest: 88 donors underwent left lateral segmentectomy (LLS), 10 donors underwent extend LLS or left lobectomy (LL), and 67 donors underwent right lobectomy (RL). Groups LLS and LL were later combined as group LH (left hepatectomy, n = 98). There were 68 men and 97 women. The mean age was 32.9 ± 8.1 yr. The total liver volume (LV) and spleen volume (S1) before graft harvest, graft weight (GW), regenerated liver volume (LV6m) and spleen volume (S2) six months post-donation were calculated. Results: There were no significant differences in the regenerated liver volume six months postoperation (LV6m) and recovery ratio (LV6m/LV × 100%) among the different groups, albeit significant smaller LV6m in both groups compared with the initial liver volume was noted. Postoperative spleen volume (S2), average spleen ratio (S2/S1) and spleen change ratio were significantly larger and higher in group RL than in group LH. A significant increase in spleen volume was noted in both groups six months after graft harvest. A significantly higher TB in group RL (4.1 ± 1.7 mg/dL, range: 1.4–8.5 mg/dL) was noted compared with that of group LH (1.6 ± 1.0 mg/dL, range: 0.7–6.2 mg/dL). Conclusion: There was a significant increase in the regenerated remnant liver and splenic volumes six months postoperation in all types of hepatectomy following living donor hepatectomy, and there was no difference in the mean TB levels among donors whether the MHV was included or not in the graft.

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Key words: living donor liver transplantation – middle hepatic vein – remnant liver – splenic volume

Abbreviations: LH, left hepatectomy; PC, platelet count; RL, right lobectomy; SV, spleen volume.

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Living donor liver transplantation (LDLT) was developed to alleviate organ shortage due to a markedly limited deceased donor graft supply and to decrease mortality while on the waiting list. Initially, LDLT was performed only in pediatric recipients using a left lateral segment graft. With experience in these cases, the indications for LDLT have been extended to adult patients where a right lobe graft is mainly used because of volume requirement.

The liver segments have been described according to a classification developed by Couinaud and later modified by Bismuth (1, 2). In some donors, the middle hepatic vein (MHV) drains segments 4,
5 and 8 of the liver. The hepatic vein anatomy of segment 4 which mainly includes the MHV has been a matter of concern since the introduction and use of an extended right lobe graft. Graft harvest with or without the MHV affects venous return and function of the remaining liver. The success of LDLT depends both on the provision of an adequate graft weight and vessels. Computed tomographic (CT) volumetry calculates the graft and remnant liver volumes with satisfactory results (3).

Hemodynamic changes after graft harvest influence the portal system flow which in turn may affect spleen volume. Splenomegaly is a frequent finding in patients with liver disease. However, splenomegaly per se does not predictably induce hypersplenism or cause abdominal discomfort. It is usually asymptomatic but may cause hypersplenism.

Because of the liver’s regeneration capacity, the remaining liver in the donor is expected to increase in size to compensate for the loss of hepatic volume and to assure normal function. The purpose of this study is to compare the remnant liver volume and spleen changes in the donors of different types of graft harvest which include left lateral segmentectomy (LLS), extend LLS or left lobectomy (LL), and right lobectomy (RL) after LDLT. In group RL, we evaluate the influence of resection with or without the MHV on the remnant liver volume regeneration, spleen volume change and serum total bilirubin (TB).

**Patients and methods**

Between June 1994 and June 2004, 185 healthy individuals donated part of their liver to 183 recipients including one re-transplantation and one dual graft transplantation. Data were collected prospectively and analyzed retrospectively which included preoperative total liver volume and spleen volume, harvested graft weight, and postoperative remnant liver volume and spleen volume measurements. In all, a total of 165 donors were grouped according to the type of graft harvest: 88 donors underwent LLS (group LLS), 10 donors underwent extend LLS or LL (group LL), and 67 donors underwent RL (group RL). Groups LLS and LL were later combined as group LH (left hepatectomy, n = 98). Twenty donors (20) were excluded from this study because of incomplete data which included four foreign donors, one pregnant donor, and 15 other donors who were lost to follow up. Thalassemia minor was identified in two donors – one in group LLS and the other in group RL. There were no other major systemic illnesses identified among the donors aside from thalassemia. There were 68 men and 97 women. The mean age was 32.9 ± 8.1 yr (mean ± SD). The average body height, body weight, and body mass index (BMI) were 162 cm, 61 kg, and 23.0, respectively (Table 1).

**Volume**

The liver and spleen volumes were measured by hand tracing the organ outline on the axial portal venous phase images on CT. Examinations were performed before and six months after liver donation. All the major vessels (including the inferior vena cava and extrahepatic portal vein) and major fissures (such as the fissure for the ligamentum teres) were excluded. The area of the liver and spleen on each section was multiplied by the slice thickness to calculate the volume. The total volume of the liver and spleen was then determined by adding the individual volumes through the organs. This method of calculating hepatic and splenic volumes had been validated in previous studies in adult subjects (4, 5). The absolute graft weight was assumed as the actual graft volume because the liver had nearly the same density as water (6).

We measured the total liver volume (LV) and spleen volume (S1) before graft harvest, graft weight (GW), regenerated liver volume (LV6m) and spleen volume (S2) six months after the operation. According to the measured volume data, we then calculated the resection ratio (graft weight vs. initial liver volume ratio, G/L), liver...

### Table 1. Donor demographic characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>M/F</th>
<th>Age (yr)</th>
<th>BH (cm)</th>
<th>BW (kg)</th>
<th>BMI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>ALL</td>
<td>165</td>
<td>68/97</td>
<td>33 ± 8</td>
<td>20-58</td>
<td>162 ± 8</td>
<td>144-187</td>
</tr>
<tr>
<td>LH</td>
<td>98</td>
<td>33/65</td>
<td>33 ± 7</td>
<td>20-58</td>
<td>161 ± 8</td>
<td>144-178</td>
</tr>
<tr>
<td>RL</td>
<td>67</td>
<td>35/32</td>
<td>33 ± 10</td>
<td>20-56</td>
<td>165 ± 9*</td>
<td>148-187</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with group LH.
remnant volume (total liver volume minus graft weight, $L_{\text{Rem}}$), liver remnant volume increase rate $[\text{LV}_{6\text{m}} - L_{\text{Rem}}]/L_{\text{Rem}} \times 100\% = L_{\text{Inc}}]$, recovery ratio $(\text{LV}_{6\text{m}}/\text{LV} \times 100\%)$, spleen ratio $(\text{S2}/\text{S1} \times 100\%)$ and spleen change ratio $[(\text{S2} - \text{S1})/\text{S1} \times 100\%]$. $S_{\text{change}}$.

The group RL was subdivided into groups with or without the MHV in the remnant liver. All prospective right lobe liver donors were evaluated to ensure that the MHV could be removed safely without compromising venous outflow from the remaining liver. Serum TB was recorded preoperatively ($B_0$), and the peak values within the first week ($B_{1\text{w}}$), the second week ($B_{2\text{w}}$), and six months ($B_{6\text{m}}$) after the operation.

Statistical analysis

All data were expressed as mean ± SD. The Student’s t-test was used to determine statistically significant differences before and after LDLT in the different graft harvest groups. The Pearson correlation was used to determine significant differences between remnant liver vs. body weight and liver remnant volume increase rate in the groups studied with regards to time. A p-value < 0.05 was considered significant.

Results

Liver volume

There was no donor mortality. There were no significant differences noted in all studied demographic variables between groups LLS and LL except for the mean graft weight. The groups LLS and LL were combined as group LH. There was no significant difference with regards to mean age among the different groups (Table 1). The body height, body weight, and BMI were significantly higher and heavier in group RL than in group LH. The average initial total liver volume, graft weight, and remaining liver volume in donors were also significantly larger in group RL (Table 2). There were no significant differences in the regenerated liver volume six months after operation ($\text{LV}_{6\text{m}}$) and recovery ratio $(\text{LV}_{6\text{m}}/\text{LV} \times 100\%)$ among the different groups, albeit significant smaller $\text{LV}_{6\text{m}}$ in both groups compared with the initial liver volume (Table 3) was noted. The liver remnant volume increase rate $[\text{LV}_{6\text{m}} - L_{\text{Rem}}]/L_{\text{Rem}} \times 100\% = L_{\text{Inc}}$ was significantly larger in group RL. The Pearson correlation was significant between remnant liver vs. body weight and liver remnant volume increase rate in both groups ($p < 0.01$). No change in the remnant liver volume six months after operation was found in the 10 donors who underwent LL.

Spleen volume

There was no significant difference in the spleen volumes in both groups before operation (Table 2). Postoperative spleen volume ($\text{S2}$), average spleen ratio ($\text{S2}/\text{S1}$) and spleen change ratio were significantly larger and higher in group RL than in group LH. A significant increase in spleen volume was noted in both groups six months after liver graft harvest (Table 3). Fifteen donors, all in group LLS, showed a decrease in spleen volume six months after liver donation. Only one donor (in group LLS) showed both a decrease in liver remnant volume and spleen volume after donation.

Table 2. Preoperative liver volume, graft volume, liver regeneration, and spleen volume changes among the different graft harvest groups

<table>
<thead>
<tr>
<th>Group</th>
<th>ALL</th>
<th>LH</th>
<th>RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV (cm$^3$)</td>
<td>1189 ± 203</td>
<td>1154 ± 191</td>
<td>1240 ± 21*</td>
</tr>
<tr>
<td>GW (g)</td>
<td>453 ± 230</td>
<td>275 ± 57</td>
<td>713 ± 108*</td>
</tr>
<tr>
<td>G/L (%)</td>
<td>38 ± 18</td>
<td>24 ± 5</td>
<td>58 ± 6*</td>
</tr>
<tr>
<td>$L_{\text{rem}}$ (cm$^3$)</td>
<td>736 ± 236</td>
<td>878 ± 173</td>
<td>527 ± 144*</td>
</tr>
<tr>
<td>$\text{LV}_{6\text{m}}$ (cm$^3$)</td>
<td>1083 ± 204</td>
<td>1065 ± 205</td>
<td>1111 ± 201</td>
</tr>
<tr>
<td>$L_{\text{Inc}}$ (%)</td>
<td>63 ± 62</td>
<td>24 ± 24</td>
<td>121 ± 55*</td>
</tr>
<tr>
<td>Recovery (%)</td>
<td>92 ± 14</td>
<td>93 ± 15</td>
<td>90 ± 12</td>
</tr>
<tr>
<td>S1 (cm$^3$)</td>
<td>155 ± 57</td>
<td>151 ± 51</td>
<td>162 ± 64</td>
</tr>
<tr>
<td>S2 (cm$^3$)</td>
<td>200 ± 84</td>
<td>174 ± 61</td>
<td>239 ± 99*</td>
</tr>
<tr>
<td>S2/S1 (%)</td>
<td>130 ± 33</td>
<td>117 ± 21</td>
<td>150 ± 37*</td>
</tr>
<tr>
<td>$S_{\text{change}}$ (%)</td>
<td>30 ± 33</td>
<td>17 ± 21</td>
<td>50 ± 37*</td>
</tr>
<tr>
<td>$B_0$ (mg/dL)</td>
<td>0.7 ± 0.3</td>
<td>0.7 ± 0.3</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>$B_{1\text{w}}$ (mg/dL)</td>
<td>2.6 ± 1.8</td>
<td>1.6 ± 1.0</td>
<td>4.1 ± 1.7*</td>
</tr>
<tr>
<td>$B_{2\text{w}}$ (mg/dL)</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td>$B_{6\text{m}}$ (mg/dL)</td>
<td>0.7 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>0.9 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with group LH.

*A negative value means a decreased volume after donation with respect to volume before the operation.

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No significant differences were noted between donors with increased spleen size and donors with decreased spleen size in group LH (LV, GW, LRem, LV6m, LInc, recovery ratio, G/L, and mean spleen volume).

Right lobe with or without the MHV

The TB, in all donors, reached the highest level (8.5 mg/dL in one donor) within the first three d after the operation and returned to below 1.5 mg/dL within two wk. A significantly higher TB in group RL (4.1 ± 1.7 mg/dL, range: 1.4–8.5 mg/dL) was noted compared with that of group LH (1.6 ± 1.0 mg/dL, range: 0.7–6.2 mg/dL).

In group RL, there was no difference in the levels of TB between subgroups with or without the MHV in the remnant liver (Table 4). The TB reached peak level on the first to the third day ranging from 1.4 to 8.5 mg/dL in the subgroup with the MHV in the remnant liver, and from 1.6 to 7.0 mg/dL in the subgroup without the MHV. In both subgroups, the TB returned to below 1.5 mg/dL within the second week after donation.

In the subgroup without the MHV in the liver remnant, significant small LV, LRem, and LV6m were noted. Likewise, this subgroup also showed significantly large G/L, and LInc. However, there were no significant differences in the GW and recovery ratio (recovery) between the subgroups.

In group RL where peak TB was more than 3 or 5 mg/dL within the first week after the operation, there were no differences in volume changes and in the follow up TB after the operation. If the graft resection ratio was larger than 66% (G/L > 66%), the LRem and the LV6m were smaller compared with those with G/L < 66% but the LInc was greater in donors with G/L > 66% than in donors with G/L < 66%. In the subgroup RL with the MHV, only LRem was significantly smaller if the peak TB was >5 mg/dL or if the G/L was >66%. In the subgroup without the MHV, the G/L was >66%, and the LRem was smaller but the GW and LInc were larger than those with G/L < 66%. There were no statistical differences in all liver or spleen volume changes and TB levels between subgroups with peak TB > 3 mg/dL and TB < 3 mg/dL whether in the subgroup with or without the MHV.

Discussion

The proportion of each segment in the human liver has been estimated as 65% for the right lobe (segments 5, 6, 7, and 8), 20% for the segment 4 and 15% for the left lateral segment (segments 2 and 3) (7). Either the graft-to-recipient weight ratio (GRWR) or the graft volume to estimated standard liver volume (ESLV) of the recipient has been used to determine the ideal liver volume for recipients. In pediatric recipients, the left lateral segment or the left lobe of graft is usually sufficient. Large-for-size grafts may cause vascular compression and difficulty in abdominal closure. In adult LDLT, in addition to providing adequate liver mass for the recipient to maintain liver function and to avoid small-for-size syndrome, sufficient remnant for the donor should also be ascertained to permit metabolic function during regeneration. Therefore, the required graft volume should be determined individually to choose the ideal donor among the donor candidates, if possible.

Liver regeneration has been reported after hepatectomy for hepatocellular carcinoma, metastatic liver tumor or liver trauma. Although livers with benign diseases, such as hepatolithiasis or traumatic injury, have been regarded to be almost normal functionally and anatomically, there may be certain pathologic factors that have already induced altered hemodynamics or vasculature at the time of liver resection (8). Because of the liver’s ability to regenerate, the remaining liver in the
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donor is expected to regenerate and compensate for the loss of hepatic volume. Portal flow is important in restoring liver function after hepatectomy. When a hepatic lobe is removed, portal flow to the liver remnant is increased immediately (9). In the non-cirrhotic liver, the bulk of the remaining liver remnant can increase rapidly because of vascular engorgement and interstitial edema. It has been reported that liver regeneration terminates after the liver has achieved 75–95% of its original weight. There might be a certain redundancy of liver mass that would account for the reason regeneration halts before full recovery of the pre-transplant volume (10).

All the variances (LV, GW, LRem, LV6m, recovery ratio, Linc, and mean spleen volume) in this study showed that there were no significant differences between groups LLS and LL. We grouped together all donors who underwent LLS, extended LSS and LL into one group – group left hepatectomy (group LH). The body height, body weight and initial total liver volume were significantly bigger in group RL donors. This may be due to the fact that these donors were chosen for the larger liver graft volume that they can provide.

The mean LV6m and recovery ratios did not show any differences between both groups. The mean recovery ratio of all donors was 92% ± 14% (range, 66–141%). The livers will regenerate to a certain required volume but this regeneration is independent from the initial liver remnant volume or the different types of hepatectomy. Although the mean LV6m was not different between the groups, the volume revealed significant different changes before and after graft harvest. Significant more GW was removed in group RL (713 ± 108 g) than in group LLS (267 ± 50 g) and group LL (288 ± 66 g) resulting to a smaller remnant liver in group RL (527 ± 144 g) than in group LLS (900 ± 144 g) and group LL (842 ± 209 g). The Pearson correlation was significant between remnant liver vs. body weight and liver remnant volume increased rate in all groups (p < 0.01). The liver regeneration is dependent on the amount of liver volume contained in the graft removed. Chen et al. (11) previously reported on remnant liver regeneration after major hepatectomy (n = 17). In a non-cirrhotic group (n = 12), liver remnant volume was increased by 28.4% ± 9.5% and 48.4% ± 17.8% at three and six months after major hepatectomy, respectively. In five patients with right hepatectomy (65% resection) the liver remnant volumes were increased by 38.4% ± 11.7%, 48.0% ± 16.2% and 95.1% ± 4.5%. In the study by Kamel et al. (12), their donors’ (n = 10) liver volume after right lobe resection increased by 42% ± 26%, 67% ± 41% and 74% ± 46% at one month, two months, and six months, respectively. In our present series, the liver volume increased by 24% ± 24% and 121% ± 55% in groups LH and RL, respectively.

The patients studied by Chen et al. (11) included liver trauma (n = 3), hepatolithiasis (n = 4) and hepatocellular carcinoma (n = 5). As mentioned previously, there may be certain pathologic factors that may have already induced altered hemodynamics or vasculature at the time of liver resection in these patients. After RL, healthy donors seem to have higher liver remnant increase rate than liver non-regeneration. Our findings are in corollary with that of Chen et al., where the remnant liver regeneration capacity showed a linear relationship with either the resected liver volume or the remnant liver volume.

Splenomegaly is a frequent finding in patients with liver disease. It is usually asymptomatic but may cause hypersplenism. Kamel et al. (12) noted that in all their donors (n = 10), the spleen increased in volume in the immediate postoperative period, reaching a peak of 45% at one month, followed by a plateau for up to six months, and then a gradual decline, reaching the preoperative volume after approximately one yr. In our study, almost all donors developed a significant increase in spleen volume after resection and group RL had the most significant spleen volume increase. The increase in splenic volume may be due to an increase in portal blood flow (5, 13). However, some donors did not show increased remnant liver and spleen volume after graft harvest. All donors in groups LL and RL revealed increased remnant liver volume and spleen six months after operation. A few donors, however, showed a decrease in size after operation. Decreased remnant liver volume six months after operation was found in some donors in group LLS (n = 10). The decreased liver remnant volume rate ranged from −1% to −21%, and is only found in group LLS (n = 10). Likewise, 15 donors revealed decreased spleen volume six months after liver donation (range, −0.5 to −44) in group LLS (n = 15). As in the recipient, the left lateral segment graft has a more rapid growth ratio than the medial segment graft (14). The decreased remnant liver volume in some donors in group LLS may be because of the atrophy of the remaining segment 4 brought about by the absence of portal blood supply (with left portal vein removed together with the LLS graft). After hepatectomy, spleen volume in some donors in group LLS did not show a linear increase with the increase in liver remnant regeneration.
There is a significantly higher TB in the RL group than in the LH group (4.1 ± 1.7 mg/dL; range, 1.4–8.5 mg/dL vs. 1.6 ± 1.0 mg/dL; range, 0.7–6.2 mg/dL). This may be due to a smaller remnant liver in the RL group. In some donors, the MHV drains both parts of segments 4, 5, and 8. Inadequate venous return will cause liver congestion followed by atrophy. The mean serum TB did not differ in groups whether the MHV was removed with the graft or not in this study (Table 4). The peak TB reached its highest level (8.5 mg/dL in one donor in our study) within the first three d after operation and returned to below 1.5 mg/dL within two wk. In the subgroup without the MHV in the liver remnant, a significant large resection ratio (G/L), and liver remnant volume increased rate (LInc) were noted. However, there was no significant change in the recovery ratios in both subgroups. Without the MHV, the liver remnant will regenerate more liver volume to compensate and to resume functional demand. If the graft resection ratio is larger than 66% (G/L > 66%), the increase rate was greater than G/L < 66% (Table 5). This finding is consistent to that of donors with a larger liver volume resected which developed a larger regenerated volume albeit without redundant size. In the subgroup RL with the MHV, when peak TB is > 5 mg/dL, only LRem is significantly small. There was no difference in volume change or TB levels (including LV, GW, G/L, LRem, LVrem, LInc, recovery, B0, B1w, B2w, and B6m) after postoperative follow up whether the peak TB was > 3 mg/dL or > 5 mg/dL within the first week after operation among donors. A right lobe graft with the MHV does not increase donor risk. Living donor right lobe grafts which include the MHV can be performed safely in selected donors. Regardless of the donor hepatectomy procedure, serious complications did not occur after surgery in this series.

Conclusion

There was a significant increase in the regenerated remnant liver and splenic volumes six months after operation in all types of hepatectomy following living donor hepatectomy. The remnant liver regeneration capacity showed a linear increase with the increase in the amount of volume resected. The liver will regenerate to a certain required volume but will not lead to a redundant size. This observation is independent of the different types of hepatectomy among the donors. TB reached its peak level within the first three d after the operation and returned to within normal range after the one wk. There was no difference in the mean TB levels among donors whether the MHV was included or not in the graft. In contrast to most donors, some donors after LLS developed a decrease in remnant liver and splenic volumes six months after hepatectomy. This decreased remnant liver and splenic volumes in some donors in group LLS may be because of the absence of the left portal blood supply (where the left portal vein was removed with the LLS graft) which causes atrophy of the remaining segment 4.

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