Functional assessment of the liver with gadolinium–ethoxybenzyl-diethylenetriamine penta-acetate-enhanced MRI in living-donor liver transplantation

M. Ninomiya¹, K. Shirabe¹, H. Kayashima¹, T. Ikegami¹, A. Nishie², N. Harimoto¹, Y. Yamashita¹, T. Yoshizumi¹, H. Uchiyama¹ and Y. Maehara¹

Departments of ¹Surgery and Science and ²Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Correspondence to: Dr M. Ninomiya, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812–8582, Japan (e-mail: nino-m@surg2.med.kyushu-u.ac.jp)

Background: A precise estimation of the capacity of the remnant liver following partial liver resection is important. In this study, the regional function of the liver in patients undergoing living-donor liver transplantation was evaluated by gadolinium–ethoxybenzyl-diethylenetriamine penta-acetic acid (EOB)-enhanced MRI, with special reference to the congested region.

Methods: EOB-MRI analysis was performed before hepatectomy in donors, and 7 days after surgery in both the donor and recipient. In the hepatocyte phase, from images obtained 15 min after Primovist® injection, the signal intensity in each liver segment was measured and divided by the signal intensity of the erector spinae muscle (liver to muscle ratio, LMR) for standardization. Inter-regional differences in LMRs were analysed in donors and recipients.

Results: Thirty-two living donors and 31 recipients undergoing living-donor liver transplantation were enrolled. In donors, the LMRs of the remnant left lobe were almost equivalent among the liver segments. In the remnant right lobe without the middle hepatic vein, the mean(s.d.) LMR for congested segments (S5 and S8) was significantly lower than that for non-congested segments (S6 and S7): 2.60(0.52) versus 3.64(0.56) respectively (P < 0.001). After surgery, values in the non-congested region were almost identical to those in the preoperative donor liver. LMR values in the left and right lobe graft were significantly lower than those in the corresponding segment before donor surgery (P < 0.001).

Conclusion: The function of the congested region secondary to outflow obstruction in the remnant donor liver was approximately 70 per cent of that in the non-congested region. EOB-MRI is a promising tool to assess regional liver function, with good spatial resolution.

Paper accepted 5 March 2015
Published online 29 April 2015 in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.9820

Introduction

Accurate estimation of the remnant functional liver capacity is a prerequisite for the safety of patients undergoing liver resection for malignancy or partial liver grafting. In living-donor liver transplantation, the donor liver is usually divided at the right side of the middle hepatic vein. Hence, the anterior segment of the right liver, regardless of whether it is remnant in the donor or transplanted into the recipient, can become congested owing to impaired venous outflow. This may cause hepatic dysfunction and affect postoperative recovery of the patient. Although preoperative imaging techniques can estimate the congested regional volume of the liver, the extent of functional decrease in such regions remains unclear.

Gadolinium–ethoxybenzyl-diethylenetriamine penta-acetate (Gd–EOB-DTPA) is a liver-specific contrast medium for MRI that is often used for the detection of hepatic malignancy. Gd–EOB-DTPA is transported from portal blood into hepatocytes via several organic anion transporters and excreted into bile canaliculi via multidrug resistance proteins 2 and 3. Therefore, uptake of Gd–EOB-DTPA in the hepatocyte phase of dynamic MRI (EOB-MRI) is thought to reflect liver function.

Previous studies have shown good correlation between EOB-MRI and other liver function tests including ⁹⁹ᵐTc-labelled galactosyl human serum albumin (GSA)
Functional assessment of the liver in living-donor liver transplantation

scintigraphy, indocyanine green (ICG) retention rate of the liver and prothrombin time. This suggests that EOB-MRI could be used for the quantitative analysis of regional liver function. The present study investigated regional liver function using EOB-MRI in patients undergoing living-donor liver transplantation, with special reference to liver regions with an impairment of venous outflow.

Methods

The study was conducted with the approval of the Institutional Ethics Review Board of Kyushu University (26–300). All patients scheduled for living-donor liver transplantation between November 2011 and December 2012 at Kyushu University Hospital, Fukuoka, Japan, were invited to participate. Written informed consent was obtained from all patients before surgery.

The selection criteria for partial liver grafts from living donors and postoperative management have been described previously.5,6 A left lobe graft was preferred if the predicted graft volume to standard liver volume ratio was over 35 per cent. Otherwise, a right lobe graft was considered, provided that the donor’s estimated remnant liver volume exceeded 35 per cent of total liver volume. In general, the hepatic venous drainage pattern was not accounted for in selecting the graft, although various other factors including recipient condition, donor age and anatomical variations were noted. All left lobe grafts included the middle hepatic vein, whereas right lobe grafts did not. In the remnant right lobe of the donor, the tributaries of the middle hepatic vein (veins from segments 5 and 8) were not reconstructed principally. In patients where the right lobe was used as a graft, if the predicted graft volume excepting congestion volume was considered to be insufficient, transected middle hepatic vein tributaries from the anterior segment in the liver graft were reconstructed using the recipient’s left internal jugular vein or portal vessels from the recipient’s explanted liver.

Imaging studies

All recipients and donors underwent multidetector CT before the operation and on postoperative day (POD) 7. Preoperative CT images were reconstituted into three-dimensional (3D) images using a Synapse Vincent 3D-image analyser (Fujifilm, Tokyo, Japan), and used for vascular mapping, prediction of graft volume and estimation of potential venous congestion volume associated with middle hepatic vein tributaries (Fig. 1a,b). In donors, EOB-MRI was performed before surgery in ten patients and on POD 7 in all patients. For the recipients, EOB-MRI was performed only on POD 7.

EOB-MRI and measurement of liver to muscle ratio

EOB-MRI was performed on a 1.5-T scanner (Intera Achieva Nova Dual; Philips Medical Systems, Best, The Netherlands). A multiphase dynamic study, including arterial, portal and late phases, was performed using axial 3D cTHRIVE (enhanced 3D T1 high-resolution isotropic volume excitation) after intravenous injection of 0.1 ml/kg Primovist® (Bayer, Osaka, Japan). Hepatocyte phase images obtained 15 min after injection of Primovist® were used for image analysis. The signal intensity of each liver segment (S1, S2/3, S4, S5, S6, S7, S8) was measured on the digital imaging and communications in medicine (DICOM) viewer, at the largest possible region of interest, avoiding vessels and artefacts. The signal intensity of the erector spinae muscle was also measured for standardization. Because functional impairment in the congested region was not homogeneous, the mean of three signal intensities was calculated, and the liver to muscle ratio (LMR) was recorded for each segment. Because the major objective of the study was to evaluate the function of the congested region at the right anterior segment, which was not always identical to the area of segments 5 and 8 in the postoperative EOB-MRI images, the congested area that appeared to have a lower signal intensity around the middle hepatic vein tributaries was recorded as segment 5 or 8 (Fig. 1c).

The ratio of LMRs of congested and non-congested regions in the remnant donor livers was calculated using the formula (LMRS6/7−LMRS5/8)/LMRS6/7×100 (%), which estimates the percentage of decreased function of the right lobe due to outflow obstruction of the anterior segment.

Correlation between predicted functional liver volume and postoperative functional parameters in the donor

The relative function in the congested region was calculated with respect to the non-congested region in the postoperative donor liver. Predicted functional liver volume (PFLV), which takes the impact of venous congestion into account, was calculated as follows: PFLV = volume of non-congested region + volume of congested region × relative function of the congested region.

Correlation between PFLV and postoperative functional parameters total bilirubin levels and international normalized ratio of prothrombin time (PT-INR) on POD 1, 3, 5 and 7 were analysed in the donor.
Fig. 1  a,b Preoperative three-dimensional (3D) CT images to predict graft volume and to estimate potential venous congestion volumes associated with middle hepatic vein tributaries (a right lobe, b left lobe). Arrows indicate tributaries of the middle hepatic vein (V5 and V8) and the corresponding potential congested region. c Postoperative gadolinium–ethoxybenzyl-diethylenetriamine penta-acetate (Gd–EOB-DTPA) MRI of the remnant donor liver. The congested region associated with occlusion of middle hepatic vein tributaries appeared as an area of low signal intensity with a clear delineating line. Black arrowheads indicate congested region in the anterior segment. RHV, right hepatic vein. d Remnant left lobe with no sign of congestion. e In the arterial phase of multidetector CT (MDCT) of the remnant donor liver, the congested area in the right anterior segment is depicted as a vague region of slightly higher intensity (white arrowheads) because of arterioporal shunt flow in the corresponding region. f MDCT of the remnant left lobe with the middle hepatic vein showed good parenchymal enhancement within the entire left lobe.
Table 1  Donor characteristics

<table>
<thead>
<tr>
<th></th>
<th>Remnant right lobe (n = 18)</th>
<th>Remnant left lobe (n = 14)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>40·4(9·6)</td>
<td>40·1(10·9)</td>
<td>0·910</td>
</tr>
<tr>
<td>Sex ratio (M : F)</td>
<td>12 : 6</td>
<td>6 : 8</td>
<td>0·177†</td>
</tr>
<tr>
<td>V5 reconstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V8 reconstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin on POD 7 (mg/dl)*</td>
<td>0·82(0·32)</td>
<td>1·03(0·41)</td>
<td>0·119</td>
</tr>
<tr>
<td>PT-INR on POD 7*</td>
<td>1·06(0·07)</td>
<td>1·07(0·08)</td>
<td>0·566</td>
</tr>
<tr>
<td>Congested volume on POD 7 (ml)*</td>
<td>196·9(92·5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remnant liver volume on POD 7 (ml)*</td>
<td>897·4(190·5)</td>
<td>605·9(141·3)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Congested/remnant liver volume × 100 (%)*</td>
<td>21·8(7·6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean(s.d.). V5, drainage vein from segment 5; V8, drainage vein from segment 8; POD, postoperative day; PT-INR, international normalized ratio of prothrombin time. †Student’s t test, except χ² test.

Table 2  Recipient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Right liver graft (n = 14)</th>
<th>Left liver graft (n = 17)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>51·4(13·5)</td>
<td>52·1(12·9)</td>
<td>0·886</td>
</tr>
<tr>
<td>Sex ratio (M : F)</td>
<td>8 : 6</td>
<td>3 : 14</td>
<td>0·031†</td>
</tr>
<tr>
<td>V5 reconstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V8 reconstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative total bilirubin (mg/dl)*</td>
<td>5·5(4·8)</td>
<td>7·6(6·8)</td>
<td>0·329</td>
</tr>
<tr>
<td>Preoperative PT-INR*</td>
<td>1·52(0·24)</td>
<td>1·52(0·31)</td>
<td>0·984</td>
</tr>
<tr>
<td>Total bilirubin on POD 7 (mg/dl)*</td>
<td>5·44(2·96)</td>
<td>5·13(2·90)</td>
<td>0·774</td>
</tr>
<tr>
<td>PT-INR on POD 7*</td>
<td>1·07(0·10)</td>
<td>1·12(0·08)</td>
<td>0·143</td>
</tr>
<tr>
<td>Congested volume on POD 7 (ml)*</td>
<td>66·4(89·9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remnant liver volume on POD 7 (ml)*</td>
<td>1067·5(144·7)</td>
<td>825·9(134·0)</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Congested/remnant liver volume × 100 (%)*</td>
<td>6·3(8·4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean(s.d.). V5, drainage vein from segment 5; V8, drainage vein from segment 8; POD, postoperative day; PT-INR, international normalized ratio of prothrombin time. †Student’s t test, except χ² test.

Statistical analysis

Descriptive statistics are expressed as mean(s.d.) and compared using a two-tailed, unpaired Student’s t test. Categorical data are compared with the χ² test. Correlations between parameters were determined by linear regression analysis. Statistical analyses were performed using JMP9 software (SAS Institute, Cary, North Carolina, USA). P < 0·050 was considered statistically significant.

Results

Some 41 living-donor liver transplants were performed. Two patients who underwent right posterior sector graft transplantation and four paediatric transplantations were excluded. Three donors and four recipients did not give informed consent. The characteristics of the remaining 32
Postoperative congested region in the remnant donor liver

In the remnant right donor liver, EOB-MRI images displayed congested regions as areas of low signal intensity with a clear delineating line (Fig. 1c), in accordance with multidetector CT images (Fig. 1e). Congested regions were not observed in the remnant left lobe (Fig. 1d,f). The mean(s.d.) congested volume in the remnant right lobe was 196.9(92.5) ml, which was 21.8(7.6) per cent of the remnant liver volume on POD 7 (Table 1).

Changes in liver to muscle ratio of remnant donor livers

Baseline preoperative LMR values in donor livers were almost identical among all segments. After right lobectomy, LMRs in the remnant left lobe (n = 14) were similar for all segments and no different from values before surgery (Fig. 2a). After left lobectomy, the mean(s.d.) LMR of congested segments (S5 and S8) was significantly lower than that in non-congested segments (S6 and S7): 2.60(0.52) versus 3.64(0.56) respectively (P < 0.001).
The difference ratio of LMR values for congested and non-congested regions in remnant donor livers was 27.9(13.0) per cent (Fig. 3).

**Correlation between PFLV and postoperative functional parameters in donors**

PFLV correlated with PT-INR on POD 1 \( (R^2 = 0.201, \ P = 0.001) \) and POD 3 \( (R^2 = 0.250, \ P = 0.003) \) (Fig. S1, supporting information).

**Changes in liver to muscle ratios of transplanted recipient livers**

Fig. 4 shows a comparison of LMRs for each segment between donor livers before surgery \((n = 10)\) and transplanted recipient livers 7 days after transplantation \((n = 31)\). LMRs in left lobe grafts were significantly lower than those in the corresponding segment before donor surgery \((P < 0.001)\). There were no differences in LMRs between segments in the transplanted liver grafts, even between the anterior and posterior sector in the right lobe graft \((\text{mean(s.d.)} \ 3.63(0.93) \text{ and } 3.77(1.14) \text{ respectively; } \ P = 0.733) \) (Fig. 4b). Mean(s.d.) congested volume in the grafts was only 66.4(89.9) ml, corresponding to approximately 6 per cent of the right lobe graft volume on POD 7 (Table 2). The difference ratio of LMR values between the congested and non-congested regions in recipient liver grafts was 1.7(13.0) per cent (Fig. 3).

**Discussion**

Recent advances in imaging techniques have enabled accurate identification of the volume of the anticipated congestion area of middle hepatic vein tributaries that would be occluded. However, there is no consensus on the permissible threshold for the congestion volume in terms of the postoperative hepatic functional reserve. Based on clinical experience, almost all remnant living-donor livers after left lobe donation are thought to have a sufficient functional reserve, even when a large congestion area in the anterior segment is present. Consequently, the authors do not reconstruct the tributaries of middle hepatic vein in the remnant right lobe of the donor. However, in the recipient’s transplanted right liver, significant tributaries of middle hepatic vein are reconstructed to maximize liver graft function. If a decline of liver function in the congestion region could be predicted, this would help to identify patients who are candidates for middle hepatic vein tributary reconstruction. In addition, this information could be of help to estimate remnant functional liver in patients with hepatobiliary malignancy undergoing major hepatectomy, including middle hepatic vein resection.

The present study shows that, in the normal livers of donors, the decrease in liver function in the postoperative congested region of the remnant right lobe is approximately 30 per cent compared with that in the non-congested region. Thus, it could be estimated that function in the postoperative congested region was approximately 70 per cent of that in the non-congested region. However, when individual values in the remnant donor liver were considered, the difference ratio varied from almost zero to nearly 50 per cent (Fig. 3). This variation could be explained by differences in venous congestion and venous collateral formation between occluded middle hepatic vein tributaries and the right hepatic venous system\(^15\). This implies that, if sufficient venous collaterals were not formed after surgery, postoperative function in the corresponding congested region could be reduced to 50 per cent of that in the non-congested region. Therefore, in terms of risk management, when estimating the postoperative functional reserve by taking the impact of venous congestion into consideration, it might be better to use the possible minimum value of 50 per cent, rather than 70 per cent, as the relative function of the congested region, to avoid the risk of postoperative liver failure.

Kawaguchi and colleagues\(^16\) investigated the portal uptake function in veno-occlusive regions with ICG fluorescence and reported that portal uptake was approximately 40 per cent of that in non-veno-occlusive regions. An explanation for the discrepancy with the present study could be the difference in the time points of measurement: Kawaguchi and co-workers measured fluorescent intensity during surgery, whereas the present data were obtained 1 week after operation. It is known that some occluded middle hepatic vein tributaries in the remnant right lobe after donor surgery can develop venous collaterals into the right hepatic venous system during the course of postoperative recovery\(^15,17\), thereby gradually alleviating the extent of venous congestion in the anterior segment. It may be possible that the alleviation of venous congestion led to improved liver function in the anterior segment of the remnant donor right lobe. In addition, it should be noted that the method described by Kawaguchi et al.\(^16\) captured ICG fluorescence only on the liver surface, whereas EOB-MRI can evaluate the entire liver parenchyma, reflecting the unevenness inside the liver.

The present study also found that postoperative LMR values for the remnant donor liver without congestion were very similar to those noted before surgery, whereas a significant reduction in the LMR was observed in the
transplanted livers of recipients. The LMR is considered to represent liver function per unit liver volume. These facts suggest that living donors, whose liver function is usually considered to be good, may regain original unit liver function almost completely within 1 week of operation, whereas the recipients do not. The difference between donors and recipients may be attributable to issues in the transplanted liver, such as cold and warm ischaemic injury, portal hypertensive state, abrupt regenerative responses of small-for-size graft and metabolic overload after transplantation.

The other modality for quantitative liver function tests anticipated at present includes 99mTc-GSA scintigraphy. GSA is a receptor-binding agent specific for the asialo-glycoprotein receptor which resides exclusively on the plasma membrane of hepatocytes. It is bound only by this receptor and thus provides valuable information about the receptor population density, which also directly reflects the functioning hepatocyte mass and enables regional assessment of liver function to some extent. However, the spatial resolution of GSA scintigraphy is inferior to that of EOB-MRI. The advantages of EOB-MRI include high spatial resolution that enables detailed assessment of regional liver function concomitantly with diagnostic information of liver tumours.

In the setting of clinical living-donor liver transplantation, predicted graft size often comes close to its acceptable limits; therefore the influence of functional decrease in the congested region on already predicted marginal function is important. Using EOB-MRI and the results of the present study, postoperative functional liver volume, which includes the impact of congestion, could be estimated as shown in the findings for PFLV in the donor. Although the correlation between PFLV and the recipient's postoperative graft function was not analysed, because the present series showed only 6 per cent of congested region on already predicted marginal function, EOB-MRI could be a useful measure for estimating graft function, as well as postoperative functional reserve in patients undergoing liver surgery for hepatobiliary malignancy. However, the adequacy of such a predictive method requires validation in future studies.

Acknowledgements

This study was supported by a Japan Surgical Society Young Researcher Award and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (grant no. 26462044).

References


Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Correlation between predicted functional liver volume and postoperative functional parameters in the donor (Word document)