The Utility of Doppler Sonography for Assessing the Severity and Treatment Response of Acute Rejection in Adult to Adult Living Donor Liver Transplantation

Aim: We explored whether monitoring of graft hemodynamic changes by Doppler sonography can be useful for the treatment of acute rejection in adult to adult living donor liver transplantation (LDLT).

Materials/Methods: 29 acute rejection episodes were confirmed by liver biopsy in 21 of 51 adult patients who underwent LDLT. We classified 29 acute rejection episodes into two groups based on the presence (n=8) or absence (n=21) of graft hemodynamic changes detected by Doppler sonography. The postoperative onset time of acute rejection episodes, the peak level of alanine aminotransferase (ALT), and Rejection Activity Index (RAI) were compared between two groups. The pattern of graft hemodynamic changes and response to treatment were analyzed.

Results: Acute rejection episodes with graft hemodynamic changes (n=8) were characterized by earlier postoperative onset, higher levels of serum ALT and more severe RAI compared with acute rejection episodes without graft hemodynamic changes (n=21). The graft hemodynamic changes recorded in the former group included reduced mean portal venous flow velocity, pulsatile wave pattern of graft portal vein and increased peak systolic velocity of graft hepatic arterial flow. These graft hemodynamic changes could be reversed by effective antirejection therapy. Acute rejection episodes with graft hemodynamic changes are less likely to respond to steroid pulse therapy.

Conclusions: These results suggested that monitoring of graft hemodynamic changes by Doppler sonography could assess the severity and treatment response of acute rejection, contributing to the precise selection of antirejection therapy after adult to adult LDLT.

Key words: living donor liver transplantation, acute rejection, doppler sonography, rejection activity index, hemodynamic change, portal venous flow

Doppler-Sonographie zur Beurteilung von Schwere und Therapie-Response bei akuter Abstoßung nach Leberlebendspende-Transplantation unter Erwachsenen

Ziel: Wir untersuchten, ob eine dopplersonographische Überwachung der hämodynamischen Veränderungen im Transplantat für die Behandlung von akuten Abstoßungen nach Leberlebendspen-
de-Transplantation unter Erwachsenen (LDLT = living donor liver transplantation) von Nutzen sein könnte.

**Personen/Methoden:** 29 akute Abstoßungsepisoden wurden durch Leberbiopsie bei 21 von 51 erwachsenen Patienten bestätigt, die sich einer LDLT unterzogen hatten. Wir teilten die 29 akuten Abstoßungsepisoden in zwei Gruppen ein, je nachdem, ob in der Doppler-Sonographie hämodynamische Veränderungen beim Transplantat entdeckt werden konnten (n=8) oder nicht (n=21). Die postoperative Dauer bis zum Beginn der akuten Abstoßungsepisoden, der Spitzenspiegel von Alanin-Aminotransferase (ALT) und der Abstoßungs-Aktivitäts-Index (RAI) wurden zwischen den zwei Gruppen verglichen. Das Muster der hämodynamischen Veränderungen im Transplantat sowie das Ansprechen auf die Behandlung wurden analysiert.

**Ergebnisse:** Im Vergleich zu akuten Abstoßungsepisoden ohne hämodynamische Veränderungen im Transplantat (n=21) zeichneten sich akute Abstoßungsepisoden mit hämodynamischen Veränderungen in der Gruppe (n=8) durch einen schnelleren postoperativen Beginn, höhere Serum-ALT-Spiegel und höheren RAI aus. Zu den beobachteten hämodynamischen Veränderungen gehörten eine verringerte mittlere portal-venöse Flussgeschwindigkeit, pulsatile Wellenmuster der Pfortader im Transplantat und erhöhte systolische Spitzengeschwindigkeit des arteriellen Flusses im Lebertransplantat. Diese hämodynamischen Veränderungen im Transplantat konnten durch eine effektive Behandlung der Abstoßung rückgängig gemacht werden. Akute Abstoßungsepisoden mit hämodynamischen Veränderungen im Transplantat sprechen auf eine Steroid-Pulstherapie eher weniger an.

**Schlussfolgerungen:** Diese Ergebnisse legten nahe, dass sich durch die Überwachung der hämodynamischen Veränderungen mittels Doppler-Sonographie sowohl die Schwere einer akuten Abstoßung als auch das Ansprechen auf die Behandlung beurteilen lassen. Mit diesem Vorgehen könnte nach LDLT von einem erwachsenen Spender auf einen erwachsenen Empfänger übertragen werden.

**Schlüsselwörter:** Leberlebendspende-Transplantation, akute Abstoßung, Doppler-Sonographie, Abstoßungs-Aktivitäts-Index, hämodynamische Veränderungen, portal-venöser Fluss

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**Abbreviations**

Alanine aminotransferase (ALT), Rejection activity index (RAI), Resistive index (RI), Pulsatility index (PI), Systolic acceleration time (SAT), Cytomegalovirus (CMV), Methylprednisolone (MP)

**Introduction**

Controversial results have been reported regarding the utility of Doppler sonography for predicting and assessing acute rejection in cadaveric donor liver transplantation [1-8]. Mohr et al. [8] identified acute rejection episodes with the decrease in graft portal venous flow and concluded that monitoring of graft portal venous flow by Doppler sonography could be useful for predicting and assessing acute rejection. However, the role of Doppler sonography for acute rejection in adult to adult living donor liver transplantation (LDLT) has not been well defined. Aims of this study were 1) to identify acute rejection episodes with graft hemodynamic changes detected by Doppler sonography, and 2) to explore whether monitoring of graft hemodynamic changes by Doppler sonography can be useful for the treatment of acute rejection in adult to adult LDLT.

**Materials and Methods**

**Patients**

During the period from August 1996 to December 2003, 51 adult patients underwent 51 partial liver transplantation using right lobe (38) and left lobe (13) from adult living donor at our institution. The mean age was 44.4 ± 11.2 years, ranging from 22 to 61 years. They included no cases of ABO blood incompatible mismatched pairs and no cases of T-lymphocytotoxic cross match positive. Posttransplant immunosuppression was induced by FK506, steroids and mycophenolate mofetil. We maintained the trough level of FK506 at about 15 ng/ml during the first two weeks after liver transplantation and reduced it gradually thereafter. Because the mean body weight of Japanese adult recipients in this study was 55.1 ± 7.2 kg and was relatively lighter than those of American and European recipients, acute rejection episodes, histopathologically diagnosed as mild active in liver biopsy, were at first treated with intravenous infusion of methylprednisolone (MP) at a dose of 10 mg/kg in our institution. If histopathological findings of liver biopsy were graded as moderate-to-severe active, or acute rejection episodes were refractory to the above protocol, we used three daily intravenous infusions of MP at a dose of 20 mg/kg to reverse acute rejection, or considered the infusion of OKT3.

**Doppler Sonography Studies**

Doppler sonography was performed twice a day between the first and 14th
posttransplantation. Additional Doppler examinations were performed electively for clinical or biochemical abnormalities. Hepatic hemodynamics were evaluated with color Doppler image and pulsed Doppler by a 3.5-MHz curvilinear array transducer (SSD-2000; Aloka, Tokyo, Japan). Each subject was examined in the supine position during quiet breathing or mechanical ventilation. The velocity measurement in a Doppler study was performed with an exploration angle < 60° as far as possible. Doppler tracings of portal vein were obtained from the right branch of the portal vein in the case of right lobe graft and from umbilical portion of the portal vein in the case of left lobe graft. Doppler tracings of hepatic artery were obtained from the right hepatic artery in the case of right lobe graft and from the left hepatic artery in the case of left lobe graft. Resistive index (RI), Pulsatility index (PI), systolic acceleration time (SAT) and peak systolic velocity of the hepatic artery were evaluated with angle corrected measurements. The mean velocity and the pulsatility of waveform were measured from the right hepatic vein of the right lobe graft and from left hepatic vein of the left lobe graft.

When clinical or biochemical evidence of acute rejection was detected during the postoperative course, liver needle biopsy was performed. Based on histopathological findings, grading of acute rejection and Rejection Activity Index (RAI) were estimated according to Banff schema [9]. Hemodynamics of liver graft were monitored serially in all acute rejection episodes using Doppler sonography. In addition, we also used Doppler sonography to investigate the hemodynamics of liver graft in other postoperative complications, such viral hepatitis, especially cytomegalovirus (CMV) hepatitis, and biliary complications.

Acute rejection was diagnosed by liver biopsy in 21 of 51 (41%) patients. There were 29 episodes of specimen-proven acute rejection in those 21 patients. In eight acute rejection episodes of eight patients, graft hemodynamic changes were detected by Doppler sonography. We classified 29 acute rejection episodes into two groups based on the presence (n=8) or absence (n=21) of graft hemodynamic changes detected by Doppler sonography.

### Statistical Analysis

Postoperative onset time of acute rejection episodes, the peak level of alanine aminotransferase (ALT) during acute rejection period, and RAI were compared between two groups using the Mann-Whitney U test for statistical analysis. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using StatView J-4.5 software.

### Results

#### (1) Clinical and Biochemical Data (Table 1)

The mean postoperative onset time of eight acute rejection episodes with graft hemodynamic changes (8.8 ± 2.2 days) was significantly shorter than that of 21 acute rejection episodes without graft hemodynamic changes (38.7 ± 29.6 days, p < 0.01). In addition, the peak level of ALT in acute rejection episodes with graft hemodynamic changes (427 ± 136 IU/L) were significantly higher than that in acute rejection episodes without graft hemodynamic changes (198 ± 64 IU/L, p < 0.05).

#### (2) Graft Hemodynamic Changes Associated with Acute Rejection

Graft hemodynamic changes in eight acute rejection episodes consisted of the reduction of graft portal venous flow and an increased peak systolic velocity of graft hepatic arterial flow. A sharp decrease of the mean graft portal ve-
nous velocity was observed from $23.0 \pm 4.3$ cm/sec measured before rejection to $11.9 \pm 2.8$ cm/sec measured during rejection ($p<0.01$, Figure 1). The wave pattern of graft portal venous flow changed from stationary before rejection to pulsatile during rejection. In these eight cases, stenosis and thrombosis of portal vein were ruled out on abdominal CT scan or angiography examined when a decrease of graft portal venous flow was detected by Doppler sonography. At the same time, the peak systolic velocity of graft hepatic arterial flow increased significantly from $38.0 \pm 5.7$ measured before rejection to $73.1 \pm 26.7$ cm/sec measured during rejection, without any changes in RI, PI and SAT ($p<0.05$, Figure 2). Effective antirejection therapy resulted in a recovery of the mean graft portal venous velocity, in the change to stationary wave pattern of graft portal vein and in the decrease of the peak systolic velocity of graft hepatic arterial flow. These graft hemodynamic changes were not detected in all of the six cases of CMV hepatitis, diagnosed by liver biopsy, and in all of the eight cases of cholangitis due to biliary stricture.

(3) Histopathological Grading of Acute Rejection (Table 2)

In eight acute rejection episodes with graft hemodynamic changes, there were five moderately active and three severely active rejections histologically proven by liver biopsy. The RAI of eight acute rejection episodes with graft hemodynamic changes were more severe compared with that of acute rejection episodes without graft hemodynamic changes ($5.9 \pm 1.1$ vs $3.0 \pm 0.6$, $p<0.01$).

(4) Treatment Response between two Groups (Figure 3)

19 of 21 acute rejection episodes without graft hemodynamic changes could be reversed by three daily intravenous infusions of 10 mg/kg MP and the other two episodes were necessary to be treated with the infusion of 20 mg/kg MP. On the other hand, five of eight acute rejection episodes with graft hemodynamic changes needed to be treated with three daily infusion of 20 mg/kg MP to reverse acute rejection. The other three rejection episodes were resistant to steroid pulse therapy and required the infusion of OKT3. Two episodes was reversible by OKT3. One case was irreversible by OKT3 and fell into graft liver failure.

Discussion

This study suggested that monitoring of graft hemodynamic changes by Doppler sonography could assess the severity and treatment response of acute rejection after adult to adult LDLT, contributing to the precise selection of antirejection therapy. In fact, we identified eight acute rejection episodes with graft hemodynamic changes in our series of adult to adult LDLT and these acute rejection episodes with graft hemodynamic changes were associated with severe clinical and histopathological findings. These graft hemodynamic changes could be reversed by effective antirejection therapy. In addition, acute rejection episodes with graft hemodynamic changes were less likely to respond to steroid pulse therapy and three of eight acute rejection episodes were resistant to steroid pulse therapy, requiring the infusion of OKT3. Mohr et al. [8] also identified acute rejection episodes with a decrease in graft portal venous flow in cadaveric liver transplantation and reported that these graft hemodynamic changes were improved by effective antirejection therapy, indicating the utility of Doppler sonography.

Fig. 2: Peak systolic velocity of graft hepatic arterial flow before, during, and after eight acute rejection episodes with graft hemodynamic changes.

Tab. 2: Histological grading and rejection activity index between acute rejection episodes with and without graft hemodynamic changes

<table>
<thead>
<tr>
<th>Grading</th>
<th>Acute rejection episodes with graft hemodynamic changes (n = 8)</th>
<th>Acute rejection episodes without graft hemodynamic changes (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Rejection Activity Index (Mean value):
- Acute rejection episodes with graft hemodynamic changes: $4, 5, 5, 6, 6, 7, 7, 7$ ($5.9 \pm 1.1$)
- Acute rejection episodes without graft hemodynamic changes: $2, 2, 2, 3(x14), 4, 4, 4, 4$ ($3.0 \pm 0.6$)

$P < 0.01$
sonography for the treatment of acute rejection. In contrast, Kok et al. [7] reported that monitoring of graft portal venous flow by Doppler sonography could not specifically predict acute graft rejection in cadaveric liver transplantation. Because they focused on the specificity of Doppler sonography for the diagnosis of acute rejection, it was possible that the utility of Doppler sonography could not be indicated in that study. We believe that Doppler sonography has an important meaning for assessing the severity of acute rejection non-invasively and promptly.

Monitoring of graft hepatic arterial flow by Doppler sonography was reported to be useless for predicting and assessing acute rejection after liver transplantation [1-3]. Two studies found that the detection of changes in hepatic venous wave pattern by Doppler sonography can contribute to the diagnosis of acute rejection in pediatric liver transplantation [4,5]. However, in adult liver transplantation, Zalasin et al. [6] reported that monitoring of hepatic venous wave pattern by Doppler sonography was useless in the diagnosis of acute rejection. The graft hemodynamic changes by acute rejection consisted of the reduction of graft portal venous flow and the increase in the peak systolic velocity of graft hepatic arterial flow. Because it has been reported that hepatic arterial buffer response is preserved even in transplanted liver graft [10-14], the increased peak systolic velocity of graft hepatic arterial flow is thought to be the result of hepatic arterial buffer response to the reduction of graft portal venous flow. A sufficient restoration of the liver vascular bed could not be achieved in the early postoperative period after adult to adult LDLT because the regeneration of liver graft was still in progress about one week after transplantation [15-17]. Therefore, we think that acute rejection of sufficient clinical and histological severity could cause the reduction in graft portal venous flow and the change to pulsatile wave pattern in early postoperative period after adult to adult LDLT.

In conclusion, these findings suggested that monitoring of graft hemodynamic changes by Doppler sonography could assess the severity and treatment response of acute rejection after adult to adult LDLT, contributing to the precise selection of antirejection therapy. Although further investigations are necessary, it may be possible that monitoring of graft hemodynamic changes by Doppler sonography dispenses demand liver biopsy in the early postoperative period after adult to adult LDLT.

References

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