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Introduction

In liver transplantation, adequate tissue oxygenation of the graft is essential to the initial functioning. Since the energy metabolism of the liver greatly depends on the oxygen supply that the hepatocytes receive through the portal vein and the hepatic artery, serious complications in the early postoperative period are primarily associated with insufficient blood flow to the graft liver [6, 10, 20, 24, 26]. Clinically, duplex Doppler sonography has been widely used to measure the blood flow in the main vessels, including the portal vein, the hepatic artery, and the hepatic vein [14, 23]. However, it is difficult to monitor

Intraoperative measurement of the graft oxygenation state in living related liver transplantation by near infrared spectroscopy

Abstract Graft oxygenation plays an important role in successful liver transplantation. Intraoperative changes in the oxygenation state of the liver graft were measured by near infrared spectroscopy in 28 cases of living related liver transplantation. Oxygen saturation of hemoglobin in the liver (hepatic SO₂) changed from $81.2\% \pm 1.5\%$ $(mean \pm SEM)$ before donation (in the donor) to $49.7 \% \pm 4.2 \%$ after portal reflow, to $58.4\% \pm 5.0\%$ after arterial reflow, and then to 71.4 $\% \pm 3.9 \%$ before closure. Mean hepatic SO₂ was positively correlated with portal flow rate as measured by duplex Doppler sonography. Cases with low portal flow rate showed a high coefficient of variation (SD/mean) of hepatic SO_2 , indicating heterogeneous tissue oxygenation. Though graft size was expected to affect the graft oxygenation state, hepatic SO_2 was fairly independent of the graft-to-recipient weight ratio. In two cases with markedly low hepatic SO_2 , postoperative graft dysfunction occurred. This study suggest that the method of near infrared spectroscopy is reliable and useful for assessing the graft oxygenation state in liver transplantation.

Key words Viability, infrared spectroscopy, liver \cdot Living related liver transplantation, infrared spectroscopy \cdot Liver transplantation, infrared spectroscopy, living related donation

the oxygenation state at the tissue level by duplex Doppler sonography. This technique can be erroneous, especially in a case in which the intrahepatic blood flow is heterogeneously distributed, since the flow rate measured in the main vessels does not always reflect the local tissue oxygenation. Even if a fairly high flow rate is maintained, low-flow areas, which tend to remain ischemic, may suffer postoperative hepatocellular damage.

Graft size is one special concern in living related liver transplantation because the size of the graft liver that can be donated from living relatives is restricted in size by the anatomical structures [1, 5, 19, 22, 25]. There are usually two options; lateral segment transplantation or left lobe transplantation. The graft liver, however, may be too large for a small baby or too small for a large adolescent recipient. Graft function depends upon tissue oxygenation, which is determined by the balance between oxygen supply and consumption. In the case of a small graft, the oxygen consumption may exceed the oxygen supply due to the increased metabolic demand. In the case of a large graft, on the other hand, the graft may not receive an adequate supply of blood. It is, therefore, important to measure the oxygenation state at the tissue level, as well as the blood flow in the main vessels.

Intersegmental differences pose another problem in living related liver transplantation, especially in left lobe transplantation. Since the safety of the donor has the highest priority, graft harvesting that jeopardizes the donor cannot be done. It is sometimes difficult to preserve the artery or the hepatic vein with the medial segment of the graft in the optimal condition for anastomosis due to anatomical variations [5, 16, 25]. In such cases, the medial segment may be subject to ischemia or congestion.

This study employed near infrared (NIR) spectroscopy, a means of optical measurement that takes advantage of the ability of near infrared light to penetrate deep into tissue, something which visible light is unable to do. Previous studies have demonstrated the utility of NIR spectroscopy in detecting the oxygen saturation of tissue hemoglobin as an indicator of tissue oxygenation [3, 8, 12]. Since oxygen is transported to tissue exclusively by hemoglobin, a decrease in the oxygen saturation of tissue hemoglobin should be one of the earliest warnings of tissue hypoxia. The noninvasive, real-time NIR method has advantages for clinical application. In previous studies, we introduced a new method using NIR spectroscopy by which oxygen saturation of tissue hemoglobin can be quantitatively measured [12]. In this study, we assess the oxygenation state of the graft liver in living related liver transplantation by NIR spectroscopy. We further evaluate the clinical implications by comparing the data of oxygenation state with those of the blood flow to the graft liver measured by duplex Doppler sonography and with the recipient's postoperative course.

Materials and methods

Subjects

Twenty-eight cases of living related liver transplantation performed in Kyoto University Hospital were studied. Table 1 shows the profiles of the recipients and donors. Preoperative examination revealed no abnormal findings in liver function in any of the donors.

In cases in which the lateral segment was transplanted (S2 + 3), the left hepatic vein of the graft liver was anastomosed to the combined orifice of the left and middle hepatic veins of the recipient. In four out of six cases of left lobe transplantation (S2+3+4), ei-

 Table 1 Clinical profiles of 28 cases of living related liver transplantation

Recipients			
Age	3.5 ± 0.7 years		
	(range 3 months to 13 years)		
Sex	Male 7		
	Female 21		
Body weight	$14.2 \pm 2.2 \text{ kg}$		
	(range 4.0–40.4 kg)		
Original disease	Biliary atresia	22	
	Intrahepatic cholestasis	1	
	Wilson's disease	1	
	Fulminant hepatitis	1	
	Liver cirrhosis	1	
	Hypertyrosinemia	1	
	Alagille's syndrome	1	
Donors			
Age	32.9 ± 1.1 years		
-	(range 25-40 years)		
Relationship	Father 12		
-	Mother 16		
Graft weight	268.8 ± 10.5 g		
	(range 200–440 g)		
Type of operation			
Lateral segment trans-			
plantation	22		
Left lobe transplantation	6		

ther the middle hepatic vein was included with the graft side and the common stem of the left and middle hepatic veins was used for anastomosis, or else the two hepatic veins were plastied to form a single orifice for anastomosis. In the other two cases (S2+3+ partial S4), the middle hepatic vein was left with the donor side. In one of these two cases, a relatively large hepatic vein was anastomosed to the recipient's right hepatic vein as well as the left hepatic vein (two hepatic vein anastomosis). In the other case, a partial drainage vein of the medial segment was ligated. The portal vein of the graft liver was anastomosed to the recipient's portal venous trunk or to the confluence of the splenic vein and the superior mesenteric vein. Venous grafts were used in five cases. The hepatic artery of the graft liver was anastomosed to the right or left hepatic artery of the recipient using a microvascular surgical technique [16]. Two-artery anastomosis was performed in five cases. During the operation, the patients were ventilated with 33 %-40 % oxygen, and PaO₂ was maintained between 100 mm Hg and 250 mm Hg. Circulation and ventilation were stable in all recipients and donors at the time of measurement. Hemoglobin concentration in the peripheral blood was between 7 g/dl and 13 g/dl. Although venovenous bypass was not employed during portal clamping, no intestinal congestion was observed. University of Wisconsin (UW) solution was used to wash out all liver grafts. Cold ischemia time and warm ischemia time were $71.0 \pm 9.2 \text{ min} \text{ (mean} \pm \text{SEM)}$ and $45.6 \pm 3.1 \text{ min}$, respectively.

NIR spectroscopy

A photodiode scanner MCPD 1000 (Otsuka Electronics, Japan) with quartz optical fibers was used. Two optical fiber probes, one for light emission and the other for light detection, were brought into contact with the surface of the liver. The absorption spectrum was measured at wavelengths from 700 nm to1000 nm.

The spectral analysis has been described elsewhere [12]. The effect of photon scattering on the absorption spectrum was corrected by the following equation:

corrected %abs $(\lambda) = 1/7 \{\%$ abs (λ) exp(1.927 %abs $(\lambda))$ + %abs (λ) exp(0.827 %abs $(\lambda))\}$

where % abs (λ) represents % absorption at the wavelength of λ .

Multicomponent curve fitting was performed to the corrected absorption spectrum, following the Beer-Lambert law (Fig. 1):

O.D. $(\lambda) = L(\lambda) \{\varepsilon_1(\lambda) \text{ [oxyhemoglobin]} + \varepsilon_2(\lambda) \text{ [deoxyhemoglobin]} + \varepsilon_3(\lambda)\Delta[\text{oxidized cytochrome } aa_3] + \varepsilon_4(\lambda)\Delta[\text{reduced cytochrome } aa_3] + a_1(\lambda) \text{ [blood-free liver]} + a_2(\lambda) \text{ [UW solution]} \}$

where O.D. represents optical density, absorbance of the liver; L represents mean light pathlength in the liver; and $\varepsilon 1$ -4, a1-2 the extinction coefficient or absorbance of each component.

Blood-free liver spectrum was measured at the back table after excision of the graft liver. Oxygen saturation of hemoglobin in the liver (hepatic SO₂), and total content of hemoglobin in the liver (hepatic THb) were calculated as follows:

hepatic $SO_2 = [oxyhemoglobin]/([oxyhemoglobin] + [deoxyhemoglobin]) \times 100 \%$ hepatic THb = ([oxyhemoglobin] + [deoxyhemoglobin])/(the sum of all components' ratios)

The changes in the hepatic THb were expressed relative to that of the donor before donation. Measurements were done at 10 or 14 points along the anterior convexity of the graft liver at the following times: (1) before donation (in the donor), (2) after reflow of the portal vein, (3) after reflow of the hepatic artery, and (4) at the end of the operation. A coefficient of variation (CV = SD/mean) of hepatic SO₂ was used as a measure of heterogeneity of the tissue oxygenation.

The blood flow in the main vessels was estimated by duplex Doppler sonography after arterial reflow and at the end of the operation. Blood flow volume was calculated from the cross-sectional area and the mean velocity. The cross-sectional area was measured on the B-mode image, which was scanned perpendicular to the long axis of the blood vessel. The mean velocity was measured from the Doppler shift of the frequency corrected by the incident angle. Judging from the portal flow rate of normal adults, reported as 16 ml/kg body weight, a flow rate under 8 ml/kg body weight was defined as a decreased portal flow and higher rates as good portal flow [17].

Informed consent was obtained from the patients' parents and relatives. The study protocol was approved by the Ethics Committee of Kyoto University and performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

All data were expressed as mean \pm SEM. Statistical analysis was performed by analysis of variance. A *P* value less than 0.05 was considered significant. When analysis of variance showed a significant difference, Student's *t*-test was additionally performed.

Results

Figure 2 shows the changes in the mean and CV of hepatic SO_2 and the mean of THb. The mean values of the hepatic SO_2 and THb increased gradually following operative procedures. The CV of hepatic SO_2 , representing the heterogeneity of tissue oxygenation, was the highest after portal reflow and gradually decreased thereafter.

In 12 of the 28 cases, duplex Doppler sonography demonstrated decreased portal venous flow (< 8 ml/kg



Fig.1 Typical absorption spectrum of the liver and the result of multicomponent analysis. The six components used were: oxyhemoglobin (oxy Hb), deoxyhemoglobin (deoxy Hb), oxidized cytochrome aa_3 ($oxi cyt aa_3$), reduced cytochrome ($red cyt aa_3$), blood-free liver, and UW solution

body weight) in association with spontaneous portosystemic shunts and/or stenosis at the anastomotic site after arterial reflow. Ligation of the shunts and/or reanastomosis of the portal vein were additionally performed in these case until a good portal flow image was obtained by duplex Doppler sonography. Patency of the hepatic artery and of the hepatic vein was verified by duplex Doppler sonography at the time of measurement in all cases. As shown in Fig. 3, the mean hepatic SO₂ was significantly lower in cases of decreased portal flow than that in cases of good portal flow. The higher CV values of hepatic SO_2 in the case of decreased portal flow indicates that the tissue oxygenation was more heterogeneous in such cases. Figure 4 shows the relationship between the portal flow rate and the hepatic SO₂ in 29 measurements of 18 cases in which the flow rate at the postanastomotic site of the portal vein could be quantified by duplex Doppler sonography. A positive correlation between them, apparently in two-phase fashion, was demonstrated; $y = 6.24 \times \pm 26.2$, (portal **Fig.2 A** The mean hepatic SO₂ value gradually increased after reperfusion. **B** In contrast, CV gradually decreased. **C** The mean hepatic THb value gradually increased. P < 0.001 for time-course changes in hepatic SO₂ and CV (analysis of variance). * P < 0.05; ** P < 0.01; *** P < 0.001 compared to the value before donation (unpaired *t*-test)



flow < 8 ml/kg body weight), $y = 0.02 \times \pm 76.2$ (portal flow > 8 ml/kg body weight).

Figure 5 shows the relationship between the mean values of hepatic SO₂ and THb at the end of the operation and the graft-to-recipient weight ratio. Excluding two cases with extremely low mean values of hepatic SO₂, which were probably due to the disturbed microcirculation, the hepatic THb showed a negative correlation ($y = 14.3 \times \pm 139.9$, r = 0.52, P < 0.01), indicating that relatively smaller grafts contained more blood. However, the correlation between hepatic SO₂ and the graft-to-recipient weight ratio was not statistically significant ($y = -2.3 \times +81.9$, r = 0.28).

Table 2 shows the comparison of hepatic SO₂ and THb in the lateral segment and in the medial segment in six cases of left lobe transplantation. Hepatic SO₂ in the medial segment was significantly lower than that in the lateral segment after portal reflow, although the values varied widely from case to case. A low hepatic SO₂ value was usually associated with a high hepatic THb value indicating that tissue congestion occurred in the medial segment. In one case in which the middle hepatic vein was left to the donor and a small drainage vein from the medial segment was ligated, the hepatic SO_2 in the medial segment was calculated as 0 % after portal reflow and recovered to 53.4 % after arterial reflow, whereas those in the lateral segment were 58.5% and 81.6%, respectively. Duplex Doppler sonography showed no blood flow after portal reflow and portal regurgitation after arterial reflow in the medial segment. The postoperative course was uneventful. In two out of the other five cases, the mean hepatic SO_2 values in the medial segment were less than half of those in the lateral segment, but they increased to the same levels after arterial reflow.

Figure 6 shows the relationship between the mean hepatic SO_2 at the end of the operation and the maximal value of serum ALT on the 1st postoperative day. In two cases with extremely low mean hepatic SO₂ values, the serum ALT level was markedly elevated. In one of these cases (# 1 in Fig. 6), duplex Doppler sonography showed that the blood flow in the main vessels was within the normal limit and that the intrahepatic color flow image was also good. However, the hepatic SO₂ value in one part of segment 3 did not increase. Hepatic THb in the low hepatic SO₂ areas was 117.4% (mean), which was rather high compared with the hepatic THb value of 62 % in the high hepatic SO₂ areas. Arterial ketone body ratio (AKBR; acetoacetate/ β -hydroxybutyrate) increased over 1.0 within 24 h after reflow, which is a sign of good graft functioning [18, 19]. Although the elevation of ALT was prolonged for a few weeks, the recipient recovered thereafter. In the other case of extremely low hepatic SO₂ (# 2 in Fig. 6), prolonged ischemia during the operation was probably the cause. No significant portal flow was obtained after reperfusion due to obstruction of the recipient's portal vein at the confluence and massive spontaneous splenorenal shunts. Even though the portal flow became de-



Fig.3 A, B Differences in: A mean and **B** CV of the hepatic SO₂ between the groups of good (> 8 ml/kg body weight) and decreased (< 8 ml/kg body weight) portal flow as assessed by duplex Doppler sonography. The differences were significant after arterial reflow. * P < 0.01; ** P < 0.001

tectable after reanastomosis of the portal vein and ligation of the collaterals, the hepatic SO_2 did not increase as efficiently as it did in other cases. The hepatic THb increases to as high as 507.7 % at the end of the operation, which was extremely high compared with other cases, although the patency of the hepatic vein was proven by duplex Doppler sonography. The recovery of AKBR was delayed and the postoperative course was compromised. The patient died on the 20th postoperative day. In the other 26 cases, with hepatic SO_2 values higher than 60 %, the patients had uneventful postoperative courses. AKBR increased over 1.0 within 24 h after reflow in all of these cases. There was no statistically significant correlation between hepatic SO_2 and postoperative ALT level.



Fig. 4 Relationship between portal flow rate and mean hepatic SO_2 . Data points represent 29 measurements in 18 cases in which the portal flow rate could be quantitated by duplex Doppler sonography: 14 points after arterial reflow and 15 points at the end of operation

Discussion

Studies indicate that NIR spectroscopy is a promising method for assessing the tissue oxygenation state [3, 8], 12]. Liver transplantation would be one useful clinical application of this technology since an adequate blood supply and tissue oxygenation of the graft is essential to its initial functioning [6, 10, 20, 24, 26]. The positive correlation between the hepatic SO₂ value measured by NIR spectroscopy and the portal flow rate measured by duplex Doppler sonography indicates that the method employed in this study is a reliable one with potential application in the intraoperative assessment of the graft oxygenation state. The data shown in Fig.4 indicate that hepatic SO_2 sharply dropped when the portal flow rate decreased to under 8 ml/kg body weight, whereas in the cases with the portal flow rate over 8 ml/kg body weight, hepatic SO₂ was independent of the portal flow rate and was maintained at 76.7 % \pm 2.6 %, as high as that before donation $(81.2\% \pm 1.5\%)$. It is, therefore, suggested that the portal flow rate should be kept over 8 ml/kg body weight. The two-phased correlation between portal flow rate and hepatic SO_2 is attributed to the dual blood supply, which is characteristic of the hepatic circulation. The portal flow is superimposed on the hepatic arterial flow, which provides approximately half of the total oxygen supply to the liver, and the arterial flow is controlled under autoregulatory mechanisms to compensate for the decrease in portal flow [2]. The tissue oxygenation would, therefore, be maintained until the portal flow decreases to fairly low levels. In addition, since the oxygen saturation of the portal blood is lower than that of the arterial blood, an extremely increased portal flow does not cause hepatic hyperoxia.



Fig.5 A, B Relationship between the graft-to-recipient weight ratio and: A hepatic SO₂ and B hepatic THb. Twenty-six cases (\bullet) were analyzed, excluding two (\odot) that showed extremely low hepatic SO₂ due to disturbed circulation

The present method can measure the local tissue oxygenation in areas as small as the optical fiber separation. The results demonstrated that the hepatic tissue was heterogeneously oxygenated at the times immediately after reperfusion and that the heterogeneity tended to



Fig.6 Relationship between hepatic SO₂ and postoperative ALT level. Two cases with extremely low hepatic SO₂ showed elevated serum ALT levels (\bullet)

remain in cases with a decreased portal flow rate. It is likely that the high-flow areas exist as functional intrahepatic shunts and that the low-flow areas remain ischemic. Such conditions must be unfavorable to graft function and may cause postoperative hepatocellular damage, even if the total hepatic blood flow is not critically decreased. The heterogeneity of graft oxygenation shortly after reflow may be attributed to the disturbed microcirculation. It has been reported that ischemic-reperfusion of the graft liver causes endothelial cell derangement and Kupffer cell activation, followed by the release of reactive oxygen compounds and various chemical mediators. These induce neutrophils and platelets to adhere to the sinusoidal lining cells and hypercoagulability, leading to stagnant or stopped flow in the sinusoids [4, 15]. Recent reports have suggested that the contraction of Ito cells, which are located in Disse's space, contributes to the microcirculatory disturbance in pathological conditions such as ischemia-reperfusion [21].

Graft size is a serious concern in living related liver transplantation [1, 7, 9, 19, 22], since too small a graft cannot support the metabolic demand and too large a graft cannot be accommodated in the recipient's abdomen. It is possible that the graft-to-recipient weight ra-

Table 2 Comparison of hepatic SO_2 and THb between the lateral segment and the medialsegment in six cases of left lobetransplantation

* P < 0.05 for the difference between the segments (Student's *t*-test)

Hepatic SO ₂ (%)			
~ _ ~ /	Portal reflow	Arterial reflow	End of operation
Lateral segment	63.8 ± 3.5	79.5 ± 3.1	81.3 ± 4.1
Medial segment	$40.9 \pm 14.9*$	74.8 ± 5.4	74.0 ± 7.4
Hepatic THb (%)			
•	Portal reflow	Arterial reflow	End of operation
Lateral segment	109.3 ± 17.5	122.0 ± 14.3	129.3 ± 14.0
Medial segment	120.6 ± 19.5	137.2 ± 19.8	141.7 ± 15.4

tio is a factor affecting graft oxygenation. In a case with large graft size relative to recipient weight, the oxygen supply per unit tissue ought to decrease, since the portal flow is dependent upon the recipient weight rather than upon the graft size. On the other hand, in a case with small graft size relative to recipient weight, oxygen consumption per unit tissue ought to increase, due to the relatively increased metabolic load to the graft liver. Since the tissue oxygenation state is determined by the balance between oxygen supply and consumption, both cases can result in a low oxygenation state. As shown in Fig. 5, however, only a slight correlation, probably with no clinical significance, was demonstrated with hepatic SO₂, while hepatic THb was fairly dependent upon the graft-to-recipient weight ratio. These results suggest that oxygen supply and consumption compensate for each other, with the result that the tissue oxygenation state is fairly independent of the graft-to-recipient weight ratio. For example, in a case of a low graft-to-recipient weight ratio, the blood supply was high, but the oxygen consumption was also high to keep the oxygenation state at nearly constant levels. The same was true in a case of high graft-to-recipient weight ratio. Although the lower limit of the graft size is unknown, there are reports of successful results with (graft weight)/(recipient's estimated liver weight) of as little as 0.46 and 0.27 [7, 9], which correspond to the graft-to-recipient weight ratio of approximately 1.1% and 0.7%, respectively. This study showed that as long as the ratio is between 0.8% and 6%, the graft oxygenation state is quite constant.

The assessment of intersegmental differences by NIR spectroscopy is of great use in left lobe transplantation. Although the number of trials was small, this study suggests that the drainage vein from the medial segment should be kept patent even if it is a small segmental vein. It is also suggested that reconstruction of the artery to the medial segment is important, especially in cases of poor venous drainage. Arterial reconstruction is sometimes difficult in cases in which the artery to the medial segment originates separately from the artery to the lateral segment. The microvascular surgical technique was of great help in such cases [16].

The ultimate purpose of clinical examination is to predict postoperative graft function. In this study, since the liver graft was donated from a healthy donor and immediately implanted in a recipient, pre-existing or preservation liver injury was minimal. Although the number of cases with complicated postoperative courses was very small for these very reasons, the serum ALT level was significantly elevated, or the postoperative course was compromised, in two cases with very low mean hepatic SO_2 values, suggesting that hepatic SO_2 is possibly useful as a prognostic parameter. Previous reports suggest that the sinusoidal lining cells are the site most vulnerable to ischemia-reperfusion injury and that disturbed microcirculation is one of the main factors leading to subsequent hepatocellular damage [4, 13, 15]. Our previous study showed that prolonged liver ischemia prevents redox recovery after reflow, especially in areas with the greatest concentration of hemoglobin [11]. This would suggest that in these two cases the hypoxic areas detected by NIR spectroscopy showed low hepatic SO₂ values and high hepatic THb values, meaning that tissue congestion had occurred in spite of patient hepatic veins. It is speculated that local stagnation of the intrahepatic blood flow caused tissue congestion and hypoxia, resulting in postoperative hepatocellular damage.

The technical advantages of NIR spectroscopy – that it is rapid, noninvasive, and simple to use – make it suitable for clinical use. This study has shown that the graft oxygenation state measured by NIR spectroscopy correlated well with portal blood flow as measured by duplex Doppler sonography and with the recipient's postoperative course. With further improvement, it would be possible to expand the use of this technology to postoperative monitoring after liver transplantation. It is concluded that NIR spectroscopy is a reliable method for measuring the oxygenation state of the liver graft and potentially useful as a prognostic parameter in liver transplantation.

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