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Akira Tanaka
Koichi Tanaka
Atsuo Tokuka
Toshiyuki Kitai
Hisashi Shinohara
Etsuro Hatano
Seiji Sato
Takuya Inomoto
Yasutsugu Takada
Hiroshi Higashiyama
Yoshiaki Nakamura
Yuzo Yamamoto
Hiroto Egawa
Shinji Uemoto
Iwao Ikai
Nobuhiro Ozaki
Yukihiro Inomata
Yoshio Yamaoka

Graft size-matching in living related partial liver transplantation in relation to tissue oxygenation and metabolic capacity

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A. Tanaka (✉) · K. Tanaka · A. Tokuka
T. Kitai · H. Shinohara · E. Hatano · S. Sato
T. Inomoto · Y. Takada · H. Higashiyama
Y. Nakamura · Y. Yamamoto ·
H. Egawa · S. Uemoto · I. Ikai · N. Ozaki ·
Y. Inomata · Y. Yamaoka
Second Department of Surgery,
Faculty of Medicine, Kyoto University,
54 Kawaracho, Shogoin, Sakyoku,
Kyoto 606 Japan
Fax: + 81 75 751 3099

Abstract The influence of graft size-matching on tissue oxygenation and metabolic capability was studied in living related partial liver transplantations for 47 pediatric patients. Their age ranged from 4 months to 17 years 3 months, their body weight from 4.0 to 58.0 kg, graft weight from 191 to 440 g, and graft weight/recipient body weight ratio from 0.61 % to 6.0 %. Tissue oxygenation and its heterogeneity were investigated by measuring oxygen saturation of hemoglobin in the liver sinusoid (SO_2), coefficient of variation of SO_2, and arterial ketone body ratio. The metabolic capacity of the graft was investigated by measuring bilirubin clearance, recovery of cholesterol esterification, and ketone body production. In infants with a relatively large liver graft, both intra- and extracellular oxygenation remained low soon after reperfusion but recovered to the control value by the end of the operation. In adolescent recipients of a relatively small graft, by contrast, synthetic and detoxification capacities were relatively deficient; however, these improved with time. These results indicate that sufficient tissue oxygenation and liver regeneration are essential for successful liver transplantation with relatively large and small grafts, respectively.

Key words Liver transplantation, living related · Living related liver transplantation · Segmental liver transplantation · Tissue oxygenation, liver transplantation · Metabolic capacity, liver transplantation

Introduction

Graft size matching and ABO blood group are major concerns in liver transplantation [3, 10, 11, 19, 21]. In partial liver transplantation with a living related donor, when the left lateral segment or left lobe is employed as a graft, the graft size and weight are anatomically limited to within a narrow range. By contrast, recipient body size is distributed along a wide range, namely, from infancy to adolescence [14, 22, 25]. Furthermore, the indication of living related partial liver transplantation is now being extended to adult cases. It has been reported that normal ratios of whole liver weight relative to body weight (BW) are 2 % and 3 % in adults and newborns, respectively. Therefore, the ratio of graft weight to recipient body weight (G/R ratio) is a matter of serious concern in living related liver transplantation.

Portal blood flow to the liver in healthy volunteers has been reported to be 16.3 ± 5.0 ml/min per kilogram BW at fasting, indicating that portal blood flow is deter-

mined by body weight [9]. By contrast, portal blood flow is decreased or the direction of the blood flow in the portal and splenic veins is occasionally even retrograde in the terminal stage of liver cirrhosis and biliary atresia with gastrosplenorenal shunts. Therefore, when the G/R ratio exceeds the ideal value, it is likely that the blood supply to the graft will be inadequate after reflow of the portal vein and hepatic artery, resulting in relative hypoxia and portal vein thrombosis.

The graft liver has to resume the ATP-requiring processes of elimination of bilirubin and ammonium from the blood immediately after reflow of the blood supply [17, 24]. Since liver transplantation is performed for treatment of terminal liver diseases classified as Child C, the preoperative values of bilirubin and ammonium are so high that even minor hepatic resection cannot be tolerated. It is well known that major hepatic resection without sufficient hepatic regeneration afterwards results in liver failure, indicating that sufficient liver mass is necessary for proper metabolic function. Therefore, when the G/R ratio falls far below the ideal value, it is likely that the acute and massive metabolic load to the relatively small graft will contribute to graft dysfunction until the graft volume increases as in successful major hepatectomy. However, clearance of the metabolic load by the relatively small graft before regeneration and the increase in metabolic capacity by early regeneration remain unresolved problems. It is likely that a postoperative decrease in total bilirubin and an increase in cholesterol esterification will be delayed in relatively small grafts until there is sufficient liver regeneration. It is also likely that a relatively high blood flow to the small graft will cause damage to the vascular bed of the liver.

In the present study of 47 pediatric cases, we have investigated the tissue oxygenation and the synthetic and detoxification capabilities of the graft as a function of the G/R ratio. Oxygen saturation of hemoglobin in the liver sinusoid (SO_2) and the coefficient of variation of SO_2 (CV) were measured using near-infrared spectroscopy at multiple points as indices of extracellular oxygenation and its heterogeneity. We determined arterial ketone body ratio (AKBR) as an index of intracellular oxygenation; aspartate aminotransferase as an index of graft injury; and bilirubin clearance, cholesterol esterification, and the production of total ketone bodies as indices of the metabolic capability of the graft.

Materials and methods

Subjects

To study the effects of graft size-matching on tissue oxygenation and metabolic capacity, we analyzed 47 pediatric living related partial liver transplantations in which spectrophotometric measurement and biochemical analysis were successfully performed. The mean, SEM, and range of recipient age, recipient body weight (BW), graft weight, and graft weight/recipient body weight (G/R ratio) are summarized in Table 1.

Table 1 Profiles of recipients and donor grafts in 47 pediatric cases of living related liver transplantation

Male/female	13/34
Age of recipient (years)	3.95 ± 0.59 (4 months–17 years 3 months)
Body weight of recipient (kg)	14.7 ± 1.8 (4.0–58.0)
Graft weight (g)	266.0 ± 8.3 (191–440)
Graft weight/recipient body weight (%)	2.48 ± 0.17 (0.61–6.0)
Recipients' diseases	Number of cases
Biliary atresia	38
Alagille syndrome	2
Intrahepatic cholestasis	1
Wilson's disease	2
Fulminant hepatitis	1
Tyrosinemia	1
Glycogen storage disease	1
Liver cirrosis	1

Six left lobes with both middle and left hepatic veins, 3 left lateral segments with partial middle segments and left hepatic veins, and 38 left lateral segments were employed as grafts, depending on the recipient's age and body weight. There were no correlations between G/R ratio and cold ischemia time (67.8 ± 4.2 min) or between G/R ratio and blood loss/body weight (226 ± 37 g/kg), respectively.

Oxygen saturation of hemoglobin in liver sinusoid

Continuous wave spectrums of the liver, from 700 to 1000 nm, were measured and analyzed for quantification of oxy- and deoxy-hemoglobin (oxyHB, deoxyHB) in the liver tissue, as described previously [6]. Oxygen saturation of hemoglobin (SO_2) was calculated using the following equation: SO_2 = [oxyHB]/([oxyHB] + [deoxyHB]). SO_2 was measured at ten given points on the graft liver during three periods of time, i.e., after reperfusion of the portal vein, after reperfusion of the hepatic artery, and before closure of the abdominal wall. The heterogeneity of distribution of SO_2 at these ten points was expressed as a coefficient of variation [CV (%); (standard deviation/mean) × 100].

Measurement of arterial ketone bodies

The acetoacetate and β-hydroxybutyrate concentrations in arterial blood were measured at 1, 3, 6, 12, 24 and 48 h after reflow of the portal vein. Total ketone body concentration [TKB; (acetoacetate) + (β-hydroxybutyrate)] and arterial ketone body ratio [AKBR; (acetoacetate)/(β-hydroxybutyrate)] were calculated to evaluate capability of ketone body production by the graft liver and to estimate intramitochondrial oxidoreduction state related to tissue oxygenation after reflow of the vessels, respectively [13, 14, 20]. These ketone bodies were assayed using highlypurified β-hydroxybutyrate dehydrogenase as described elsewhere [23].

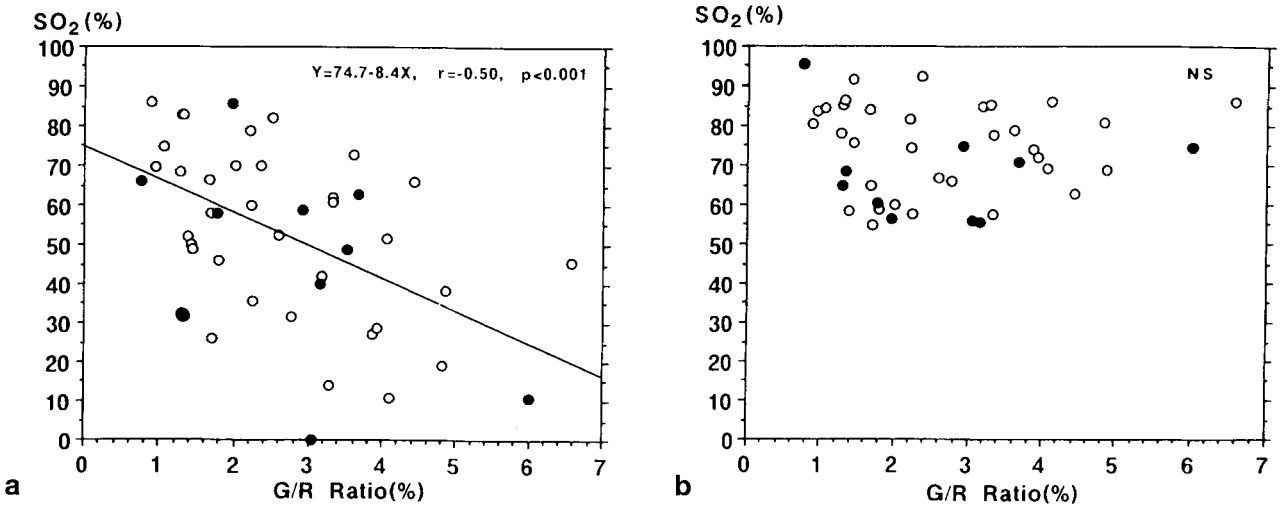


Fig. 1 a,b Correlation between G/R ratio and tissue oxygenation expressed as mean value of oxygen saturation of hemoglobin in the liver sinusoid (SO_2) at ten points: **a** after reflow of portal vein; **b** at end of operation (○ cases without ligation of collaterals, ● cases with ligation of collaterals)

Biochemical analysis of liver parenchymal injury, bilirubin, and cholesterol metabolism

Aspartate aminotransferase (AST) was measured to evaluate injury to the graft associated with preservation and reperfusion. Changes in total bilirubin (TBIL) and cholesterol esterification were employed to evaluate the metabolic ability of the graft liver [4, 15]. The ester ratio (ER) of cholesterol was calculated as the ratio of esterified cholesterol to total cholesterol. TBIL and ER were analyzed as a logarithm$_e$ of relative changes between two periods.

Statistical analysis

Statistical analysis was performed by linear regression analysis. *P* values less than 0.05 were regarded as statistically significant. The values are expressed as mean ± SEM.

Results

Tissue oxygenation in relation to G/R ratio

Intraoperative changes in SO_2 and CV

Figure 1 a shows that tissue oxygenation of the graft, expressed as oxygen saturation of hemoglobin in the liver sinusoid (SO_2) after reflow of the portal vein (PV), was closely correlated with G/R ratio. SO_2 in a relatively small graft reached a near-normal value of 80 % after reflow of the PV, while SO_2 in a relatively large graft remained low, at around 30 %. By contrast, Figure 1 b shows that SO_2 at the end of transplantation was independent of the G/R ratio and that SO_2 in a relatively large graft recovered to near the control value of 80 %, which was observed in the living related donor before procurement [20].

Figure 2 a shows that the heterogeneity of tissue oxygenation, expressed as a coefficient of variation (CV) of SO_2, was correlated with the G/R ratio after reflow of the PV, while Fig. 2 b shows that CV of SO_2 decreased to the control value of 10 %, which was observed in the donor operation [20] and that CV was independent of the G/R ratio.

Arterial ketone body ratio

Figure 3 a shows that the AKBR was correlated with the G/R ratio at 1 h after reflow of the PV, while Fig. 3 b shows that the dependency of AKBR disappeared 6 h after reflow of the PV.

Postoperative elevation of AST

Figure 4 indicates that AST at 1 postoperative day (POD) was correlated with the G/R ratio.

Metabolic capability in relation to G/R ratio

Bilirubin clearance

$\log_e$ [TBIL(POD1)/TBIL(preop)] (BC(1/0)) and $\log_e$ [TBIL(POD14)/TBIL(POD7)] (BC(14/7)) were employed as indices of bilirubin clearance capability (BC) of the graft liver. Figure 5 shows that bilirubin clearance, expressed as BC(1/0), was correlated with the G/R ratio while BC(14/7) was not.

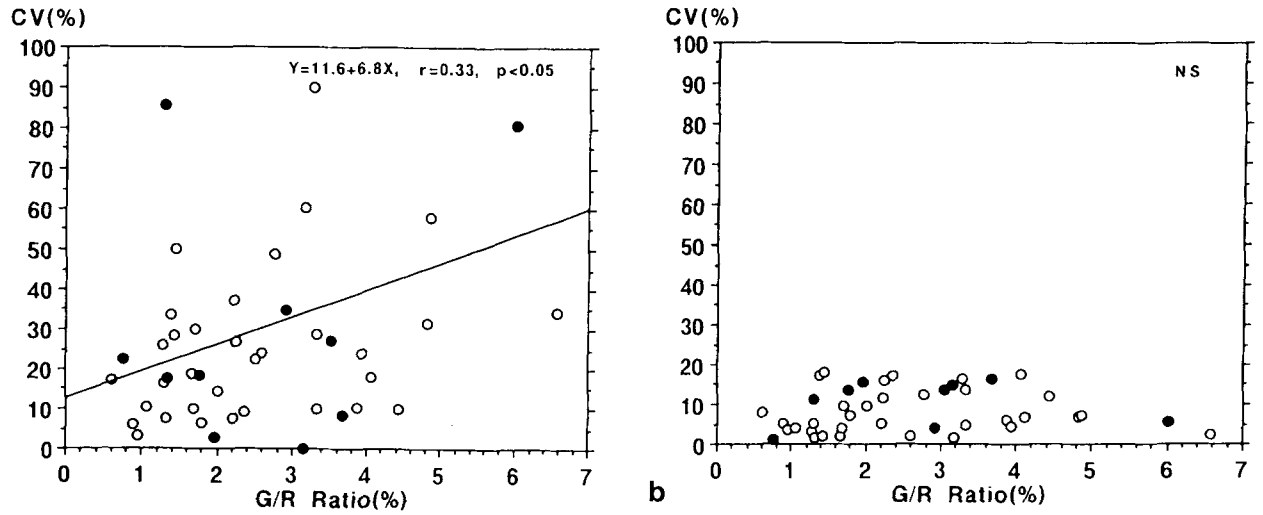


Fig. 2a,b Correlation between G/R ratio and heterogeneity of tissue oxygenation expressed as coefficient of variation (CV) of SO_2 at ten points; **a** after reflow of portal vein; **b** at end of operation (○ cases without ligation of collaterals, ● cases with ligation of collaterals)

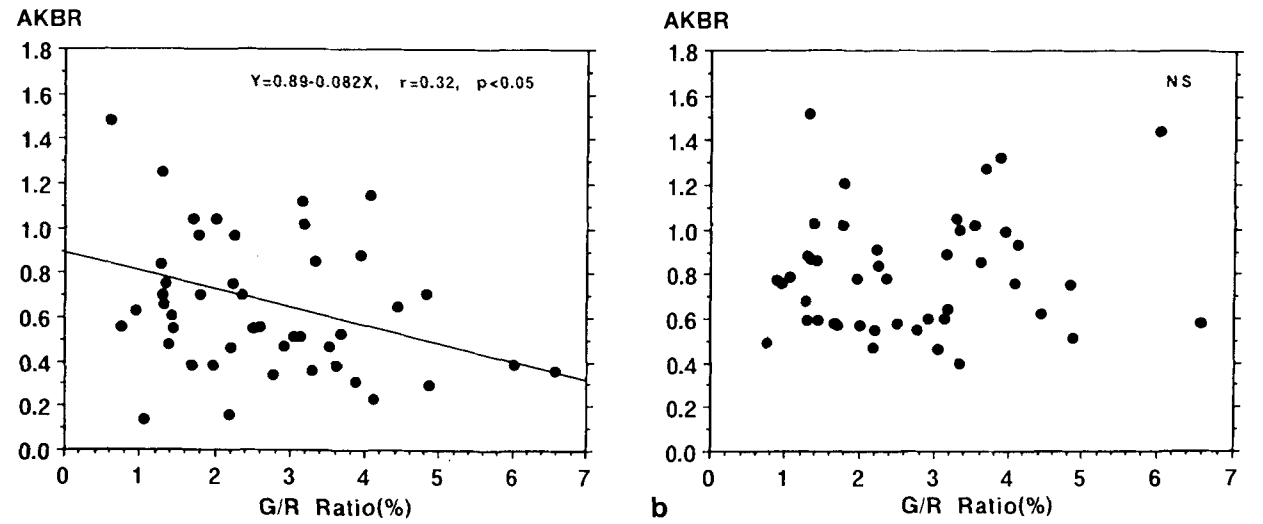
Cholesterol esterification

$\log_e$ [ER(POD14)/ER(preop)] (RER(14/0)) and $\log_e$ [ER(POD28)/ER(POD14)] (RER(28/14)) were employed as indices of recovery of cholesterol ester ratio (RER). Figure 6 shows that recovery of the ester ratio of cholesterol, expressed as RER(14/0), was correlated with the G/R ratio while RER(28/14) was not.

Ketone body production

Figure 7a shows that ketone body production by the graft liver was correlated with the G/R ratio at 1 h after reflow of the PV, while Fig. 7b indicates the absence of a correlation at 6 h after reflow of the PV.

Fig. 3a,b Correlation between G/R ratio and arterial ketone body ratio (AKBR): **a** 1 h after reflow of portal vein; **b** 6 h after reflow of portal vein



Discussion

Although graft size-matching is a critical problem in liver transplantation, the influence of graft size-matching on the oxygen supply to the graft and on the metabolic capability has yet to be analyzed clinically. In our series of living related partial liver transplantations, the cold

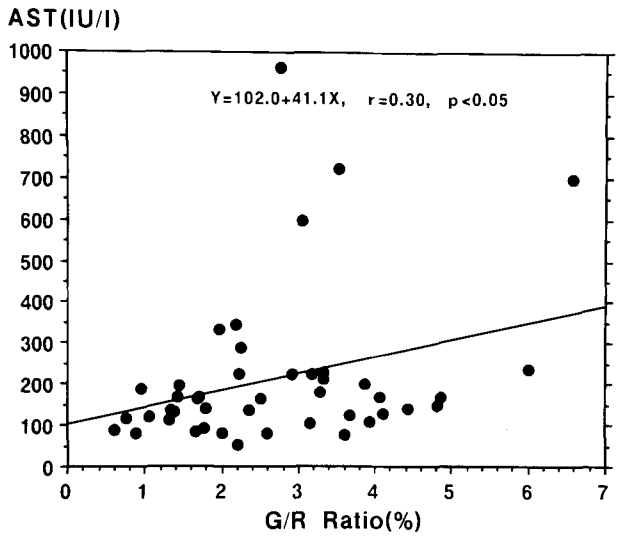


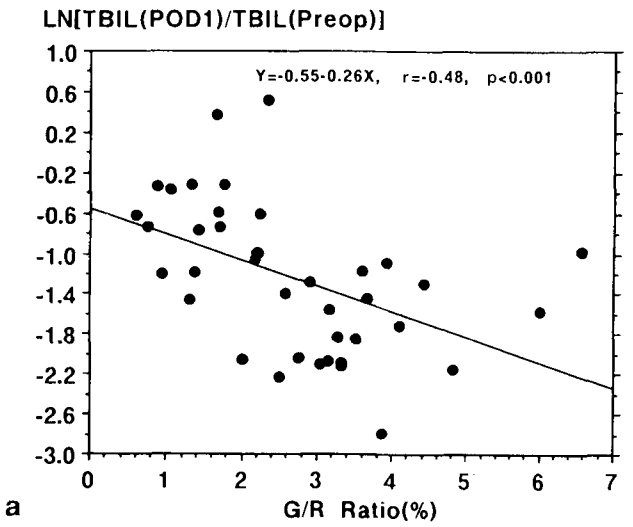
Fig. 4 Correlation between G/R ratio and AST at postoperative day 1

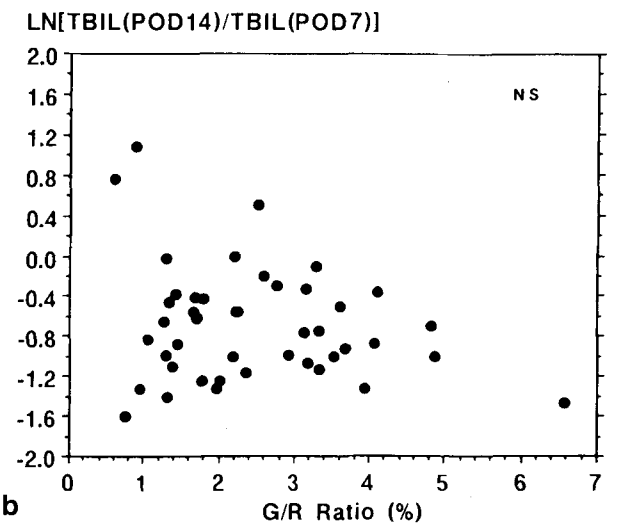
ischemia time was short, resulting in minimal preservation injury and good viability, since graft procurement was performed in parallel with the recipient operation. Therefore, the present series of living related liver transplantations for pediatric patients with a wide range in age, body weight, graft weight and graft/BW ratio is suitable for analysis of the effect of graft size-matching.

Fig. 5a,b Correlation between G/R ratio and bilirubin clearance: **a** LN[TBIL(POD1)/TBIL(Preop)]; **b** LN[TBIL(POD14)/TBIL(POD7)]. [*TBIL(preop)* most recent total bilirubin before operation; *TBIL(POD1)*, *TBIL(POD7)*, and *TBIL(POD14)* total bilirubin value at postoperative days 1, 7, and 14, respectively; *LN* logarithm$_e$]

The present study in living related liver transplantation clearly demonstrated that tissue oxygenation of the graft was determined by graft size-matching in the early postreperfusion phase but that it became independent of graft size-matching in the late phase. In a relatively large graft, a relatively low blood supply resulted in a low oxygen saturation of hemoglobin of red cells in the liver sinusoid concomitant with heterogeneous tissue oxygenation after reflow of the portal vein. A slow recovery of the intramitochondrial oxidoreduction state, from reduction to oxidation, could also be ascribed to a relatively low blood supply to the relatively large graft. However, these effects disappeared at the end of the operation, although a postoperative elevation of AST was dependent on the G/R ratio. In a relatively small graft, by contrast, tissue oxygenation reached a normal value soon after reperfusion and did not exceed this value very much. These results indicate that an adaptive mechanism is at work between the blood supply and tissue oxygenation in order to maintain appropriate oxygen supply to the hepatocytes [1, 7, 16]. It should be noted that ligation of the gastrosplenorenal shunt was performed in several cases in which duplex Doppler sonography indicated a low flow rate in the portal vein [2]. Such efforts may help to keep tissue oxygenation from becoming dependent upon graft size-matching.

As for the metabolic capability of the graft, clearance of bilirubin at POD 1 was determined by the G/R ratio, while the clearance between PODs 7 and 14 was not. The observed dependence of bilirubin clearance on the G/R ratio cannot be ascribed to blood exchange due to intraoperative blood loss since blood loss/body weight was not correlated with the G/R ratio. Therefore, a relatively small graft would be unable to efficiently eliminate bilirubin soon after transplantation as compared with a relatively large graft. In a relatively small graft,





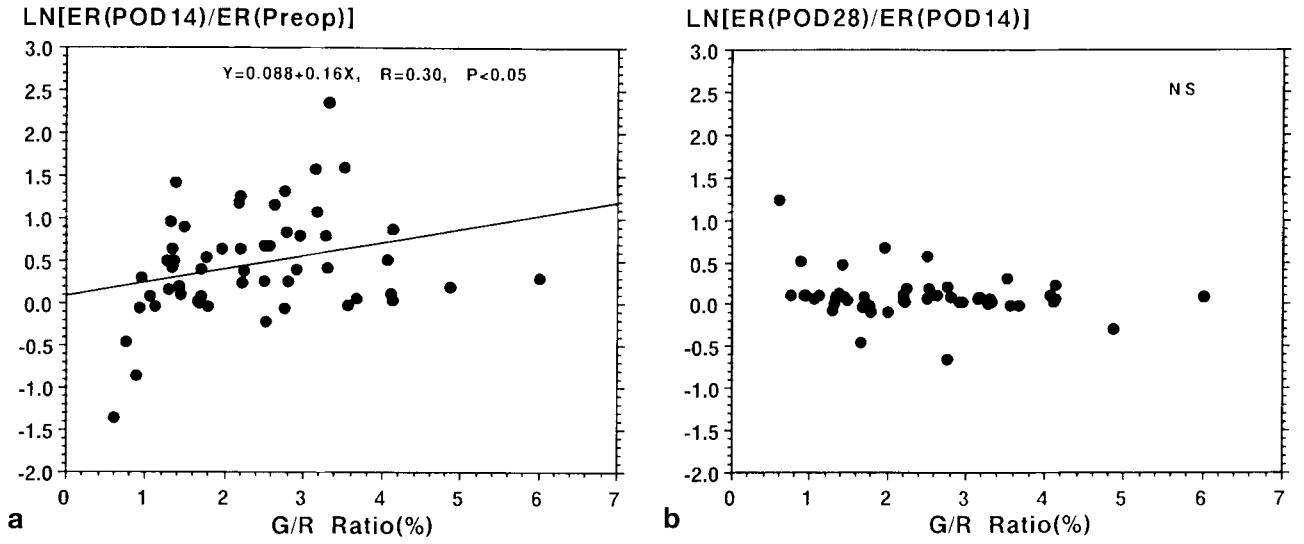
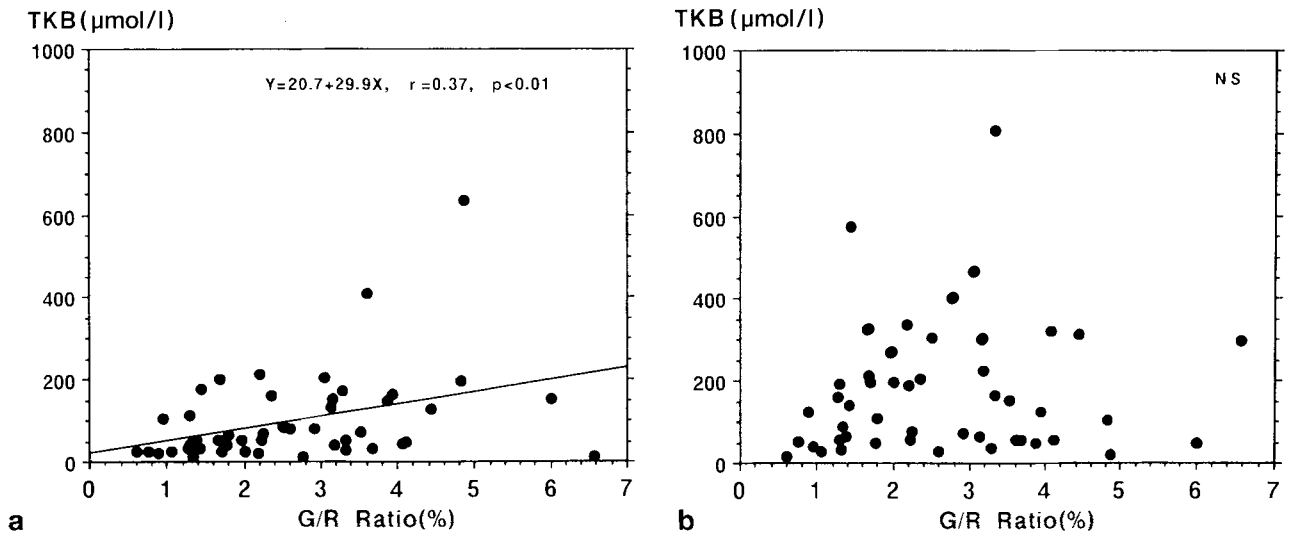


Fig. 6 a,b Correlation between G/R ratio and recovery of cholesterol esterification: **a** LN[ER(14POD)/ER(Preop)]; **b** LN[ER(28-POD)/ER(14POD)]. [*ER(Preop)*, *ER(14POD)*, and *ER(28POD)* the most recent ratio of esterified cholesterol relative to total cholesterol before operation, and at postoperative days 14 and 28, respectively; *LN* logarithm$_e$]

the recovery of cholesterol esterification, which is a useful index of graft function, was delayed for 2 weeks due to a deficient synthesis of lecithin-cholesterol acyltransferase and apoprotein A1 by the liver. Since ketone bodies are synthesized from acetyl-CoA via hydroxymethylglutaryl-CoA by the liver, ketone body production could also be considered an index of the metabolic capacity of the graft [10]. The present study showed that total ketone body concentration was determined by the G/R ratio after reflow of the portal vein. These three results may also indicate that a relatively small graft has some inherent disadvantages in terms of synthetic and detoxification capabilities.

A substantial increase in liver volume of 60 %–200 % has been reported to occur at 1 month after liver transplantation when the graft liver has a smaller than ideal volume [5]. To obtain early and sufficient regeneration after liver transplantation, sufficient flow in the portal vein, including hepatotrophic factors, should be considered. It has been reported that a successful increase in weight and active DNA synthesis was observed in reduced-size partial orthotopic liver transplantation in dogs with grafts whose weights were between 25 % and

Fig. 7 a,b Correlation between G/R ratio and production of ketone bodies (TKB): **a** 1 h after reflow of portal vein; **b** 6 h after reflow of portal vein



30 % of the standard liver volume [18]. Hepatotrophic factors are supplied to the liver from the pancreas via the portal vein since unilateral deprivation of portal blood induces atrophy of the flow-occluded lobe and hypertrophy of the contralateral lobe [8]. In clinical liver transplantation for the terminal stage of liver cirrhosis with well-developed collaterals or retrograde portal flow, a sufficient supply of portal blood, including hepatotrophic factors and a sufficient oxygen supply via the hepatic artery are essential for regeneration of the relatively small graft. In our series of pediatric living related partial liver transplantations, the minimal G/R ratio was 0.61 %, which corresponds to 30 % (0.61 %/2.0 %) of the ideal graft volume, since the ideal ratio of liver weight to body weight is 2.0 %. It is known that the normal liver can tolerate right trisegmentectomy with resection of the caudate lobe, which reduces the liver volume by 80 % since the left lateral segment is 20 % of the total liver volume. Taking the disadvantages of procurement, cold preservation, and reperfusion injuries into consideration, the minimal value of 30 % in living related partial liver transplantation seems to be reasonable.

In conclusion, graft size-matching is not so serious a problem for living related partial liver transplants with a graft/BW ratio ranging from 0.61 % to 6.0 % with respect to blood supply, tissue oxygenation and metabolic capacity, as long as the graft liver is anatomically fitted to the recipient. Living related partial liver transplantation for small infants with relatively large grafts can be performed successfully when the blood flow to the graft is ensured. Shunt ligation should be performed as needed by duplex Doppler sonography. Living related partial liver transplantation for adolescents or adults with relatively small grafts can be performed successfully when early regeneration is ensured.

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