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Study of Donor-Recipient Liver Size Match for Transplantation

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Objective
This animal experiment investigated the donor-recipient liver size match for safe liver transplantation.

Background
In spite of refinements in surgical techniques in reduced liver transplantation, the liver size disparity remains one of the most common complications in pediatric patients. Optimal size matching remains unknown.

Methods
The experiment compared eight groups of liver-transplanted rats with designated ratios of donor and recipient liver weights. Donor livers harvested from rats weighing 420–520 g were reduced to the designated size by liver lobectomy and implanted in rats weighing 170–240 g. Bile secretion and serum aspartate aminotransferase (AST) activities in groups 2, 4, and 6 were studied after surgery.

Results
Stepwise increase of the ratio of donor and recipient liver weights from 1.04:1 in group 4 to 1.26:1 in group 3, 1.56:1 in group 2, and 2.04:1 in group 1 caused stepwise decrease of survival rates from 83.3% to 66.7%, 16.7%, and 0%, respectively. Stepwise decrease of the ratio from 1.04:1 in group 4 to 0.79:1 in group 5, 0.53:1 in group 6, 0.35:1 in group 7, and 0.24:1 in group 8 also caused stepwise reduction of survival rates from 83.3% to 66.7%, 50%, 0%, and 0% in each group.

Conclusion
The range of ratios of donor and recipient liver weights for successful rat liver transplantation is from 0.53:1 to 1.26:1. Increase and decrease of ratios of donor-recipient liver weights from equal size do not increase the recipient survival rates. Recipients of reduced donor liver weights tend to have a higher survival rate than recipients of increased donor liver weights.

To overcome shortage of small donor livers, transplantation techniques of reduced-size liver, split liver, and living related donors have evolved into clinically useful procedures.[1-3] However, unlike whole liver transplantation, unexpected size mismatch between the reduced-size donor liver and the recipient's liver has become one of the most common graft-related complications.[4,5] Optimal size of the reduced-size donor liver for safe grafting into the recipient remains undefined. This experiment investigated the optimal size matching between donor and recipient livers using a rat liver transplantation model.

Table 1. LIVER SIZE MATCHING FOR RAT LIVER TRANSPLANTATION

Group No.	Grafted Liver Lobe	Donor Liver Weight (g)	Recipient Liver Weight (g)
1	Whole liver	17.39 ± 0.45	8.53 ± 0.18
2	Median + left + R or RP	14.18 ± 0.34	9.11 ± 0.36
3	Median + right + caudate	11.85 ± 0.28	9.39 ± 0.26
4	Median + right	9.72 ± 0.18	9.37 ± 0.21
5	Median + caudate	6.97 ± 0.30	8.83 ± 0.24
6	Median	5.26 ± 0.05	9.95 ± 0.14
7	Right	3.01 ± 0.15	8.62 ± 0.23
8	Right posterior	2.07 ± 0.21	8.52 ± 0.54

R: right lobe; RP: right posterior lobe.
Liver weight values are mean ± SEM.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats weighing 420–520 g and aged 3–4 months were obtained from Hilltop Lab Animals, Inc.(Scottdale, PA) and used as liver donors. Male Sprague-Dawley rats weighing 170–240 g and aged 40–50 days were used as recipients. Rats were housed in the standard animal room without fast before the surgery and with free activity, water, and food after surgery.

Research Protocol

The experiment was conducted in eight groups of six liver-transplanted rats with different ratios of donor and recipient liver weights. Donor livers harvested from rats weighing 420–520 g were reduced to the designated size by liver lobectomy and implanted into recipients weighing 170–240 g. Ratios of donor and recipient liver weights from groups 1 to 8 were designated as 2:1, 1.5:1, 1.25:1, 1:1, 0.75:1, 0.5:1, 0.33:1, and 0.25:1 (**Table 1**). Rats that lived more than 7 days after transplantation were considered survivors. Bile samples from groups 2, 4, and 6 were collected 1 hour after surgery for study of bile flow rates and bile salt outputs. Blood samples were collected 3 hours after surgery for measurement of serum AST.

Operative Procedures

Surgery was performed using ether anesthesia. The hepatic artery was ligated without later reconnection. Donor livers were prepared according to the designated ratios of donor and recipient liver weights. Whole donor livers were used for recipients in group 1. After partial hepatectomy, median, left, and right or right posterior lobes remaining intact were used for group 2; median, right, and caudate lobes were used for group 3; median and right lobes were used for group 4; median and caudate lobes were used for group 5; median lobes were used for group 6; right lobes were used for group 7; and right posterior lobes were used for group 8. Partial hepatectomy on the donor liver was done by lobe ligation. Constriction of the inferior caval vein lumen was carefully avoided during each ligature to ensure intact hepatic circulation. The donor liver was perfused via the portal vein with 5 mL hepar cold saline and stored in the cold saline with cold ischemic time of 60 minutes. Prepared donor livers and recipient livers were weighed after hepatectomy. Actual donor and recipient liver weights and their ratios are listed in Tables 1 and 2. The suprahepatic vena cava was reconstructed using continuous 6-0 polypropylene sutures. The infrahepatic vena cava and portal vein were reanastomosed using the cuff technique described by Kamada and Calne.[6] The common bile duct was connected by telescoping a tube in the donor bile duct into a larger diameter tube in the recipients[6] in groups 1, 3, 5, 7, and 8. The common bile duct was anastomosed using a mini T-tube for postoperative bile collection in groups 2, 4, and 6, as previously described.[7] Four milliliters of 10% dextrose infused via the rat's penile vein after liver revascularization was given to all groups as fluid resuscitation, and no further treatments were given.

Sample Collection and Laboratory Assays

Bile flow rates were measured in mL/100 g body weight/hour from the mini T-tube in groups 2, 4, and 6

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Table 2. SURVIVAL RATES IN RATS WITH DIFFERENT RATIOS OF DONOR-RECIPIENT LIVER WEIGHTS

Group No.	Designated Ratio (D:R)	Actual Ratio (D:R)	Survival Rate (%)
1	2.00:1	2.04:1	0 (0/6)*
2	1.50:1	1.56:1	16.7 (1/6)*
3	1.25:1	1.26:1	66.7 (4/6)
4	1.00:1	1.04:1	83.3 (5/6)
5	0.75:1	0.79:1	66.7 (4/6)
6	0.50:1	0.53:1	50.0 (3/6)
7	0.33:1	0.35:1	0 (0/6)*
8	0.25:1	0.24:1	0 (0/6)*

D:R: donor liver weight:recipient liver weight.
* $p < 0.05$ *versus* group 4.

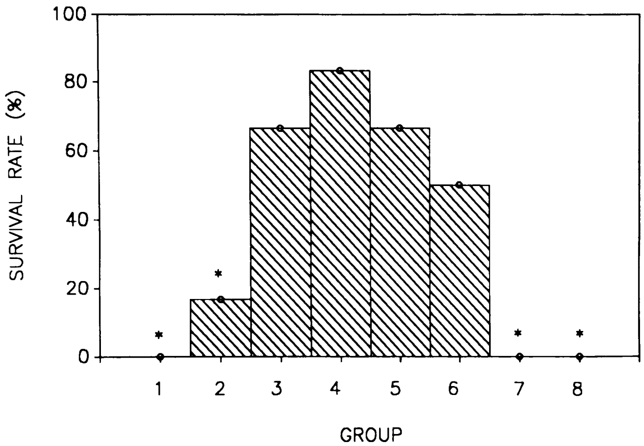

Figure 1. Rat survival rates in each experimental group. * = $p < 0.05$ compared with group 4.

during the second postoperative hour. The concentration of the total bile salts was determined by the modified 3α-hydroxysteroid dehydrogenase technique[8] using sodium taurocholate as the standard. The enzymes, hydroxysteroid dehydrogenase, β-nicotinamide adenine dinucleotide (NAD), and sodium taurocholate, were obtained from Sigma Chemical Company (St. Louis, MO). Bile salt output was calculated in μmol/100 g body weight/hour. A blood sample of 0.2 mL was collected from the rat's tail vein three hours after surgery in groups 2, 4, and 6. Serum AST activity (u/L) was determined using research kits from Sigma Chemical Company.

Statistical Methods

Results of bile flow rates, bile salt outputs, serum AST levels, and liver weights are expressed as mean ± standard error of the mean (SEM). Significant differences were compared among groups 2, 4, and 6 and tested by the unpaired Student t test using a computer program of Sigmaplot, version 4.0 (Jandel Scientific, Corte Madera, CA). The survival rates in each experimental group were compared with group 4 and tested by the chi-square test. Probability values less than 0.05 were considered significant.

RESULTS

By the direct observation of the donor-liver surface after blood reperfusion, livers looked pale in groups 1 and 2, with a large donor-recipient-size mismatch and livers looked congested in groups 7 and 8, with a small size mismatch.

The rat survival rates in each experimental group are shown in Figure 1 and Table 1.

The highest survival rate was found in group 4, which had equal donor and recipient liver weights. Stepwise increase of the ratio of donor and recipient liver weights from 1.04:1 in group 4 to 1.26:1 in group 3, 1.56:1 in group 2, and 2.04:1 in group 1, caused stepwise decrease of the rat survival rates from 83.3% to 66.7%, 16.7%, and 0% in each group. Stepwise decrease of the ratio from 1.04:1 in group 4 to 0.79:1 in group 5, 0.53:1 in group 6, 0.35:1 in group 7, and 0.24:1 in group 8, also caused stepwise reduction of the survival rates from 83.3% to 66.7%, 50.0%, 0%, and 0%, respectively. By comparison with group 4, which had the same donor-recipient liver matching size, survival rates of liver-transplanted rats in groups 1, 2, 7, and 8 decreased significantly ($p < 0.05$) because of the over-unmatched donor and recipient livers. No significant differences were found among groups 3, 4, 5, and 6, with donor-recipient ratios between 1.26:1 and 0.53:1.

Study of bile flow rates, bile salt outputs, and serum

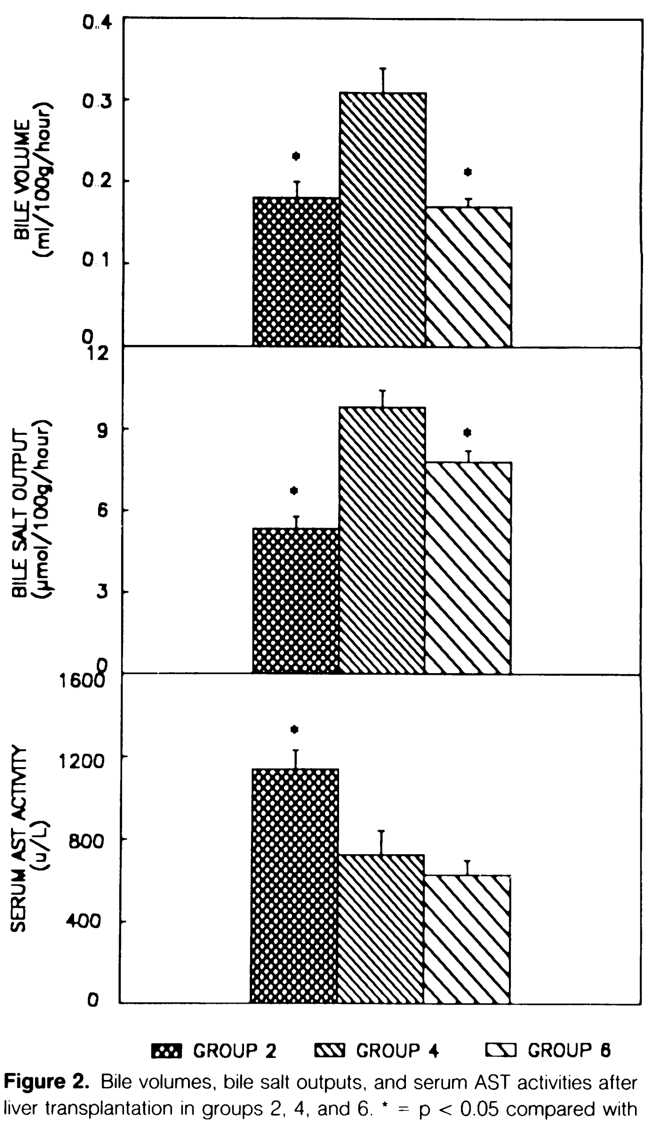

Figure 2. Bile volumes, bile salt outputs, and serum AST activities after liver transplantation in groups 2, 4, and 6. * = $p < 0.05$ compared with group 4.

Table 3. COMPARISON OF BILE VOLUMES, BILE SALT OUTPUTS, AND SERUM AST LEVELS

Group No.	Matched Liver (D:R)	Bile Volume (mL/100 g/h)	Bile Salt Output (μmol/100 g/h)	Serum AST (U/L)
2	1.56:1	0.18 ± 0.02*	5.35 ± 0.45*	1138.1 ± 91.6*
4	1.04:1	0.31 ± 0.03	9.78 ± 0.62	725.5 ± 118.2
6	0.53:1	0.17 ± 0.01*	7.79 ± 0.43*	628.0 ± 70.9

Values are mean ± SEM. D: donor liver weight; R: recipient liver weight.
* $p < 0.05$ *versus* group 4.

AST activities in groups 2, 4, and 6 showed that increasing the ratio of donor and recipient liver weights from 1.04:1 in group 4 to 1.56:1 in group 2 significant reduced bile flow rates from 0.31 ± 0.03 to 0.18 ± 0.02 mL/100 g/hour ($p < 0.05$) and bile salt outputs from 9.78 ± 0.62 to 5.35 ± 0.45 μmol/100g/hour ($p < 0.05$), elevated serum AST activities from 7.25.5 ± 118.2 to 1138.1 ± 91.6 u/L ($p < 0.05$), and resulted in decrease of the rat survival rate from 83.8% to 16.7% ($p < 0.05$). Decreasing the ratio from 1.04:1 in group 4 to 0.53:1 in group 6 also significantly reduced bile flow rates to 0.17 ± 0.01 ml/100g/hour ($p < 0.05$) and bile salt outputs to 7.79 ± 0.43 μmol/100g/hour ($p < 0.05$), but did not significantly increase serum AST levels or decrease survival rate (Fig. 2 and Table 3).

DISCUSSION

Since Bismuth and Houssin[9] initially reported the successful use of reduced-size liver transplantation from Paris in 1984, the technique has been further developed and become widely accepted.[1,5,10,11] Based on the clinical experiences of the donor liver size modification, new surgical techniques of liver transplantation in children using the split liver[2,12] and the liver from living related donors[3] have been successfully introduced to overcome the shortage of small donors. However, in spite of refinements of surgical techniques and perioperative management in the reduced liver transplantation, liver size disparity between the donor and recipient remains one of the most common complications in pediatric patients.[4,5] Broelsch et al.[4] reported that three of nine patients had large donor-recipient size mismatch, which caused poor blood perfusion of the large bulk of parenchyma, unfavorable orientation of the vessels, and difficulties in abdominal closure, resulting in two cases of liver retransplantations and one case of secondary abdominal closure. Study of favorable ratios of donor-recipient liver weights is expected to produce an important parameter for a better choice of donor liver size during surgery.

Results show that optimal donor liver size for transplantation should be as close to the recipient as possible. Stepwise decrease of donor liver weights caused stepwise decrease of recipient survival rates, especially when the ratio of the donor-recipient liver weights stepped down to 0.35:1 or less. On the other hand, stepwise increase of the donor liver weight also caused stepwise decrease of the recipient survival rates, especially when the ratio stepped up to 1.56:1 or more. The range of ratios for a successful rat liver transplantation is from 0.53:1 to 1.26:1.

Additionally, by comparison of rat survival rates among groups 2, 4, and 6, we found that increase of the donor liver weight caused significant reduction of rat survival rate in group 2 rather than in group 6, which had reduced-sized donor liver. The results show that increase or decrease of donor liver weight ratios reduce recipient survival rates. Also, recipients with reduced donor liver size have higher survival rates than those with increased size.

Poor rat survival rates in groups 7 and 8 can be explained by compensation failure in the small liver after transplantation, when the donor liver mass was reduced to 35% or less of the recipient. Why larger liver size disparity between the donor and recipient shows a poorer outcome than the smaller in the liver-transplanted rat is unclear. The following factors may explain the findings: poorer donor liver reperfusion because of the large donor-recipient liver size mismatch; more severe hemodynamic disturbance following unclamping of the portal vein and abdominal vena cava; increased uneven pressure on the large liver residing in a relatively smaller abdominal cavity; and poor fit of the donor liver, which may kink reconnected blood vessels.

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