Graft Inflow Modulation in Living-Donor Liver Transplantation: Hepatic Hemodynamic Changes in Splenic Artery Ligation and Splenectomy

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Background: Excessive portal flow to an allograft was a key mechanism for small-for-size syndrome in living-donor liver transplantation (LDLT). Good outcomes in LDLT by graft inflow modulation (GIM) using a small graft were reported, but the effect on hepatic hemodynamics is undefined. This report summarizes our experience with GIM and compares the effects of splenic artery ligation (SAL) and splenectomy on hepatic hemodynamic changes.

Material/Methods: Ninety-nine patients who underwent adult-to-adult LDLT from June 2014 to December 2020 were included in this study. GIM was performed in 36 patients (17 patients with SAL and 19 with splenectomy).

Results: The GIM group had lower graft-to-recipient weight compared to the no-modulation group (median, 0.91% versus 1.04%, \( P = 0.022 \)). Initial portal venous flow (PVF) was higher in the GIM group (median, 311 versus 156 ml/min/100 g, \( P < 0.001 \)). After GIM, PVF decreased to 224 ml/min/100 g. One-year graft survival with GIM was 89.9%, and for the no-modulation group it was 86.6% (\( P = 0.945 \)). In the subgroup analysis, the efficacy of decompressing PVF was higher in the splenectomy subgroup (median, 14.3% versus 41.8%, \( P = 0.002 \)).

Conclusions: GIM was useful for grafts with high PVF. Splenectomy modulated excessive PVF more effectively than did SAL. Perioperative hepatic hemodynamic changes could assist surgeons in selecting different GIM strategies.

Keywords: Hypertension, Portal • Liver Transplantation • Splenectomy

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Background

Living-donor liver transplantation (LDLT) is an established alternative to deceased-donor liver transplantation (DDLT). Initially developed for pediatric recipients, LDLT was successively extended to adult patients with end-stage liver disease, including hepatocellular carcinoma (HCC) [1,2]. Since the introduction of LDLT, donor-recipient size matching has become a concern. Considering donor safety, the recipient may have small-for-size syndrome (SFSS) if the liver graft is too small to meet the recipient’s metabolic demand. SFSS is clinically manifested by impaired coagulation, cholestasis, and ascites, with subsequent septic complications and lower graft survival [3,4]. Excessive portal flow to the allograft was considered a key mechanism resulting in sinusoid congestion and hemorrhage [5]. Several investigators have reported good outcomes in LDLT using a small graft by surgical graft inflow modulation (GIM), including splenic artery ligation (SAL) [6,7], splenectomy [8,9], and portosystemic shunt (PSS) [10,11]. SAL decreased splenic vein flow, with a corresponding increase in hepatic artery (HA) flow. Splenectomy can produce a major reduction in portal venous flow (PVF), comparable to PSS, without the risk of portal steal syndrome. Modulation to keep portal venous pressure (PVP) <15 mmHg [8] or PVF <250 ml/min/100 g graft weight [12] was associated with favorable outcomes. However, the effect on hepatic hemodynamics by different types of surgical GIM in LDLT is not well understood. This study summarizes our experience with GIM and compares the effects of SAL and splenectomy on hepatic hemodynamic changes and clinical outcomes.

Material and Methods

Study Design

We retrospectively reviewed the data for patients who underwent adult-to-adult LDLT from June 2014 to December 2020 at the National Cheng Kung University Hospital in Taiwan. Re-transplant patients were excluded. The patients were followed up after surgery until June 2021, death, or the date of the last follow-up visit, whichever came first. The study was approved by our institutional review board (B-ER-110-304).

Preoperative Donor Evaluation

Indications for LDLT were equivalent to those for DDLT except for patients with HCC. Donors were selected from among candidates who volunteered to be living donors. All potential living donors were evaluated by a multidisciplinary team of transplant surgeons, transplant hepatologists, clinical psychologists, and nurse specialists. Donor computed tomography (CT) was performed for volumetric analysis. Decisions about graft types were based on the preoperatively predicted graft-to-recipient weight ratio (GRWR). In general, GRWR >0.8% was accepted. The donor liver remnant must be >30% of the total donor liver volume. Actual GRWR was calculated by graft weight measured after cold graft perfusion.

Surgery

The right lobe liver graft excluding the middle hepatic vein (MHV) was the preferred choice in our center. The MHV tributaries draining the segment 5 vein (V5), the segment 8 vein (V8), and the inferior right hepatic vein were reconstructed when their diameter was >5 mm. In left-lobe grafts, the common orifice of the MHV and left hepatic vein were directly anastomosed to the recipient’s inferior vena cava in a triangular manner.

Graft inflow modulation

Intraoperative measurement of the portal vein (PV) and HA flow used transit-time flow methods with the Medi-Stim VeriQ™ System (Oslo, Norway). Appropriate size probes (ranging from 4 to 12 mm in diameter) were applied to the HA and PV based on the target vessel diameter. PVP was measured with a 25-G catheter with direct puncture. The measurement timing was performed after PV and HA anastomosis/reperfusion and after flow modulation. The flow modulation indication was as follows: initial PVF >250 ml/min/100 g. GIM was not limited to grafts with a GRWR <0.8. A post-perfusion PVF of 100-250 ml/min/100 g was considered optimal. The preferred method for GIM was SAL. The splenic artery was isolated at the superior border of the pancreas. If portal flow or pressure changes after clamping the splenic artery were unsatisfactory, splenectomy was performed. Ligation of varices or shunting was performed in recipients with insufficient portal flow.

Postoperative Care

The patients were transferred to the intensive care unit after surgery. We performed Doppler ultrasound daily to assess the patency of the HA, PV, and hepatic vein for all recipients within 1 week after the operation. SFSS and early allograft dysfunction (EAD) were defined using criteria previously reported [3,13].

Immunosuppression

The immunosuppression protocol was standardized with calcineurin inhibitors (CNIs) (tacrolimus/cyclosporine), mycophenolate mofetil, and steroids. No induction agents were used. Intraoperative methylprednisolone was given except for emergent LDLT. Mammalian target of rapamycin (mTOR) inhibitors (sirolimus/everolimus) were added for patients with HCC at 1 month after the operation. After splenectomy, vaccination against streptococcus pneumonia was provided 1 year after LDLT.

Preoperative Donor Evaluation Indications for LDLT were equivalent to those for DDLT except for patients with HCC. Donors were selected from among candidates who volunteered to be living donors. All potential living donors were evaluated by a multidisciplinary team of transplant surgeons, transplant hepatologists, clinical psychologists, and nurse specialists. Donor computed tomography (CT) was performed for volumetric analysis. Decisions about graft types were based on the preoperatively predicted graft-to-recipient weight ratio (GRWR). In general, GRWR >0.8% was accepted. The donor liver remnant must be >30% of the total donor liver volume. Actual GRWR was calculated by graft weight measured after cold graft perfusion.
Results

A total of 112 patients underwent LDLT during the study period. Thirteen patients were excluded. One patient was a re-transplantation, 2 patients had no intraoperative measurements due to critical situations, 2 patients received jumping grafts, 1 patient received a portocaval shunt, 2 patients underwent collateral vein ligation, and 5 patients underwent splenorenal shunt ligation. Finally, a total of 99 patients were included in this study. The median follow-up duration was 31.7 months.

The patients were divided into 2 groups according to whether or not a GIM was performed. The clinical and operative characteristics are presented in Tables 1 and 2. GIM was performed in 36 patients (17 with SAL, 19 with splenectomy). The GIM group had a lower GRWR than the no-modulation group (median, 0.99% versus 0.83%, \( P \leq 0.027 \)). The donor body mass index (BMI) was lower in the GIM group than in the no-modulation group (median, 30.6% versus 14.3%, \( P \leq 0.027 \)). The donor age was similar between the 2 groups. Other recipient and donor factors, including age, sex, recipient BMI, disease indication, virus status, Model for End-Stage Liver Disease (MELD) score, ABO incompatibility, donor age, and graft type, were not different between the groups.

With respect to operative factors, the cold ischemic time and postoperative ICU stay were shorter in the GIM group. The incidence of SFSS and EAD was similar between the 2 groups. There was also no significant difference in the postoperative complication rates. Four patients developed portal vein thrombosis in the no-modulation group, and all were successfully treated with anticoagulants.

SAL Versus Splenectomy

In the GIM group, 36 patients were further divided into SAL and splenectomy subgroups. Tables 3 and 4 present a comparison of the clinical and operative characteristics. More female recipients, female donors and older donor age were observed in the splenectomy subgroup. The liver graft was smaller in the splenectomy subgroup. More left-lobe grafts were used. In the splenectomy subgroup, the median value of PVF decreased from 319 to 233 ml/min/100 g (\( P \leq 0.001 \)) and the median value of HAF increased from 70 to 83 ml/min/100 g (\( P \leq 0.001 \)). The efficacy of decompressing PVF was higher in the splenectomy subgroup than in the SAL subgroup (median, 14.3% versus 41.8%, \( P \leq 0.002 \)). After modulation, the HAF values were similar between the 2 groups (median, 100 versus 80 ml/min, \( P \leq 0.065 \)).

In the SAL subgroup, the median value of PVF decreased from 292 to 233 ml/min/100 g (\( P \leq 0.001 \)) and the median value of HAF increased from 70 to 83 ml/min (\( P \leq 0.01 \)). In the splenectomy subgroup, the median value of PVF decreased from 319 to 203 ml/min/100 g (\( P \leq 0.001 \)) and the median value of HAF increased from 40 to 73 ml/min (\( P \leq 0.01 \)). The efficacy of decompressing PVF was higher in the splenectomy subgroup than in the SAL subgroup (median, 14.3% versus 41.8%, \( P \leq 0.002 \)).

Splenectomy-Related Complications

Five (8.3%) patients had splenectomy-related complications. Pancreatic pseudocyst formation developed in 1 recipient and CT-guided drainage was performed. Pancreatic fistula was treated by prolonged drainage in 1 recipient. The other patient developed retroperitoneal hematoma and received conservative treatment. Two patients developed portal vein trombosis.

Statistical Analysis

Continuous parameters are presented as the median and interquartile range (IQR). Categorical variables are expressed as frequency and percentage. The Pearson chi-squared test for categorical variables and the Mann-Whitney U test/Wilcoxon signed-rank test for continuous variables were used to compare groups.

Graft survival was measured from the time of transplantation to death from any cause or re-transplantation. The Kaplan-Meier method was used to analyze survival, and the log-rank test was used for comparisons. Statistical significance was defined as a \( P \leq 0.05 \), and all tests were 2-tailed. SPSS 22.0 (IBM Statistics for Windows, IBM Corp., Armonk, NY) was used for all calculations.

PVF and PVP

Initial PVF (after reperfusion) was significantly higher in the GIM group than in the no-modulation group (median, 311 versus 156 ml/min/100 g, \( P \leq 0.001 \), Table 2). After modulation, PVF decreased to 224 ml/min/100 g and was still higher (\( P \leq 0.001 \)). Initial hepatic artery flow (HAF) was significantly lower in the GIM group. After modulation, the HAF values were similar between the 2 groups (median, 100 versus 80 ml/min, \( P \leq 0.065 \), Table 2).

The final PVP was measured in 47 patients in the no-modulation group, with a median value of 14 mmHg (IQR, 10-17 mmHg). The final portal pressure was measured in the SAL subgroup in 9 patients (median, 14; IQR, 13-15 mmHg). The final portal pressure was measured in 10 patients (median, 11; IQR, 9-14 mmHg) in the splenectomy subgroup. We observed that in the modulation group, there were 17 patients with a final PVP <15 mmHg (19 patients with a record).

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| Variables Modulation | Group No. | SAL+splenectomy | P-value |
|----------------------|-----------|-----------------|----------|
| N                    | 63        | 36 (17+19)      | 0.613    |
| Recipient            |           |                 |          |
| Age, years           | 58 (51-62)| 56 (49-63)      | 0.613    |
| Sex (M), n (%)       | 42 (66.7 )| 23 (63.9 )      | 0.779    |
| BMI, kg/m²           | 25.1 (23.2-29.6)| 25.2 (23.5-26.5)| 0.741    |
| Hepatitis profile    |           |                 | 0.840    |
| HBV+/HCV+            | 3 (4.8)   | 2 (6.7)         |          |
| HBV+                 | 31 (49.2 )| 15 (41.7 )      |          |
| HCV+                 | 13 (20.6 )| 8 (22.2 )       |          |
| Negative             | 16 (25.4 )| 11 (30.6 )      |          |
| Disease indication, n (%) |         |                 | 0.152    |
| Acute/acute on chronic liver failure | 16 (25.4 )| 4 (16.7 )      |          |
| Decompensated cirrhosis | 23 (36.5)| 19 (52.8 )    |          |
| Hepatocellular carcinoma | 24 (38.1)| 13 (36.1 )    |          |
| MELD                 | 13 (9-30) | 15 (11-23)      | 0.633    |
| MELD ≥25, n (%)      | 18 (28.6 )| 8 (22.2 )       | 0.490    |
| ABO incompatible, n (%) | 11 (17.5)| 7 (19.4 )      | 0.806    |
| Donor                |           |                 |          |
| Donor age, y         | 31 (25-38)| 31 (23-36)      | 0.267    |
| Donor age ≥40, n (%) | 11 (17.5)| 5 (13.9 )       | 0.642    |
| Sex (M), n (%)       | 40 (63.5 )| 16 (44.4 )      | 0.066    |
| BMI, kg/m²           | 23.5 (20.7-25.3)| 22.3 (19.6-23.6)| 0.046    |
| Liver graft          |           |                 |          |
| Actual GRWR (%)      | 1.04 (0.90-1.19)| 0.91 (0.77-1.11)| 0.022    |
| GRWR <0.8%, n (%)    | 9 (14.3) | 11 (30.6)      | 0.027    |
| Graft weight, g      | 680 (571-812)| 612 (541-703) | 0.017    |
| Graft type, n (%)    |           |                 | 0.80     |
| Right lobe           | 56 (88.9)| 31 (86.1)       |          |
| Left lobe            | 5 (7.9)  | 4 (11.1)        |          |
| Right lobe with MHV  | 1 (1.6)  | 0               |          |
| Right posterior section | 1 (1.6)| 1 (2.8)        |          |

SAL – splenic artery ligation; BMI – body mass index; HBV – hepatitis B virus; HCV – hepatitis C virus; MELD – model of end-stage liver disease; GRWR – graft-to-recipient weight ratio. Continuous variables are expressed as the median (IQR). Categorical variables are expressed as number of patients (percentage).
thrombosis after splenectomy. One patient was treated with anticoagulants successfully, and the other patient developed portal vein thrombosis on postoperative day 1 and received re-transplantation 3 days later. The cause of portal vein thrombosis in the re-transplant patient might have been due to portal vein compression because of the poor position of left-lobe graft. In addition, a huge spleen with IMV directly joining into SMV might be considered a predisposing factor. No SAL-related complications were noted.

SAL – splenic artery ligation; SFSS – small-for-size syndrome; EAD – early allograft dysfunction; ICU – Intensive Care Unit; HA – hepatic artery. * Clavien-Dindo classification. Continuous variables are expressed as the median (IQR). Categorical variables are expressed as number of patients (percentage).

Table 2. Operative characteristics of all recipients and donors.

| Variables                              | Modulation   | Group No. | GIM group (SAL+splenectomy) | P-value |
|----------------------------------------|--------------|-----------|-----------------------------|---------|
|                                        |              | N         | 63                          | 36 (17+19) | 0.016 |
| Recipient                              |              |           |                             |         |
| Cold ischaemic time, min               |              | 202       | 179 (144-210)               | 0.016   |
| Anhepatic phase, min                   |              | 80 (61-106)| 79 (64-103)                 | 0.988   |
| Operation time, min                    |              | 657 (576-746)| 685 (558-772)               | 0.825   |
| Blood loss                             |              | 3000 (1500-5850)| 3050 (1850-4400)           | 0.760   |
| SFSS                                   |              | 7 (11.1)  | 4 (11.1)                    | 0.001   |
| EAD                                    |              | 7 (11.1)  | 2 (5.6)                     | 0.355   |
| Hospital stay                          |              | 26 (21-33)| 25 (20-32)                  | 0.438   |
| ICU stay                               |              | 14 (11-21)| 12 (10-16)                  | 0.048   |
| Severe postoperative complications*    |              |           |                             | 0.464   |
| 3a                                     |              | 26 (41.3) | 13 (36.1)                   |         |
| 3b                                     |              | 8 (12.7)  | 2 (5.6)                     |         |
| 4a                                     |              | 4 (6.3)   | 1 (2.8)                     |         |
| 4c                                     |              | 1 (1.6)   | 1 (2.8)                     |         |
| Hospital mortality                     |              | 4 (6.3)   | 1 (2.8)                     |         |
| Specific postoperative complications   |              |           |                             |         |
| Hepatic artery thrombosis/pseudoaneurysm+| 1 (1.6)    | 1 (2.8)   | 0.685                       |
| Portal vein thrombosis                 |              | 4 (6.3)   | 2 (5.6)                     | 0.874   |
| Hepatic vein thrombosis                |              | 0         | 1 (2.8)                     | 0.184   |
| Bile leakage/stricture                 |              | 14 (22.2) | 6 (16.7)                    | 0.508   |
| Liver hemodynamics                     |              |           |                             |         |
| Initial portal flow, ml/min/100 g      |              | 156 (115-213)| 311 (252-384)              | <0.001  |
| Initial HA flow, ml/min                |              | 100 (68-134)| 49 (39-80)                 | <0.001  |
| Final portal flow, ml/min/100 g        |              | 156 (115-213)| 224 (179-267)              | <0.001  |
| Final HA flow, ml/min                  |              | 100 (68-134)| 80 (50-120)                | 0.065   |

SAL – splenic artery ligation; SFSS – small-for-size syndrome; EAD – early allograft dysfunction; ICU – Intensive Care Unit; HA – hepatic artery. * Clavien-Dindo classification. Continuous variables are expressed as the median (IQR). Categorical variables are expressed as number of patients (percentage).
### Table 3. Clinical characteristics of all recipients and donors in the modulation group.

| Variables Modulation | Subgroup 1 | Subgroup 2 | P  |
|----------------------|------------|------------|----|
|                      | SAL        | Slenection |    |
| **N**                | 17         | 19         |    |
| **Recipient**        |            |            |    |
| Age, years           | 58 (52-64) | 54 (49-63) | 0.253 |
| Sex (M), n (%)       | 14 (82.4)  | 9 (47.4)   | 0.029 |
| BMI, kg/m²           | 24.9 (23.4-26.1) | 25.4 (22.9-31.2) | 0.428 |
| Hepatitis profile    |            |            | 0.180 |
| HBV+/HCV+            | 0          | 2 (10.5)   |    |
| HBV+                 | 10 (58.8)  | 5 (26.3)   |    |
| HCV+                 | 3 (17.6)   | 5 (26.3)   |    |
| Negative             | 4 (23.5)   | 7 (36.8)   |    |
| Disease indication, n (%) |          |            | 0.124 |
| Acute/acute on chronic liver failure | 3 (17.6) | 1 (5.3) |    |
| Decompensated cirrhosis | 6 (35.3) | 13 (68.4) |    |
| Hepatocellular carcinoma | 8 (47.1) | 5 (26.3) |    |
| MELD                 | 15 (10-24) | 14 (12-19) | 0.799 |
| MELD ≥25, n (%)      | 4 (23.5)   | 3 (17.6)   | 0.858 |
| ABO incompatible, n (%) | 4 (21.1) | 4 (21.1) | 0.797 |
| **Donor**            |            |            |    |
| Donor age, y         | 26 (23-33) | 33 (23-37) | 0.136 |
| Donor age ≥40, n (%) | 0          | 5 (26.3)   | 0.023 |
| Sex (M), n (%)       | 11 (64.7)  | 5 (26.3)   | 0.021 |
| BMI, kg/m²           | 20.4 (18.4-23.7) | 23.2 (21.2-23.6) | 0.090 |
| **Liver graft**      |            |            |    |
| Actual GRWR (%)      | 0.99 (0.84-1.12) | 0.83 (0.71-0.99) | 0.038 |
| GRWR <0.8%, n (%)    | 2 (11.8)   | 9 (47.4)   | 0.021 |
| Graft weight, g      | 658 (575-782) | 577 (452-682) | 0.022 |
| Graft type, n (%)    |            |            | 0.74 |
| Right lobe           | 17 (100)   | 14 (73.7)  |    |
| Left lobe            | 0          | 4 (21.1)   |    |
| Right lobe with MHV  | 0          | 0          |    |
| Right posterior section | 0     | 1 (5.3)   |    |

SAL – splenic artery ligation; BMI – body mass index; HBV – hepatitis B virus; HCV – hepatitis C virus; MELD – model of end-stage liver disease; GRWR – graft-to-recipient weight ratio. Continuous variables are expressed as median (IQR). Categorical variables are expressed as number of patients (percentage).
**Table 4. Operative characteristics of all recipients and donors in the modulation group.**

| Variables Modulation | Subgroup 1 (SAL) | Subgroup 2 (Sleectomy) | P   |
|----------------------|------------------|------------------------|-----|
| **Recipient**        |                  |                        |     |
| Cold ischaemic time, min | 185 (154-234)    | 164 (137-196)          | 0.149 |
| Anhepatic phase, min  | 79 (66-107)      | 78 (59-94)             | 0.366 |
| Operation time, min   | 695 (594-838)    | 657 (552-745)          | 0.199 |
| Blood loss            | 3100 (1225-4150) | 2800 (1900-6500)       | 0.334 |
| SFSS                  | 3 (17.6)         | 1 (5.3)                | 0.238 |
| EAD                   | 0                | 2 (10.5)               | 0.169 |
| Hospital stay         | 21 (19-28)       | 26 (21-35)             | 0.172 |
| ICU stay              | 11 (10-13)       | 13 (11-18)             | 0.009 |
| Severe postoperative complications* |                 |                        | 0.391 |
| 3a                    | 6 (35.3)         | 7 (36.8)               |     |
| 3b                    | 0                | 2 (10.5)               |     |
| 4a                    | 1 (5.9)          | 0                      |     |
| 4c                    | 0                | 1 (5.3)                |     |
| Hospital mortality    | 0                | 1 (5.3)                |     |
| Specific postoperative complications |                 |                        |     |
| Hepatic artery thrombosis/pseudoaneurysm + | 1 (5.9)          | 0                      | 0.284 |
| Portal vein thrombosis| 0                | 2 (10.5)               | 0.169 |
| Hepatic vein thrombosis| 0                | 1 (5.3)                | 0.337 |
| Bile leakage/stricture| 4 (23.5)         | 2 (10.5)               | 0.296 |
| Liver hemodynamics    |                  |                        |     |
| Initial portal flow, ml/min/100 g | 292 (238-357)    | 319 (250-430)          | 0.274 |
| Initial HA flow, ml/min  | 70 (43-85)      | 40 (27-56)             | 0.013 |
| Final portal flow, ml/min/100 g | 233 (211-273)    | 203 (150-270)          | 0.188 |
| Final HA flow, ml/min  | 83 (52-137)      | 73 (49-110)            | 0.362 |
| Decreased PVF (%)      | 14.3 (11.0-23.8) | 41.8 (23.6-50.3)       | 0.002 |
| Increased HAF (%)      | 22.5 (5.3-74.7)  | 83.4 (3.8-195.2)       | 0.129 |

SAL – splenic artery ligation; SFSS – small-for-size syndrome; EAD – early allograft dysfunction; ICU – Intensive Care Unit; PVF – portal vein flow; HAF – hepatic artery flow. * Clavien-Dindo classification. Continuous variables are expressed as the median (IQR). Categorical variables are expressed as number of patients (percentage).
Graft survival according to use of modulation. The 1-year graft survival for patients with modulation was 89.9% and was comparable to that in the no-modulation group (86.6%, P=0.945).

Figure 2 shows graft survival according to modulation type. The 1-year graft survival was 90.8% for patients with SAL and 89.3% for splenectomy, but the difference was not significant (P=0.720).

Discussion

A donor liver is considered a small-for-size graft when the GRWR is <0.8 or when the ratio between the graft volume to standard liver volume is <40% [14]. High portal flow and pressure are detrimental for small-for-size grafts, leading to sinusoidal congestion, ischemic microcirculation, and subsequent graft failure [15]. During the intraoperative period, surgical GIM could reduce PVF and PVP. The most appropriate hemodynamic parameter in determining the utilization of GIM remains a subject of discussion. Ogura et al [8], in a retrospective analysis, reported that a PVP <15 mmHg was associated with good patient outcomes. Kaido et al reported improved outcomes in smaller grafts in whom the pressure could be lowered to <15 mmHg [16]. A cut-off of 250 ml/min/100 g of liver grafts was previously proposed by 2 studies [10,12]. In our study, we measured PVP and PVF simultaneously. However, we found that PVP was influenced by central venous pressure (CVP). Sainz-Barriga et al also reported that increases in the CVP were transmitted to the PVP. The evaluation of PHT severity with PVP could be misleading [17]. Therefore, we used PVF as a GIM indicator because PVF measurement was not only helpful in portal hyperperfusion state, but also avoided portal hypoperfusion. In addition, we measured PVF and HAF together to ensure adequate hepatic artery flow.

SFSS is a multifactorial phenomenon. Besides graft size, other risk factors for SFSS should be considered. Graft steatosis [18], hepatic arterial flow [19], hepatic venous outflow [20], cold ischemic time, and recipient factors (portal hypertension, MELD score) have been reported [21,22]. Thus, we had a relatively liberal indication for GIM, not only limited to grafts with a GRWR <0.8%. We think that maintaining an optimal PVF for grafts with some risk factors for SFSS is important.

Our study demonstrated that PVF could be successfully decreased to within the normal range in the GIM group. Despite the use of the smaller graft, by the aid of GIM, the incidence of SFSS and early graft survival were not inferior to those in the no-modulation group. Some studies have shown the benefit of GIM in LDLT by different techniques. A multi-center study reported by Emond et al identified a higher rate of graft dysfunction in modulated subjects; however, graft survival in modulated subjects was no different from in no-modulated subjects at 3 years [23]. In this study, we directly compared hepatic hemodynamic changes between the SAL and splenectomy subgroups in the cohort.
SAL is a simple and effective way to reduce PVF and is an alternative to splenectomy. This finding is mainly based on the principle that the level of spleen-derived perfusion is an important factor in portal inflow [7,9,24]. However, several investigators have reported that SAL is insufficient compared with splenectomy and portosystemic shunt [25,26]. In our study, the preferred method for GIM was SAL. Splenectomy was performed if the effect of portal decompression by SAL was insufficient. We found that SAL decreased portal blood flow by 14.3%. Splenectomy had higher efficacy for decompressing portal flow (41.8%) than SAL. We also found that splenectomy was indicated for smaller liver grafts and the higher PVF group.

A Tokyo group reported that splenectomy was associated with longer operative time, higher blood loss, and higher risk of venous thrombosis and infection [27]. We found that the incidence of venous thrombosis was not higher in the splenectomy subgroup than in the SAL subgroup. No severe bacterial infections were observed. The blood losses and operative times were similar between the splenectomy and the SAL subgroups. Two patients developed portal vein thrombosis after splenectomy.

In contrast, 4 patients had portal vein thrombosis in the no-modulation group. Thus, splenectomy could be considered in patients with high PVF and should have an acceptable complication rate. The Kyushu group recently reported that simultaneous splenectomy is recommended for a small graft or patients with portal hypertension or high portal pressure in adult LDLT recipients [28].

Moon et al reported that splenectomy could replace splenectomy, with lesser complications [29]. However, the effect of the procedure requires further clarification. Although PSS was considered an effective method to decrease portal flow [10,11], we did not perform portosystemic shunt routinely because of the risk of portal hypoperfusion and encephalopathy. Pharmacologic manipulation with somatostatin therapy is one method of GIM. Hessheimer et al reported that somatostatin reduced portal vein flow and protected sinusoidal endothelial cells in their model [30]. Recently, Troisi et al found that somatostatin decreased the hepatic venous portal gradient and preserved arterial flow to the graft [31]. Further research to clarify the efficacy of somatostatin infusion in LDLT recipients is necessary.

Although portal overflow might injure the graft directly, arterial vasoconstriction introduces secondary ischemic changes [32]. Our study showed that HAF increased after GIM, which was consistent with the hepatic artery buffer response [33]. However, we could not identify the optimal HAF or PVF-to-HAF ratio in our series.

A flowmeter (VeriQ™) is used to measure intraoperative flows. The system has been used in previous studies and produces reproducible measurements [34-36]. However, some limitations of this measurement were observed. First, flow rates are inevitably influenced by local and systemic factors (which are all subject to some degree of variance). Second, the instruments are sensitive to the proximity of the detector to the vessel and the manipulation required positioning of the probes.

Yagi et al reported a high-compliance (PVF/PVP) graft in which the PVF can be maintained at a high level, even though a low PVF was found to be a good graft for postoperative liver graft function [37]. Although intraoperative PVF data was incomplete in our study, we observed final PVP <15 mmHg in 89% of the patients in the modulation group.

This study had several limitations. First, this was a retrospective study with a small sample size at a single center. Second, the selection of the splenectomy over splenic artery ligation was an obligation, not an option. This might be considered a selection bias. Third, the recipients with collateral and splenorenal shunt ligation were excluded. The effect of low PVF was not studied. Finally, we did not follow a strict algorithm for GIM. In the future, we plan to develop and verify our algorithm.

Conclusions

In conclusion, we demonstrated that GIM was helpful for grafts with high PVF in adult LDLT to achieve satisfactory outcomes. Splenectomy modulated excessive PVF more effectively than SAL. Perioperative hepatic hemodynamic changes could assist surgeons in selecting strategies for GIM.

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Disclosures

The authors, Che-Min Su, Tsung-Ching Chou, Tsung-Han Yang, and Yih-Jyh Lin, have no conflicts of interest or financial ties to disclosure.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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