Impact of split completeness on future liver remnant hypertrophy in associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) in hepatocellular carcinoma: Complete-ALPPS versus partial-ALPPS

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Background. *Recent evidence suggested that associating liver partition and portal vein ligation for staged hepatectomy with a partial split could effectively induce the same degree of future liver remnant hypertrophy as a complete split in non-cirrhotic and non-cholestatic livers with better postoperative safety profiles. Our aim was to evaluate if the same phenomenon could be applied to hepatitis-related chronic liver diseases.*
Methods. *In the study, 25 patients who underwent associating liver partition and portal vein ligation for staged hepatectomy from October 2013 to January 2016 for hepatocellular carcinoma were analyzed. Partial-associating liver partition and portal vein ligation for staged hepatectomy (n = 12) was defined as 50–80% of the transection surface split and complete-associating liver partition and portal vein ligation for staged hepatectomy (n = 13) was split down to inferior vena cava. Perioperative outcomes stratified by split completeness were evaluated.*
Results. *There was no significant difference in operating times and blood loss for stage I and II operations between complete-associating liver partition and portal vein ligation for staged hepatectomy and partial-associating liver partition and portal vein ligation for staged hepatectomy. All patients underwent stage II operation without any inter-stage complications. Complete split induced greater future liver remnant hypertrophy than partial split (hypertrophy rate: 31.2 vs 17.5 mL/day, P = .022) with more pronounced effect in chronic hepatitis (P = .007) than cirrhosis (P = .283). Complete-associating liver partition and portal vein ligation for staged hepatectomy was more likely to attain a future liver remnant/estimated standard liver volume ratio >35% within 10 days (76.9% vs 33.3%, P = .024) and proceed to stage II within 14 days after stage I (100% vs 58.4%, P = .009). The overall postoperative morbidity (≥grade 3a) after stage II was 16% (complete versus partial split: 7.7% vs 25%, P = .238) and hospital mortality after stage II was 8% (complete versus partial split: 0% vs 16.7%, P = .125).*
Conclusion. *Complete-associating liver partition and portal vein ligation for staged hepatectomy induced more rapid future liver remnant hypertrophy than partial-associating liver partition and portal vein ligation for staged hepatectomy without increased perioperative risk in chronic liver diseases. (Surgery 2017;161:357-64.)*

ASSOCIATING LIVER PARTITION and portal vein ligation for staged hepatectomy (ALPPS) has been introduced recently as a novel procedure to augment future liver remnant (FLR) in patients with marginal liver volume contemplating for major hepatectomy.[1,2] Early experience of ALPPS has been hampered by the high incidence of postoperative complications, such as bile leakage, infection, and the high incidence of mortality.[3,4] With cumulative experience and modification of operative techniques, the short-term outcomes of ALPPS have improved, resulting in a postoperative morbidity rate of 28–31% and a mortality rate ranging from 7–9%.[5-7] Additional study is needed regarding the development of this new surgical technique relates to the completeness of parenchymal split and the degree of FLR hypertrophy. Recent evidence demonstrated that partial split (defined as 50–80% of the complete transection surface) was associated with the same amount of FLR hypertrophy as a complete split, and with the benefit of lower postoperative morbidity and mortality in non-cirrhotic and non-cholestatic livers.[8] However, there is insufficient data on the impact of split on liver hypertrophy in chronic liver diseases. We hereby report our experience of split completeness and its impact on the degree of FLR hypertrophy in patients with viral hepatitis-related hepatocellular carcinoma.

METHODS

From October 2013 to January 2016, a total of 25 patients underwent the ALPPS procedure for hepatocellular carcinoma (HCC) at the Department of Surgery at the University of Hong Kong. With the approval from hospital ethics committee, we collected data prospectively including patient characteristics, operative details, and postoperative outcomes. Patients were divided into 2 groups according to the in situ split completeness for analysis. The selection criteria for ALPPS procedure in our center were Child-Pugh A liver cirrhosis or normal liver biochemistry, indocyanine green retention rate <20% at 15 minutes, FLR/estimated standard liver volume (ESLV) ratio <35% for unilobar lesion/<40% for bilobar lesions that required tumor clearance in FLR, and platelet count $\geq 100 \times 10^9$/L. The ESLV was calculated by the Urata formula.[9]

Operative techniques for ALPPS. The operative techniques for stage I procedure in our center were described previously.[10] In summary, we used the anterior approach for stage I procedures to minimize adhesion formation and to prevent iatrogenic tumor rupture during right liver mobilization for large sized tumors. In situ split was performed using a Cavitron Ultrasonic Dissector (Valleylab, Inc., Boulder, CO) after right portal vein ligation. Parenchymal split was commenced in a caudal-to-cranial fashion. The avascular groove between the origin of right and middle hepatic vein was dissected to define the cranial extent of the split. A partial split was defined when parenchymal transection involved 50–80% of the complete transection surface[8] (Fig 1, *A*) and was the preferred approach in the early series of our patients due to learning curve. A complete split was defined as a full parenchymal split until the anterior surface of the retrohepatic inferior vena cava (IVC) was exposed (Fig 1, *B–C*). As the hepatic transection was conducted in a caudal-to-cranial fashion, the parenchymal split continued deep to the right hilar plate, which was then encircled and safeguarded. The right and left caudate were split apart to expose the anterior surface of IVC. An angle instrument then was passed into the avascular plane along the anterior wall of retrohepatic vena cava in order to expedite transection of the retro-hilar plate liver tissues and safeguard the anterior wall of retrohepatic IVC, which was exposed upon completion of split. A low central venous pressure was maintained during parenchymal transection. A leakage test was performed via injection of methylene blue solution into the cystic duct. Patency of right hepatic artery was checked by Doppler ultrasound before wound closure. The right hepatic artery and biliary pedicle were encircled subsequently by a loop of nonabsorbable suture to facilitate future identification in stage II operation. No placement of plastic bag, antiadhesive or drain was necessitated. Postoperative care entailed a tight control of fluid balance and early resumption of oral diet as soon as flatus was passed. Interval computed tomography (CT) with volumetry was performed within 1 week after the stage I procedure. If insufficient FLR hypertrophy was detected, another set of CT volumetry would be performed 4–5 days later followed by stage II procedure when FLR/ESLV $\geq 35\%$.

Evaluation of changes in FLR volume. FLR volumetric changes before and after the stage I procedure were expressed in the form of absolute gain in volume increment and changes in FLR:ESLV ratio. FLR kinetic growth rate was assessed by the change in volume divided by the number of waiting days to CT volumetry (mL/day), and gain in FLR:ESLV ratio divided by the number of waiting days to CT volumetry (FLR/
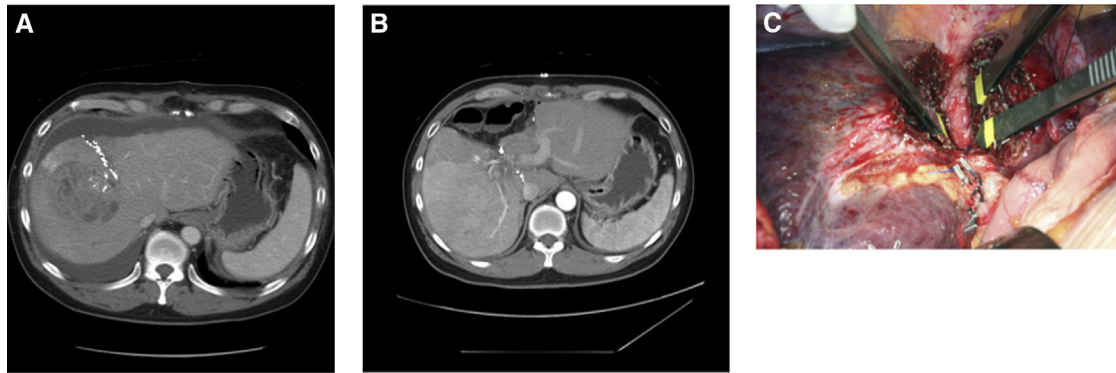
Fig 1. (*A*) A 51-year-old chronic hepatitis B (HBV) carrier with a solitary 11 cm right lobe hepatocellular carcinoma and future liver remnant/estimated standard liver volume ratio of 24.2%. Computed tomography showed a partially split liver in stage I procedure. The hypertrophied left liver may reduce the transverse distance between the 2 transection surfaces, rendering further transection of the remaining tissue plane in stage II more challenging. (*B*) A 50-year-old HBV carrier with a solitary 5 cm right lobe hepatocellular carcinoma. Computed tomography of a completely split liver. (*C*) An operative image of a completely split liver with a future liver remnant/estimated standard liver volume ratio of 19.3%.

ESLV%/day). Liver status was evaluated by histologic examination of the nontumorous liver tissue. Subgroup analysis was performed to assess the effect of ALPPS on the liver status.

Statistical analysis. All continuous variables were expressed in median and compared with Mann-Whitney U test. Categorical variables were compared between groups using χ^2 test. Statistical analysis was conducted by SPSS software package version 20.0 (IBM, Armonk, NY).

RESULTS

Postoperative outcomes between complete split and partial split. Patient demographics were depicted in Table I. The median age of our cohort was 62 years old. No significant difference with regard to liver function was observed between the 2 groups. Although both groups had similar tumor size and number, the serum alpha-fetoprotein (AFP) level was significantly higher in the complete split group. The ratio of patients with complete and partial split was almost 50:50 (complete, $n = 13$; partial, $n = 12$). Table II showed the perioperative outcomes. All patients proceeded to stage II operation (complete split: 7 days versus partial split 10.5 days, $P = .078$) without any inter-stage complications or mortality. There was a trend for increased perioperative blood loss in stage II operation for partial split that was not present for the complete split group. The perioperative blood loss for complete and partial split in stage I was 500 mL and 537.5 mL ($P = .241$), and in stage II was 350 mL and 975 mL ($P = .381$), respectively. The operative

times for complete and partial split in stage I were 385 minutes and 327 minutes ($P = .289$), and in stage II were 156 minutes and 218.5 minutes ($P = .289$), respectively. The overall postoperative morbidity ($\geq$grade 3a) rate after stage II operation was 16% (complete versus partial split: 7.7% vs 25%, $P = .238$) and hospital mortality rate after stage II operation was 8% (complete versus partial split: 0% vs 16.7%, $P = .125$). The causes for the 2 mortalities were multi-organ failure that occurred on postoperative day 14 and 60.

FLR growth profiles between complete split and partial split. Both groups shared similar size of FLR and FLR/ESLV ratio before stage I procedure (Table III). However, a complete split was associated with a much greater FLR growth than partial split (Fig 2). The absolute gain in volume (187.1 mL vs 132.6 mL, $P = .022$) and daily hypertrophy rate (31.2 vs 17.5 mL/day, $P = .022$) were significantly higher in the complete split group resulting in a much greater FLR:ESLV ratio (42.1% vs 33.9%, $P = .019$). Moreover, the complete split group had a much better chance to reach the FLR:ESLV cut-off ratio (ie, 35%) for hepatectomy within 10 days (76.9% vs 33.3%, $P = .024$), which rendered them more likely to receive the stage II operation <14 days after stage I operation (100.0% vs 58.3%, $P = .009$) and resulted in a much shorter hospital stay (17.5 vs 22 days, $P = .016$).

Growth kinetics between chronic hepatitis and cirrhosis. When stratified according to the liver status, our findings showed that complete split induced a more significant FLR growth than partial

Table I. Patient characteristics and tumor status

	Overall (n = 25)	Complete split (C) (n = 13)	Partial split (P) (n = 12)	P value (C versus P)
Age	62 (50–80)	60 (50–80)	64 (51–80)	.354
Sex (M:F)	23:2	11:2	12:0	.48
HBsAg (*n*)	21 (84%)	10 (83.3%)	11 (91.7%)	1.000
HCV	1	1	0	
Steatohepatitis	3	2	1	
Bilirubin (umol/L)	9 (5–49)	9 (5–49)	9 (5–20)	.367
AST (u/L)	48 (19–254)	46 (22–254)	58 (19–98)	.828
Platelet count (10^9/L)	166 (104–457)	207 (113–457)	150 (104–273)	.072
ICG at 15 min	12.8 (7.3–30.2)	11.5 (7.3–30.2)	13.35 (7.6–16.8)	.598
AFP (ng/ml)	131 (2–187,420)	860 (2–187,420)	21 (2–2,164)	.022
Tumor size (cm)	7.5 (2–16)	7.5 (3–16)	7.3 (2–11)	.429
Tumor no.	2 (1 multiple)	2 (1–4)	1 (1 multiple)	.704
Liver status				
Chronic hepatitis	12	7	5	.543
Cirrhosis	13	6	7	

ICG, Indocyanine green; *HBsAg*, hepatitis B surface antigen positive; *HCV*, hepatitis C carrier; *AST*, aspartate aminotransferase; *ICG*, indocyanine green retention rate; *AFP*, alpha-fetoprotein.

Table II. Intraoperative and postoperative outcomes between complete and partial split

	Overall (n = 25)	Complete split (C) (n = 13)	Partial split (P) (n = 12)	P value (C versus P)
Operating time (min)				
Stage I	360.0	385.0	327.0	.289
Stage II	187.0	156.0	218.5	.384
Blood loss (mL)				
First stage	515.0	500.0	537.5	.241
Second stage	700.0	350.0	975.0	.381
Blood transfusion (units)				
First stage	0 (0–0.96)	0 (0–0.6)	0 (0–0.96)	.441
Second stage	0 (0–4.8)	0 (0–1.28)	0 (0–4.8)	.31
Postoperative complications (≥grade 3a)	4 (16%)	1 (adhesive intestinal obstruction)	3 (rebleeding from transection surface, *n* = 1; chronic liver insufficiency, *n* = 1; multiorgan failure, *n* = 1)	.238
Hospital mortality	2 (8%)	0	2	.125
Hospital stay (d)	18 (12–40)	17.5 (12–25)	22 (12–40)	0.016

split in chronic hepatitis in terms of daily hypertrophy rate and gain in FLR:ESLV ratio (Table II). Our findings also showed that ALPPS could induce FLR hypertrophy in cirrhotic livers within a short period of time. However, despite the fact that complete split tended to induce a more rapid FLR hypertrophy than partial split in cirrhosis (hypertrophy rate 32.2 mL/day vs 16.9 mL/day, *P* = .086), the difference was less obvious for cirrhotic livers (FLR/ESLV% increment: 14.8% vs 11.0%, *P* = .668) than for chronic hepatitis (FLR/ESLV% increment: 18.1% vs 11.3%, *P* = .042).

Liver function recovery after stage I and II procedure. Serum bilirubin returned to near normal level before stage II operation for both complete and partial split. However, a complete split tended to induce a higher serum bilirubin level from the first to fourth postoperative day after stage I procedure, but a significantly faster return towards normal serum levels from the second to fifth day after stage II procedure (Fig 3, *A*). A reciprocal phenomenon was observed in the partial split group when the liver function recovered faster after stage I operation but a significantly

Table III. FLR growth kinetics between complete and partial split

	Overall (n = 25)	*Complete split (C)* (n = 13)	*Partial split (P)* (n = 12)	P *value* (C versus P)
FLR				
Before stage I	297.0 (181.9–524.0)	292.0 (181.9–524.0)	307.8 (200.0–410.0)	.870
After stage I	498.3 (316.0–795.7)	519.7 (360.0–795.7)	403.5 (316.0–565.2)	.073
ESLV (mL)	1,239.2 (1,080.8–1,440.3)	1,239.2 (1,080.8–1,440.3)	1,221.9 (1,084.1–1,429.2)	.957
FLR/ESLV%				
Before stage I	24.6 (15.7–37.1)	24.9 (16.7–37.1)	23.6 (15.7–36.5)	.828
After stage I	38.5 (26.7–56.9)	42.1 (32.7–56.9)	33.9 (26.7–50.5)	.019
Gain in volume (mL)	155.2 (67.3–348.4)	187.1 (73.8–348.4)	132.6 (67.3–205.4)	.022
Gain in FLR/ESLV%				
All patients	14.5 (6.7–39.6)	18.1 (6.7–30.7)	11.1 (6.7–39.6)	.064
Chronic hepatitis		18.1 (14.5–27.5)	11.3 (8.3–15.8)	.042
Cirrhosis		14.8 (6.7–30.7)	11.0 (6.7–39.6)	.668
Gain in FLR/ESLV%/ day				
All patients	2.0 (0.5–6.1)	2.6 (0.8–6.1)	1.5 (0.52–2.8)	.001
Chronic hepatitis		3.1 (2.1–4.6)	1.7 (0.7–1.9)	.004
Cirrhosis		2.3 (0.8–6.1)	1.3 (0.5–2.8)	.090
Hypertrophy rate (% volume gain/day)				
All patients	6.0 (1.6–23.4)	11.5 (3.2–23.4)	5.5 (1.6–11.7)	.011
Chronic hepatitis		11.5 (5.9–19.7)	5.7 (3.8–6.0)	.007
Cirrhosis		8.3 (3.2–23.4)	5.4 (1.6–11.7)	.283
No. of patients reaching ≥35% ESLV in 10 d		10 (76.9%)	4 (33.3%)	.024
No. of patients receiving stage II <14 d		13 (100%)	7 (58.3%)	.009

ESLV, Estimated standard liver volume; *FLR*, future liver remnant.

higher serum bilirubin level at the fourth and fifth postoperative day, and a higher serum Aspartate aminotransferase (AST) level from the first to third and sixth postoperative day after stage II operation (Fig 3, *B*).

Left portal flow hemodynamic changes during stage I procedure. Portal flow was measured by intraoperative Doppler ultrasonography routinely for the last 9 patients of our cohorts in order to study the relationship of flow dynamics and FLR hypertrophy (Fig 4). The portal pressure increased substantially from 7.0 mm Hg (4–22 mm Hg) to 16 mm Hg (4–23 mm Hg) after right portal vein ligation (P = .028). The median left portal flow per 100 gm of FLR increased substantially from 76.6 mL/100 gm/min (52–182.9 mL/100 gm/min) to 193.7 mL/100 gm/min (132.2–325.2 mL/100 gm/min) after right portal vein ligation and further increased to 259 mL/100 gm/min (106.6–459.8 mL/100 gm/min) after in situ split (P = .008). The left portal flow then significantly decreased to 80.4 mL/100 gm/min (66.4–192.9

mL/100 gm/min) over a median of 10 days (6–70 days) in stage II operation (P = .021) by autoregulation. Nonetheless, subgroup analysis according to the split completeness was not feasible due to the small sample size.

DISCUSSION

The recent introduction of ALPPS procedure has revolutionized the management of patients with small-for-size FLR contemplating for major hepatectomy.[1,2] However, the initial experience mainly was ascribed to colorectal liver metastasis or other malignant tumors in non-cirrhotic livers,[6,7] and data on its application to HCC arising from background chronic liver diseases is relatively scarce.[11] Recently, we have reported our experience of ALPPS for hepatitis B-related HCC resulting in a 47% volume increment in 7 days.[12] Nonetheless, it seemed that the degree of hypertrophy in chronic liver diseases was not as substantial as in non-cirrhotic livers ranging from
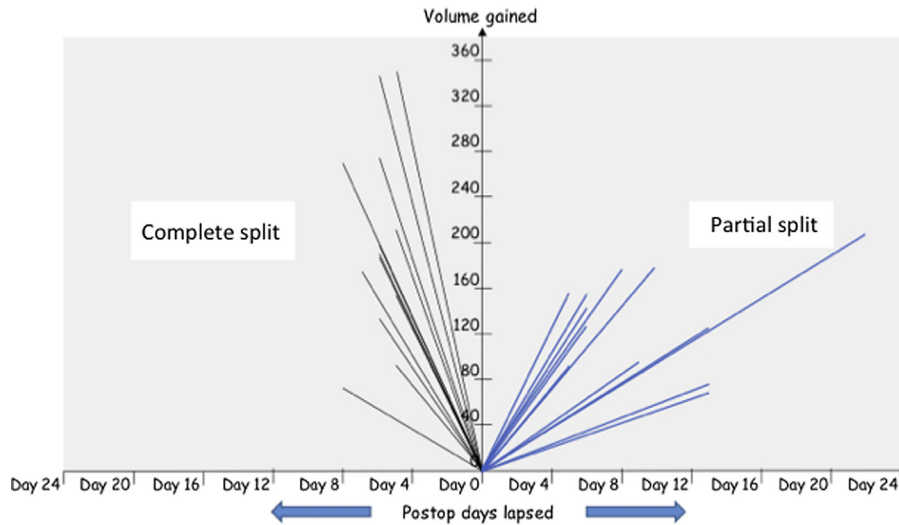
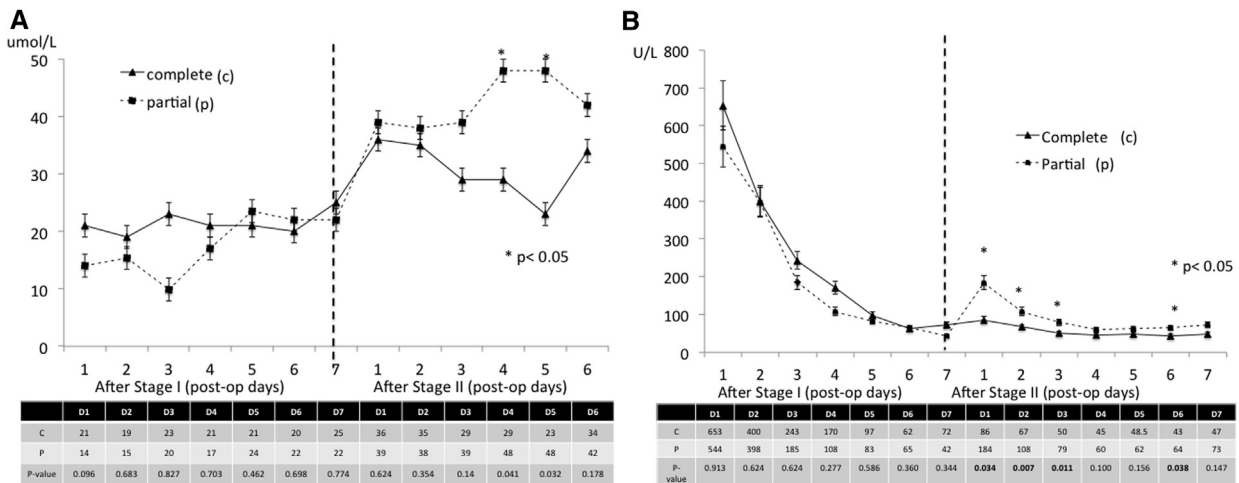**Fig 2.** Growth kinetics between a complete and partial split.

	D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6
C	21	19	23	21	21	20	25	36	35	29	29	23	34
P	14	15	20	17	24	22	22	39	38	39	48	48	42
P-value	0.096	0.683	0.827	0.703	0.462	0.698	0.774	0.624	0.354	0.14	0.041	0.032	0.178

	D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7
C	653	400	243	170	97	62	72	86	67	50	45	48.5	43	47
P	544	398	185	108	83	65	42	184	108	79	60	62	64	73
P-value	0.913	0.624	0.624	0.277	0.586	0.360	0.344	0.034	0.007	0.011	0.100	0.156	0.038	0.147

Fig 3. (*A*) The trend of serum bilirubin during an associating liver partition and portal vein ligation for staged hepatectomy procedure. (*B*) The trend of serum aspartate aminotransferase during an associating liver partition and portal vein ligation for staged hepatectomy procedure.

80–89.7% during a median of 6–7 days.[5,6] In view of the lesser extent of FLR tissue growth in chronic hepatitis compared with that in non-cirrhotic livers, it was imperative to investigate for factors that might affect FLR hypertrophy. From the surgeons' perspectives, it would be pertinent to know if the degree of in situ split would have an impact on FLR hypertrophy, because it would determine the operative strategy for parenchymal transection and the timing of stage II procedure. The findings of our study showed that a complete split induced a more significant FLR hypertrophy than partial split, with a tendency to perform the stage II operation much earlier and a quicker recovery of liver function after stage II operation. Despite the significant FLR growth, a complete split was shown to be as safe as a partial split without increased morbidity and mortality.

A complete split had several merits. The objective for "complete" portal flow diversion from a technical perspective was achieved, and therefore, no uncertainty on the effectiveness of the stage I procedure remained, even when adequate FLR hypertrophy failed to occur. Second, it rendered the stage II operation a much "cleaner" operation without the need for revisiting a semi-transected
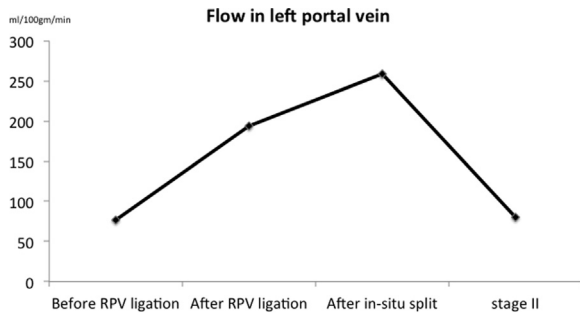
Fig 4. Changes in portal flow dynamics during an associating liver partition and portal vein ligation for staged hepatectomy procedure. *RPV*, Right portal vein.

transection surface and a quicker recovery of liver function after stage II operation as shown by an earlier return of serum bilirubin and aspartate aminotransferase to normal levels. More importantly, a higher FLR volume was attained within a short period of time, and hence improving the safety margin for major hepatectomy against postoperative liver failure while the possible technical challenges from an exceedingly delayed stage II operation was avoided.

It remained unclear if the issue of learning curve would affect the outcome of ALPPS. Partial split, as adopted more frequently in the early phase of our ALPPS program was shown to have a tendency of heavier blood loss in stage II operation and mortalities than complete split. However, given the operative technique for parenchymal transection with ultrasonic dissector in ALPPS was no different from conventional hepatectomy, we thought that it was the bleeding from transection of a recently traumatized incomplete transection surface left from stage I operation rather than immature transection techniques to account for the difference in blood loss between the 2 groups. Besides, the 2 mortalities in partial ALPPS occurred in different eras of the study period and the so the issue of the learning curve affecting the short-term outcome seemed to be unlikely. The learning curve, in our opinion, seemed predominantly to affect the operative strategy to reach a complete split and the decision for the timing of the second operation.

Timing of the second operation, in our opinion, was regarded as an important factor that determined its technical difficulty. It was conceivable that the longer interval for stage II operation, the more technically challenging in terms of adhesiolysis and parenchymal transection will become. One partial split patient in the present cohort even had the 2 partially transection surfaces fused

together when stage II operation was performed at 70 days after stage I operation due to slow FLR hypertrophy. On the other hand, a significantly higher proportion of patients in the complete split group were able to attain adequate FLR hypertrophy and became eligible for stage II operation within 14 days after stage I operation. Hence, a complete split should be considered whenever possible if substantial FLR growth was necessary to ensure postoperative recovery of liver function.

When comparing our findings with the 202 patients reported from the International ALPPS Registry,[6] it was worthwhile to highlight that the FLR growth kinetics of the present cohort corroborated well with those from the registry. Although standardization of operative technique may be difficult in such large cohorts from different centers in the registry, the consistency of findings between our study and Schadde et al[6] suggested it was unlikely that our results regarding split completeness could not be generalized to all patients.

Nonetheless, the rapid FLR hypertrophy induced by the ALPPS procedure was not understood entirely. Redistribution of portal blood flow as well as release of growth factors in response to tissue injury were thought to be the 2 main mechanisms that accounted for the rapid liver regeneration.[8] Based on the notion that portal vein embolization induced FLR hypertrophy via flow augmentation.[13] Flow dynamics was investigated and the same phenomenon in substantial FLR portal flow increment after ALPPS was observed in our study. Whether the degree of portal flow changes correlated with the split completeness remained unclear. However, the difference in the speed of FLR hypertrophy between complete and partial split was less obvious in cirrhosis when compared with chronic hepatitis. From the experience on small-for-size liver grafts in living donor liver transplantation,[14] it was postulated that while FLR portal flow augmentation would be favorable for hypertrophy in chronic hepatitis, this phenomenon might be detrimental to cirrhotic liver tissues as the shear force exerted by the enhanced portal flow on diseased hepatic sinusoids could be less favorable for tissue regeneration in background cirrhosis. As such, an intraoperative left liver biopsy should be necessitated during stage I procedure in order to guide the surgeons to predict the degree of FLR hypertrophy and the timing of the second operation. A longer interval to stage II operation may be desirable for cirrhotic livers to allow sufficient liver hypertrophy and cellular restructuring.[12,15] Nonetheless, the change in portal hemodynamics during ALPPS

and its impact on hypertrophy warranted additional studies for evaluation.

There are several limitations to our study. The findings from such a small sample size required further validation in larger cohort. The nonsignificant difference in morbidity and mortality between the 2 approaches could be related to a type II error. Selection bias also should be considered, as partial split was favored in the early phase of the ALPPS program. Despite the potential benefits, there are situations when a complete split may not be possible due to difficulty in parenchymal transection. For instance, a sizeable tumor in right anterior section stretching the middle hepatic vein could induce significant venous bleeding during in situ split for an extended right hepatectomy. A tumor located close to the IVC or caudate also would render a complete split down to the IVC not feasible. In these situations, a partial split may be preferred, and the likelihood of a slow FLR hypertrophy leading to a delayed stage II operation would be expected.

In conclusion, complete-ALPPS induced more rapid FLR hypertrophy than partial-ALPPS without increased perioperative risk in CLD. As FLR hypertrophy was less substantial for CLD than for normal livers, complete-ALPPS should be preferred for hepatitis-related HCC in order to achieve an optimal outcome.

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