

Associating Liver Partition and Portal Vein Occlusion, Including Venous Congestion, Induction in Rats

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Abstract. *Background/Aim:* Associating liver partition with portal vein occlusion for staged hepatectomy (ALPPS) is a recently developed strategy for inducing rapid hypertrophy of the future liver remnant (FLR). To explore possible mechanisms, we designed the first model of ALPPS with venous congestion (ALPPS+C) in rats. *Materials and Methods:* Rats were assigned randomly to 3 experimental groups: ALPPS, ALPPS+C and sham. Hepatic regeneration rate, Ki-67 and histopathology were assessed at 24 h, 48 h, and 7 days postoperatively. *Results:* Hepatic regeneration rate was much higher for ALPPS+C than for ALPPS at 48 h and 7 days postoperatively ($p < 0.01$). Microscopically, the regenerating liver showed greater hepatocyte density and smaller hepatocyte size in ALPPS+C than in ALPPS ($p < 0.01$ for each). *Conclusion:* Greater hepatic regeneration in ALPPS+C than in ALPPS confirmed that we established a rat model of ALPPS with benefit from venous congestion. Producing a congested area may contribute importantly to rapid FLR hypertrophy during ALPPS.

Liver resection remains the only potentially curative option for patients with primary or secondary liver tumors. Surgeons continue to expand the limits of “resectable” disease by performing extensive liver resections that challenge both the oncologic and technical definitions of resectability. Within this context of extended resection, postoperative liver failure arising from insufficient function of the future liver remnant (FLR) remains a major concern. Multiple strategies for increasing FLR size to reduce risk of postoperative liver failure have been applied.

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Key Words: ALPPS, congestion, liver regeneration, hepatectomy, portal vein occlusion, rats.

Associating liver partition and portal vein occlusion for staged hepatectomy (ALPPS) was recently found to enhance volume increase in the FLR more rapidly than that obtained with previous techniques, such as portal vein embolization (PVE) followed by hepatectomy or classical 2-stage hepatectomy (1).

Until now, exact mechanisms underlying the remarkable regenerative response of the FLR in ALPPS are not disclosed. After the first resection of ALPPS, enhancement of the effect of portal vein (PV) occlusion by interruption of vascular intercommunications during parenchymal transection, rapid atrophy of the completely avascular area after division of portal pedicles during transection as in segment (S) 4 during right (rt.) liver plus S4 resection, as well as producing a significant area with inflammatory injury, are thought to contribute to intense stimulation of liver regeneration (2, 3). However, a completely avascular area could sometimes become a focus of life-threatening sepsis. Another possible mechanism involves the area of congestion induced by interruption of hepatic vein branches during parenchymal partition. The area of venous congestion may develop considerable atrophy comparable to that in the completely ischemic area, resulting in compensatory hypertrophy of the FLR. We speculate that this congested area is possibly critical to FLR hypertrophy in ALPPS. However, little information is available regarding how closely the congested area is related to the increase in FLR volume.

In the present study, we established a model of ALPPS with venous congestion in rats to explore possible mechanisms of the spectacular regenerative response in ALPPS.

Materials and Methods

Animals. Eight-week-old male Wistar rats (Kureo, Tokyo, Japan) were maintained in a room with a 12-h light/dark cycle and given free access to tap water and laboratory food. During all experimental procedures, the animals were treated in accordance with the guidelines outlined in the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (Bethesda, MD, USA).

The experimental protocol has been reviewed and approved by our institutional animal care committee (Protocol Number: 15-025).

Experimental model of operative procedure. Rat livers have 4 lobes: rt. lobe (RL), middle lobe (right middle lobe (RML); and left middle lobe (LML)), left lateral lobe (LLL) and caudate lobe ((CL); Figure 1a). Each lobe is irrigated by its own portal pedicle and drained by its own hepatic veins. In turn, the middle lobe has 2 separate PV branches: a middle lobe right branch and a middle lobe left branch. Based on this anatomy, we developed an ALPPS experimental model that focused on the middle lobe in conducting ALPPS, since the shape and anatomy of the middle lobe are similar to those in human liver (4). All animals were anaesthetized with isoflurane and oxygen (concentration of isoflurane 1.5% at a flow rate of 0.5 l/min). Rats were assigned randomly to 1 of 3 experimental groups: sham operation (SHAM), ALPPS and ALPPS with venous congestion (ALPPS+C).

In SHAM animals, the hepatic artery, PV and bile duct were dissected without ligation, after which the abdomen was closed by a double running suture (Figure 1a). In ALPPS animals, selective PVL was performed on the CL, LLL and LML, as well as RL. After careful dissection of the hepatic artery and bile duct, corresponding portal veins of the lobes were suture-ligated with 6-0 silk. The RML was preserved to regenerate. When the common trunk of the PV of the LLL and LML was ligated, the ischemic line (*i.e.*, the border) emerged immediately to the right of the falciform ligament. Hepatic parenchymal transection then was performed along this ischemic demarcation line using bipolar scissors; these steps were performed successively until the paracaval lobe was reached (Figure 1b) (5). In ALPPS+C animals, PVL and hepatic parenchymal transection were performed as in ALPPS animals. Then, venous congestion was induced by ligation of the left hepatic vein (Figure 1c).

Arterial circulation and biliary duct branches were maintained in all animals. No deaths or serious complications occurred during operation or the subsequent observation period (7 days).

Experimental design and operative procedures. Animals were sacrificed at 24 h, 48 h and 7 days after the operation (6 rats from each group per time point). At that time, liver samples were obtained for histologic assessment. The entire liver was removed and divided into the RML, LML and the other lobes (LLL, RL and CL; OL). After weighing, approximately 200 mg of liver tissues from the RML and LML were fixed in 10% formaldehyde or snap-frozen in liquid nitrogen, with the frozen samples being stored at -80°C until use.

Measurements. To determine the effects of ALPPS and ALPPS+C on liver regeneration, we weighed the RML (WR), LML (WL) and OL (WO) using a laboratory micro-scale at each time point. Weights before surgery (preWR, preWL, and preWO) and those after surgery (sham operation or liver transection and PV ligation with or without vein ligation; postWR, postWL, and postWO) were obtained. The percentage increase or decrease in volume was calculated with the following formulas: $\text{RML}\% = [(\text{postWR} - \text{preWR})/\text{preWR}] \times 100$, $\text{LML}\% = [(\text{postWL} - \text{preWL})/\text{preWL}] \times 100$ or $\text{OL}\% = [(\text{postWO} - \text{preWO})/\text{preWO}] \times 100$.

Histologic examination. Liver tissues were immersion-fixed in 10% formaldehyde, embedded, sectioned and stained with hematoxylin-eosin (H-E). In the RML and LML at 48 h after operation,

sinusoidal narrowing or dilation, hepatocyte density and size of hepatocytes were assessed. With sinusoidal narrowing or dilation in the SHAM model used to define “none”, sinusoidal changes after each procedure were assigned a grade (none, slight, moderate or severe) according to severity of findings (6). The severe grade was defined as positive. Hepatocyte density was determined by counting hepatocytes in 4 high-power fields ($\times 400$, averaged). Size of hepatocytes was determined by measuring 10 hepatocytes in high-power fields ($\times 400$, averaged). For these analyses of density and size, non-commercial image processing software, (ImageJ; <http://imagej.nih.gov/ij/>) (7), was used.

Liver sections from the RML taken at 24 h, 48 h and 7 days after operation were deparaffinized and rehydrated with xylene and a graded ethanol series. Antigen retrieval was performed in 10 mM sodium citrate buffer (pH 6.0) in a microwave oven at 121°C for 30 minutes. Endogenous peroxidase activity was quenched by immersion in 0.3% hydrogen peroxide in methanol for 30 minutes. After non-specific binding sites were blocked with 10% rabbit serum solution for 15 minutes at 37°C , sections were incubated at room temperature for 1 h with a mouse monoclonal anti-rat Ki-67 antibody diluted 1:25 in phosphate-buffered saline (DAKO Japan Co. Ltd., Tokyo, Japan). The sections were then incubated with EnVision anti-mouse (Dakocytomation EnVision1System labeled polymer-HRP anti-mouse), followed by incubation with 3,3'-diaminobenzidine and counterstained with Mayer's hematoxylin. Ki-67-positive hepatocytes were counted in 10 randomly chosen high-power fields and the counts were averaged. All histologic analyses were performed in a blinded fashion with respect to experimental group.

Real-time reverse-transcription polymerase chain reaction (RT-PCR). To determine the effects of ALPPS and ALPPS+C on liver regeneration, we measured cytokines associated with hepatocyte proliferation in the RML. RT-PCR was performed at 48 h after operation in RML tissue to quantify messenger RNA (mRNA) expression for the genes encoding: tumor necrosis factor- α (*Tnf- α*) and interleukin-6 (*Il-6*). Total RNA was isolated from each sample using an RNAspin mini RNA isolation kit (GE Healthcare, Buckinghamshire, UK) and cDNA was synthesized from 2 mg of each total RNA sample using High Capacity RNA-to-DNA kits (Applied Biosystems, Foster City, CA, USA). Each cDNA sample was diluted 4-fold before PCR amplification. Primers were designed using TaqMan Gene Expression Assays (Applied Biosystems). RT-PCR was performed using a 7900HT Fast RT-PCR System (Applied Biosystems) and TaqMan Fast Advanced Master Mix (Applied Biosystems) according to the manufacturer's instructions. The amplification protocol consisted of an initial 10-min denaturation at 95°C , followed by 40 cycles of denaturation at 95°C for 10 sec, annealing at 60°C for 40 sec and extension at 72°C for 10 sec. Degree of expression for each target gene was normalized relative to that for the glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) gene in the same sample. Assays were performed in triplicate. Results are presented as an x-fold induction relative to baseline expression in the SHAM group.

Statistical analysis. Continuous data are expressed as mean (\pm SD) or median (range), and were analyzed using the Mann-Whitney *U*-test. The χ^2 test or Fisher's exact test was used for analysis of categorical variables. A difference was considered significant when the 2-sided *p*-value was below 0.05.

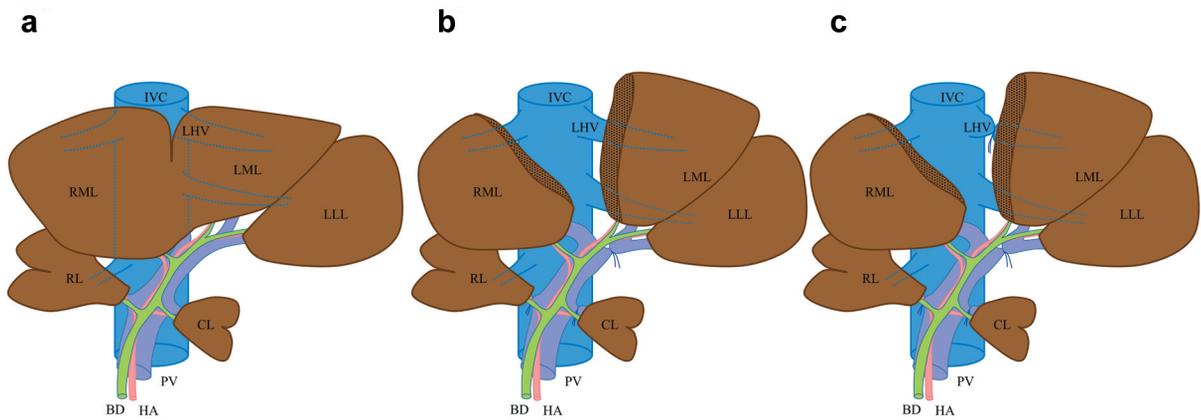


Figure 1. Surgical procedure for ALPPS and for ALPPS with venous congestion models in the rat. Preoperative rat liver anatomy is shown in panel a. In ALPPS (b), PVL is performed at the caudate lobe, left middle and left lateral lobe, as well as right lobe. Note the demarcation between the normally perfused right median lobe and the portal-depleted left median lobe, where transection is performed. In ALPPS with venous congestion (c), the same procedure (PVL and hepatic parenchymal transection) carried out in ALPPS animals is performed, followed by venous congestion induction by ligation of the left hepatic vein. ALPPS, associating liver partition and portal vein occlusion for staged hepatectomy; CL indicates caudate lobe; RML, right middle lobe; LML, left middle lobe; LLL, left lateral lobe; PV, portal vein; IVC, inferior vena cava; HA, hepatic artery; LHV, left hepatic vein.

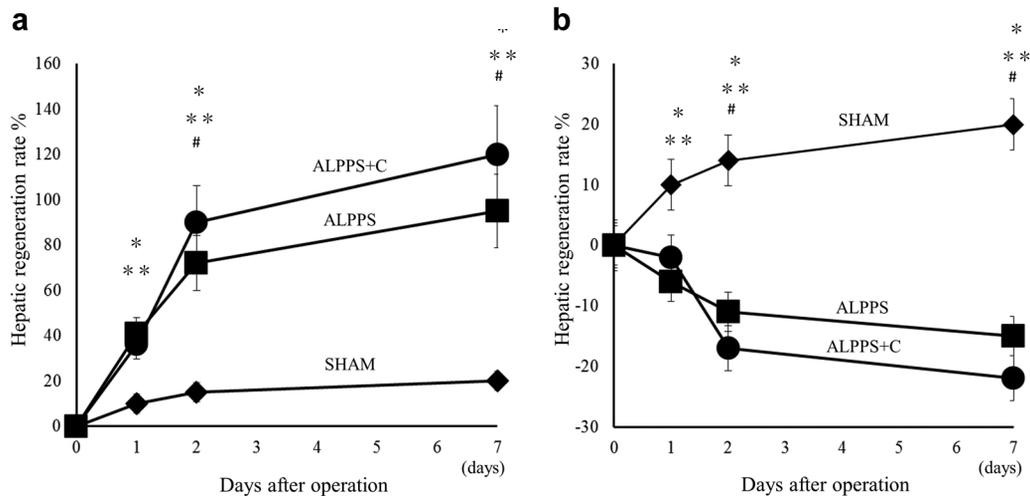


Figure 2. Hepatic regeneration rate of the RML and LML after SHAM, ALPPS and ALPPS+C. The hepatic regeneration rate in ALPPS and ALPPS+C was significantly greater than that of the SHAM group at 1, 2, and 7 days, while the hepatic regeneration rate of ALPPS+C was significantly greater than that of the ALPPS group at 2 and 7 days. Values are means±SD. #*p*<0.05 for the ALPPS+C group vs. the ALPPS group; **p*<0.05 for the ALPPS+C group vs. the SHAM group; ***p*<0.05 for the ALPPS group vs. the SHAM group. ALPPS, associating liver partition and portal vein occlusion for staged hepatectomy; ALPPS+C, ALPPS with venous congestion; RML, right middle lobe; LML, left middle lobe.

Results

Change in liver volume. PreWR, preWL and preWO for each rat were calculated as the animal's weight × 0.69, 0.29 or 1.11% (these 3 percentages, respectively, were the mean percentage of the body weight represented by the RML, LML and OL in 10 normal male Wistar rats weighing 250 to 300 g).

RML weights for both ALPPS and ALPPS+C were clearly higher than for SHAM at all time points. There was no difference in RML volume percentage between the ALPPS group (41.1±8.8%) and the ALPPS+C group (37.4±7.1%) at 24 h after operation. However, compared to the ALPPS group, ALPPS+C induced a greater regeneration response with an increased RML volume percentage at 2 days after

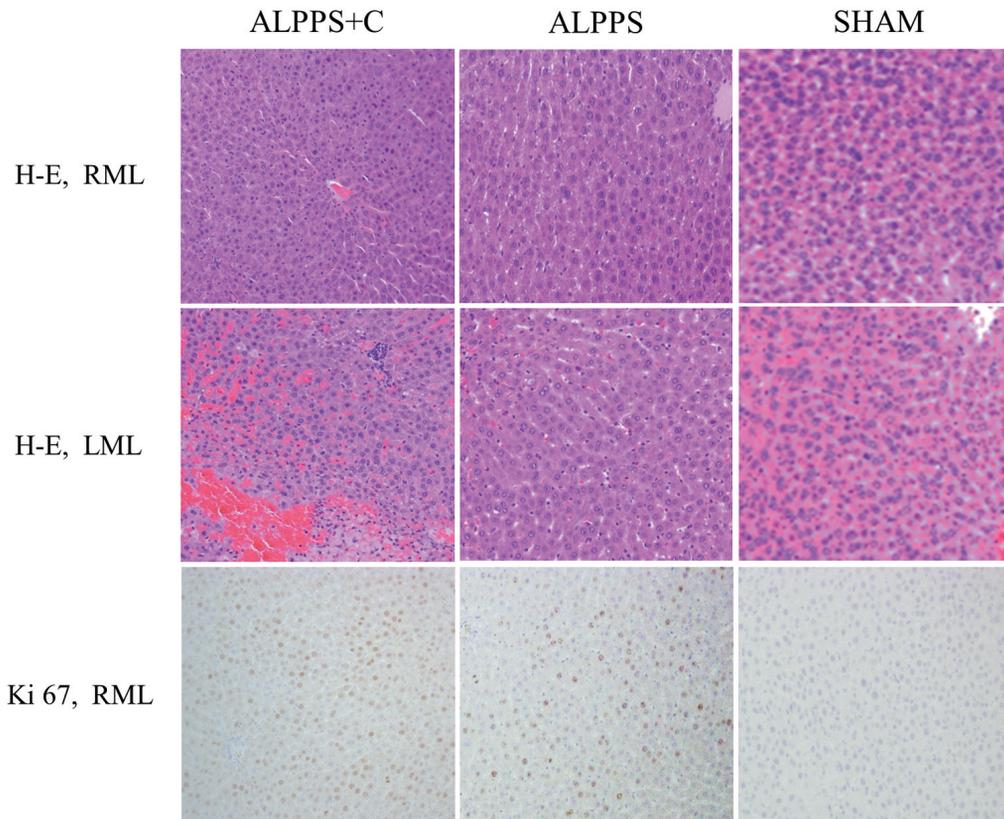


Figure 3. Hematoxylin and eosin (H-E) staining. H-E staining in the RML and LML, as well as Ki-67-positive hepatocytes in the RML, on day 2 after the procedures ($\times 100$). ALPPS, Associating liver partition and portal vein occlusion for staged hepatectomy; ALPPS+C, ALPPS with venous congestion; RML, right middle lobe; LML, left middle lobe.

operation ($90.5 \pm 15.7\%$ vs. $72.4 \pm 11.1\%$, $p < 0.01$) and at 7 days after operation ($120.2 \pm 22.7\%$ vs. $95.5 \pm 17.9\%$, $p < 0.01$) (Figure 2a). Compared to the ALLPS group, ALPPS+C reduced LML volume percentage at 2 days after operation ($-11.1 \pm 2.6\%$ vs. $-17.5 \pm 3.9\%$, $p < 0.05$) and at 7 days after operation ($-22.8 \pm 5.7\%$ vs. $-15.1 \pm 3.2\%$, $p < 0.05$), although no difference in LML volume percentage between the ALPPS group and the ALPPS+C group was observed at 24 h after operation ($-6.2 \pm 2.7\%$ vs. $-2.4 \pm 1.1\%$, $p = 0.548$; Figure 2b). Meanwhile, no significant difference in the OL volume percentage was evident between the 2 groups at all time points ($-14.8 \pm 3.1\%$ vs. $-13.8 \pm 2.9\%$, $p = 0.687$ at 24 hour, $-34.5 \pm 6.9\%$ vs. $-35.4 \pm 7.3\%$, $p = 0.612$ at 2 days and $-40.8 \pm 8.8\%$ vs. $-39.9 \pm 8.4\%$, $p = 0.551$ at 7 days).

Histologic assessment. Representative photomicrographs at 2 days (H-E and Ki-67) are shown in Figure 3. Sinusoidal narrowing in the RML was observed more frequently in ALPPS+C (75%) and ALPPS (50%) than in SHAM (0%; $p = 0.014$ and 0.046 , respectively). Sinusoidal dilation in the

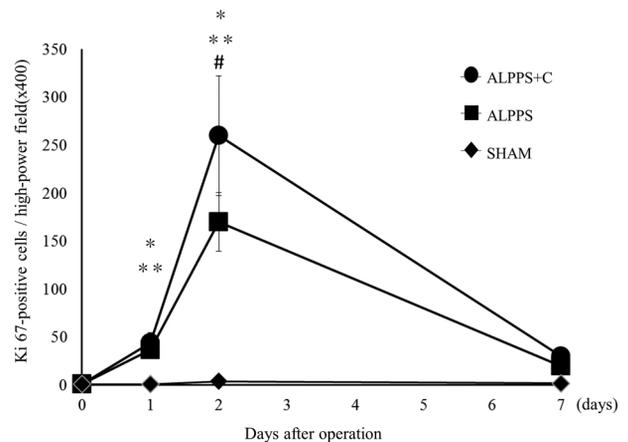


Figure 4. Numbers of Ki-67-positive hepatocytes in RML at all time points. The number of positive hepatocytes per high-power field is presented. # $p < 0.05$ for the ALPPS+C group vs. the ALPPS group; * $p < 0.05$ for the ALPPS+C group vs. the SHAM group; ** $p < 0.05$ for the ALPPS group vs. the SHAM group. ALPPS, associating liver partition and portal vein occlusion for staged hepatectomy; ALPPS+C, ALPPS with venous congestion; RML, right middle lobe.

Table I. Pathologic findings in paraffin-embedded specimens from RML and LML stained with hematoxylin and eosin at 2 days after operation

Findings	ALPPS+C (n=6)	ALPPS (n=6)	SHAM (n=6)
RML			
Narrowing of sinusoids	4 (75%)*	3 (50%)**	0
Hepatocyte density, cells/HPF	236.7±51.2*# (223, 214-355)	176.7±36.2** (167, 139-234)	122.6±19.4 (117, 94-144)
Size of hepatocytes, µm	16.7±2.2*# (15.1, 11.2-20.5)	21.7±4.5** (21.5, 19.3-27.8)	30.9±7.2 (30.1, 27.3-35.8)
LML			
Sinusoidal dilation	6 (100%)*#	1 (16%)	0
Hepatocyte density, cells/HPF	80.7±12.2*# (78, 74-99)	125.1±20.9 (119, 104-144)	119.6±18.7 (107, 99-131)
Size of hepatocytes, µm	24.3±5.1* (24.1, 22.2-29.5)	29.1±6.2 (28.6, 25.3-35.5)	31.5±7.4 (30.8, 28.3-36.8)

Values of continuous variables are means±SD. Medians and ranges are shown in parentheses. Hepatocyte density was determined by counting hepatocytes in 4 high-power fields (×400, averaged). Size of hepatocyte was determined by measuring 10 hepatocytes in high-power fields (×400, averaged). # $p<0.01$, ALPPS+C group vs. ALPPS group; * $p<0.01$, ALPPS+C group vs. SHAM group; ** $p<0.01$, ALPPS group vs. SHAM group. ALPPS, associated liver partition and portal vein ligation for staged hepatectomy; ALPPS+C, ALPPS with venous congestion; RML, right median lobe; LML left median lobe; HPF, high-power field.

LML was observed more frequently in ALPPS+C (100%) than in SHAM (0%; $p<0.01$). Hepatocyte density in the RML was greater and hepatocyte size was smaller in the ALPPS+C group than in the ALPPS group ($p<0.01$ for each). Hepatocyte density in the LML was smaller in the ALPPS+C group than in the ALPPS group ($p<0.01$, Table I). The number of Ki-67-positive hepatocytes per high-power field in the regenerating liver lobe (RML) was greater in the ALPPS+C group than in the ALPPS group at 48 hours after operation (260.3±57.5 vs. 171.1±36.6, $p=0.048$) but no significant change was observed at 24 h (44.2±9.5 vs. 37.6±7.2, $p=0.452$) or at 7 days after operation (30.5±5.9 vs. 20.1±3.4, $p=0.122$; Figure 4).

Up-regulation of mRNA expression for pro-inflammatory cytokines. Il-6 and Tnf- α mRNA were highly up-regulated in the regenerating lobes 48 h after ALPPS group or ALPPS+C group compared to SHAM. In addition, Tnf- α mRNA expression was significantly greater in the ALPPS+C group than in the ALPPS group (4.1±1.2 vs. 1.6±0.6, $p<0.01$; Figure 5).

Discussion

Volume and kinetic growth of the FLR have been reported to increase more dramatically in ALPPS than in classical 2-stage hepatectomy (1, 2, 8, 9). Complete devascularization of an area, such as S4 in rt. liver plus S4 resection, represents a strong stimulus leading to rapid and marked hypertrophy of the FLR during ALPPS (10). However, such

a devascularized ischemic area can become a nidus for life-threatening sepsis (10-13). Therefore, although ALPPS fosters a rapid regenerative response, it raises concern about increased morbidity and mortality (3, 8, 11). To avoid creating such an ischemic area, by complete devascularization, partial transection of parenchyma avoiding dissection of thick portal pedicles (partial ALPPS) (14) or preservation of major portal pedicles that emerge at the plane during parenchymal transection (15) should be considered. However, extent of FLR hypertrophy representing liver regeneration might be smaller when devascularized complete ischemia is avoided.

An alternative stimulus to regeneration involves the area of congestion induced by interruption of hepatic vein branches during parenchymal partition. This area of venous congestion experiences considerable atrophy, resulting in compensatory hypertrophy of the FLR. We believe that producing this congested area is a way to strongly stimulate FLR hypertrophy in ALPPS. In this study, we reproduced some of the physiologic consequences of ALPPS with venous congestion in a rat model. Although tumor clearing in FLR was not added in the model, the model was assumed to ALPPS procedure consisted with parenchymal transection in a plane of main portal fissure and ligation of hepatic vein (*i.e.* middle hepatic vein) within the deportalized liver with several tumor clearings in the FLR.

A greater regeneration response with an increased FLR (RML) volume percentage at 2 and 7 days after surgery was observed in the ALPPS+C group than the ALPPS group. This increase was directly related to a reduction in volume

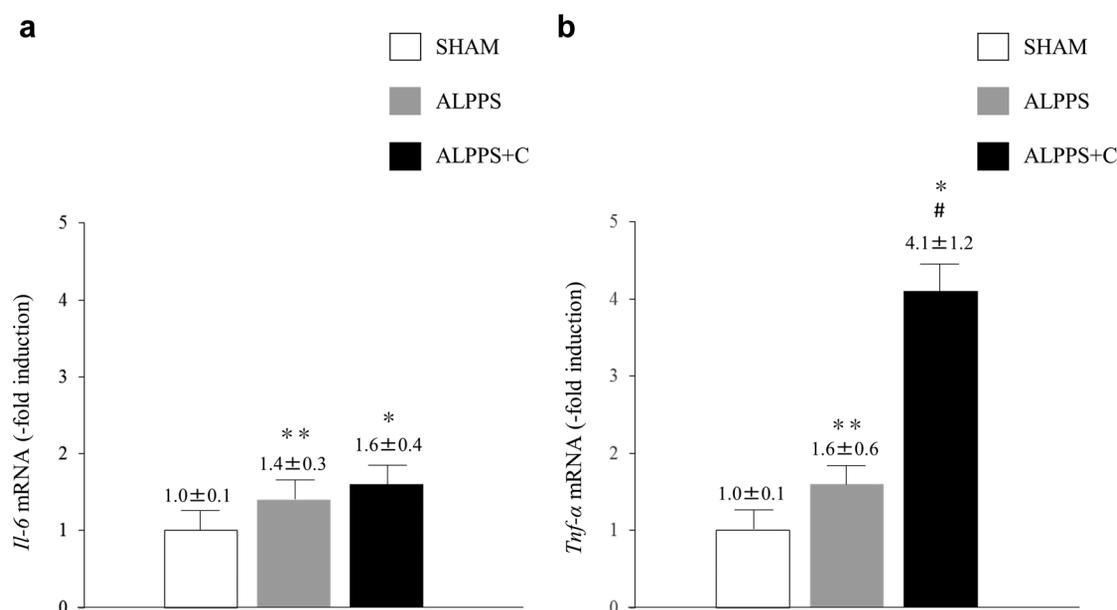


Figure 5. Expression of mRNA for cytokines in RML tissue at 2 days after the procedures. Relative mRNA expression of *Il-6* and *Tnf-α*, determined by RT-PCR, is given as multiples of expression in sham-operation livers. # $p < 0.05$ for the ALPPS+C group vs. the ALPPS group; * $p < 0.05$ for the ALPPS+C group vs. the SHAM group; ** $p < 0.05$ for the ALPPS group vs. the SHAM group. ALPPS, associating liver partition and portal vein occlusion for staged hepatectomy; ALPPS+C, ALPPS with venous congestion; RML, right middle lobe; LML, left middle lobe; RT-PCR, real-time reverse-transcription polymerase chain reaction.

of the liver portion that underwent venous congestion (LML). PVL blocks portal flow to the congested lobe, with blood flow in the congested lobe being maintained only by hepatic arterial flow. Further, hepatic arterial buffering response, commonly induced by PV occlusion (16), was regulated by hepatic vein ligation in the ALPPS+C as a gradual decrease of arterial blood flow might contribute to produce more atrophy than the original ALPPS. Producing congestion-atrophy in the deportalized liver by interruption of draining veins can, therefore, be an effective way to induce FLR hypertrophy after the first procedure in ALPPS.

Meanwhile, in the FLR (RML), H-E-stained sections showed greater hepatocyte density and smaller hepatocyte size in the ALPPS+C group than in the ALPPS group. Narrowing of sinusoidal spaces by increased numbers of hepatocytes reflected cell proliferation in the ALPPS+C group. A higher Ki-67 labeling index in ALPPS+C than in ALPPS is consistent with greater hepatocyte proliferation in the ALPPS+C group, representing greater compensatory hypertrophy of the FLR.

Tnf-α mRNA expression in the regenerative lobe (RML) showed greater up-regulation in the ALPPS+C group than in the ALPPS group. *Tnf-α* has been reported to be a likely primer of hepatocyte proliferation that increases post-resection liver regeneration (17). This suggests that venous congestion could promote the initiation of liver regeneration through up-

regulating this pro-inflammatory cytokine, in addition to the interaction between atrophy in the congested zone and compensative hypertrophy in the FLR. As previously reported, liver regeneration is a process that involves multiple intracellular events that show complex interactions with cytokines and growth factors (18, 19). This possibility is consistent with the results of our study, which indicated that the mRNA expression for *Tnf-α* and *Il-6* in regenerating liver tissues was higher in both the ALPPS and the ALPPS+C group than in the SHAM group. Among proposed factors influencing early future liver remnant (RML) regeneration, the present results support our hypothesis that an area of congestion in the deportalized liver provides an important regenerative stimulus during ALPPS+C treatment.

In conclusion, this study provides important new information concerning the significance of the congested area produced in the modified ALPPS procedure for stimulating volumetric recovery. Sepsis originating in the congested area produced by middle hepatic vein interruption in the implanted right liver graft after live donor liver transplantation has been reported (20). However, there have been no reports that the congested area within deportalized liver induces fatal sepsis. Therefore, we believe that this area of congestion is clinically important for successful ALPPS.

Financial Disclosures

The Authors have no financial disclosures.

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Received March 23, 2017

Revised April 25, 2017

Accepted April 26, 2017