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Research Article

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Is Faster Always Better? A Comparative Study between Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy vs Classic Portal Vein Ligation for Two-stage Hepatectomy in Rats

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Abstract

Background: The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been proposed to avoid liver failure after major liver resection. We thought to define the mechanism by which ALPPS enlarges liver remnant and if it is really more effective than classic two-stage hepatectomy.

Objectives: To compare if ALPPS is superior to portal vein ligation (PVL) to increase liver volume.

Methods: Sprague-Dawley rats were divided in sham, ALPPS and PVL groups. Animal weight, volumetric assessment of the liver middle lobe, mitotic index, binucleate cells index, Ki-67 index and histological evaluation were done to assess liver regeneration.

Results: No differences were found in liver volume after both procedures. (48, 65 ± 15 %, 43, 97 ± 13, 4 % and 155 ± 40 %; on 3, 7, 14 POD, for ALPPS and PVL) The liver volume/ animal weight ratios were similar in both groups. Ki67, binucleate cells and mitotic index were significantly higher in PVL and ALPPS compared with sham group, only on 3 postoperative day, (p=0.01), but were not different at the end of follow up (14 days). The histological liver damage score was slightly higher in ALPPS.

Conclusion: Both procedures are useful to achieve increases in future remnant liver volume. There is no difference in the final volume reached; observing that the increase achieved by ALPPS is faster.

Keywords: ALPPS; Portal vein ligation; Two staged hepatectomy; Liver regeneration

Introduction

The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been proposed as a new approach to avoid liver failure after major liver resection. In this technique, in addition to portal vein ligation (PVL), hepatic parenchyma transection is performed between the liver that will be resected, and the future remnant liver, followed by the hepatectomy within 1-2 weeks. ALPPS was introduced by Schnitzbauer A. in Germany and it has spread worldwide in spite of the lack of scientific evidence to support it [1].

The main advantage of ALPPS procedure is to induce rapid regeneration of the remnant liver, allowing the performance of the second operation in a short period of time. The waiting time between the first and second stages after PVE can be used to assess the biological behavior of liver metastasis. If tumor progresses or new metastases appear, perhaps this patient will not benefit from the second hepatectomy [2-4].

The mechanism by which ALPPS produces accelerated enlargement of the remnant liver has not been completely clarified. The increase in portal flow onto the remnant liver is considered one of the main stimuli for liver hypertrophy (blood flow theory) in addition to the so called ¨humoral theory¨ which proposed that the increased metabolic demand and endogenous mediators are responsible for inducing liver regeneration [5,6].

Like many surgical innovations, ALPPS was established as a clinical practice without having a basic research study to support it. In spite of that, it has been reported that ALPPS is in the third stage of the 5 developmental stages of the IDEAL concept for a new surgical procedure (IDEAL: idea-development-exploration-assessment- long term study). It is necessary to clarify that the steps did not follow the proposed IDEAL chronology, because ALPPS, is not based on animal models before being applied in the clinical field [7,8].

We published the first experimental animal model of ALPPS in rats two years after the first clinical use of ALPPS. In this study, we proved the feasibility of reproducing ALPPS procedure in an experimental model [9]. this effort was followed by others, however, there are few studies assessing how the ALPPS procedure can induce accelerated liver regeneration. But none of the published studies evaluated the liver volume beyond the first week after ALPPS [10-12].

That thought brings up a new open question, how long should we wait between the first and second step of ALPPS? Should we hurry up or should we wait longer to complete the second step? The decision to perform one or the other should be made as a rigid protocol, or should we consider performing them as two valid surgical approaches which should be applied based on each patient's associated risk factors?. The aim of this study was to compare the portal vein ligation *vs* ALPPS in a rat model, evaluating what happened to the future liver remnant (FLR) beyond the first week.

Materials and Methods

Animals

All animals were manipulated according to international standards of care for experimental animals. Sprague-Dawley rats (body weight, 270-310 g) were used. The decision to use the right middle lobe as FLR was made prior to start the experiment. When we performed this model, nobody had described an experimental ALPPS/PVL model yet. It was for the same reason that we chose rats

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for this ALPPS/PVL model, in addition to the fact that our unit had extensive experience in carrying out different experimental models in rats. They were kept in animal rooms at Favaloro University with temperature and lighting controls and they had access to rat chow and water, before and after the experiments. After 12 hours of fasting, they were anesthetized with mixture inhalation of isofluorane and oxygen (1.5%/0.5 l/ min) and were maintained with a vaporizer Isovap Model 2000, (HERLAM, Buenos Aires, Argentina). Morphine (2.5 mg/kg) was administered subcutaneously to achieve the postoperative analgesia.

Experimental design

Animals were randomly assigned to different experimental groups: Sham group (n=6), ALPPS group (n=18) and PVL group (n=18). To assess the mechanisms of liver hypertrophy In ALPPS and PVL groups, animals were sacrificed (n 6) on 3, 7, and 14 post-operative day (POD).

The step 1 of the two-staged hepatectomy was performed as described, but the step 2 was not performed. The reason for not performing the step 2 was to assess the liver regeneration capability beyond the first week, avoiding the peri-operative mortality related to the step 2. The research protocol was approved by the ethical committee and the internal review board (N DCT 0147-12).

Surgical procedure of portal vein ligation: Under sterile conditions, the liver was mobilized after a midline laparotomy. Thereafter, we performed the PVL of caudate lobe, left lateral lobe and right hepatic lobe with 7-0 silk (as previously described) [9]. The middle lobe of liver rats is the lobe that we aim to use as it is similar to human liver, because it has two main portal vein branches determining two sectors: left side (LSML) and right sector of middle lobe (RSML). In this group, the left portal branch was ligated maintaining the flow in the right portal branch. In all cases, great care was taken to avoid the hepatic artery and bile duct injuries. Finally, the incision was closed.

Surgical procedure of ALPPS: Surgical procedure of ALPPS was performed as described above. In brief, PVL in the caudate, left lateral lobe, right and branch of the middle lobes were performed, as in the PVL group. Preserving the middle lobe as the main one to be studied; thereafter, the left portal branch was ligated, and once the ischemic demarcation line was identified, on the surface of the middle lobe, transection of the liver parenchyma was carried out using U-stitches of 7-0 polypropylene, and bipolar electro cautery. Liver parenchyma was transected during parenchyma transection (Figure 1). In all cases, great care was taken to avoid the hepatic artery and bile duct injuries. Finally, the incision was closed.

Sham-operated control group: In the sham group, a midline incision without portal vein ligation or parenchyma transection was done. After 30 minutes, the incision was closed.

Biochemical assay: On the first POD, a blood sample was taken by puncture of the retro-ocular venous plexus. At the time of sacrifice, blood samples were obtained from the inferior vena cava. The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin (TB) were measured using standard laboratory methods.

Animal, middle lobe weight and volumetric assessment of the liver middle lobe: All animals were weighed on the first POD and on the same day of sacrifice. Next, the middle lobe was harvested and weighed with a laboratory micro-scale balance. After PVL, length, width and thickness of the liver middle lobe, following ischemic demarcation line, were measured. In ALPPS group measurement was performed before the parenchyma transection. The liver regeneration was estimated by changes on liver weight or volume [13].

Initial volume and final volume (day of sacrifice) were calculated using the following formula: (length x width x thickness) × 0.5 (cm^3).

Differences between the initial volume of the RSML and the final volume were expressed as percentages ((Final volume - initial volume /initial volume) × 100).

Histological examination: After sacrifice, the middle lobe (ML) was harvested. Liver tissues were fixed in 10% formaldehyde, paraffin-embedded, sectioned at 4 µm and stained with haematoxylin and eosin (H&E). Histological evaluation of ML was executed analyzing the hepatocellular damage using a modified semi-quantitative scoring system described by Dahmen [14]. The modified scoring system considers the hepatocellular necrosis (focal and confluent), eosinophilic infiltrate, sinusoidal damage, activated Kupffer cells, and cholestasis.

Measurement of hepatic regeneration by Ki-67: After formalin-fixation and paraffin-embedding, tissue specimen was cut at 4 µm and sections were mounted on Superfrost Plus microscope slides (BioGenex, Fremont, CA, USA). The tissue sections were then incubated at 60°C for 1 h, deparaffinized, rehydrated and antigen retrieval was performed in citrate buffer pH 6.0 (BioGenex) by microwave heating for 15 min. Peroxide blocking solution (BioGenex) was applied on the sections for 15 min and after washing, they were incubated with normal goat serum blocking solution for 15 min (BioGenex). Rabbit anti-Ki-67 (SP6) (Novus Biologicals, Littleton, CO, USA) was used as primary antibody, which was incubated for 1 h at room temperature followed by the use of multilink-HRP detection system (BioGenex) with 3-amino-9-ethylcarbazol (AEC). Finally, counterstaining with hematoxylin was done and sections were mounted with aqueous mounting media (BioGenex). We determined a liver regeneration index (LRI) by calculating percentage of positive Ki-67 cells over total cells in 15 high power fields.

Mitotic index and binucleate cells in RSML: Samples stained with H&E were used to calculate the mitotic index (MI) and to count the bi nucleate cells (BNC). The MI and BNC for liver tissue were

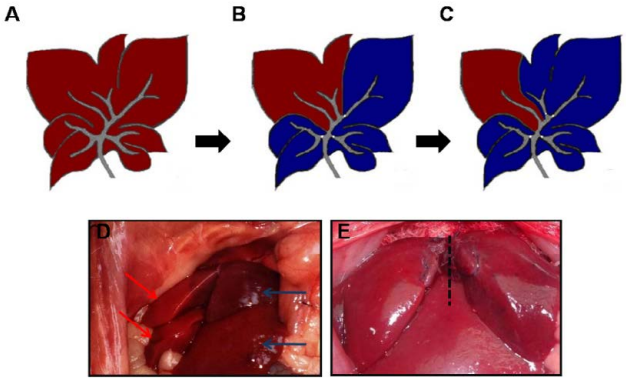

Figure 1: Schematic representation of rat liver (A). PVL procedure in the caudate, right and left lateral lobes (B). PVL of the left branch of the middle lobe (C).
Macroscopic appearance of the lobes under PVL (blue arrows) and normal irrigation lobes (red arrow) (D). Liver macroscopic aspect after complete ALPPS procedure (E).

estimated by counting the number of cells undergoing mitosis in 15 high-power fields. The MI and BNC were expressed as percentages of cells undergoing mitosis.

Statistical analysis: The results are expressed as mean ± standard deviation (SD). Student's t test, analysis of variance (ANOVA) and Bonferroni post-hoc test were used for unpaired measurements. A significant difference was considered when p was<0.05 (SPSS 7.0.1 SPSS Inc., Chicago, IL).

Results

42 animals were included in the study, 6 in the sham group and 18 in each study group. There were neither complication nor mortality related to the parenchyma transection in ALPPS group; no rats had ascites at sacrifice in any of the study groups. The transaminases and bilirubin values are summarized in Table 1.

Volumetric assessment of the middle lobe

No significant differences were found in terms of percentages of increase in RSML volume, being for PVL group on 3, 7, 14 POD of 48,65 ± 15 %, 43,97 ± 13,4 % and 155 ± 40 %; whereas, for ALPPS group were: 29,5 ± 5 %, 81,18 ± 28,7 % and 106,5 ± 41,3 %. However, it can be seen that the percentage of RSML volume was higher on 7 POD in ALPPS, but on 14 POD the percentage reached by livers in the PVL group was more significant than the observed in the ALPPS group (Figure 2A).

The RSML/ animal weight ratios were as follows: 1.6 ± 0.4 % vs. 1.5 ± 0.4 %, p=1 on 3 POD; 1.7 ± 0.5 % vs. 2.1 ± 0.6 %, p=0.39 on 7 POD and 2.4 ± 0.8 vs. 2.2 ± 0.8 %, p=0.17 on 14 POD for PVL and ALPPS groups, respectively. No significant differences were observed between groups (Figure 2B).

Analysis of liver regeneration by Ki-67

Liver regeneration was calculated applying the LRI as it was described in materials and methods. We detected a significantly higher LRI in both PVL and ALPPS groups compared to the sham group on 3 POD (34 ± 3 %, 38 ± 4 % and 1 ± 0.3 % respectively, p=0.001. On 7 POD, LRI was 2 ± 0.3 % in sham and 4 ± 1 % in PVL, and 5 ± 1 % in ALPPS, p 1. On 14 POD results were: 2.4 ± 2.4 % (sham) vs. 2 ± 0.5 % (PVL) and 5 ± 3 % (ALPPS), p= 0.197 (Figure 3).

Mitotic index and binucleate cells in RSML

The mean MI on 3 POD was significantly higher in ALPPS (0.3 ± 0.1 %) and PVL (0.3 ± 0.2 %) groups when compared to sham group (0.03 ± 0.01 %) p=0.01 (Figure 4).

Although the MI in ALPPS (0.05 ± 0.09 %) and PVL (0.04 ± 0.03%) groups tended to be higher than in sham group (0.01 ± 0.01%), on 7 POD, the differences were not significant. Similar results were observed on 14 POD (0.02 ± 0.03% (ALPPS), 0.01 ± 0.01% (PVL), and 0.06 ± 0.03% for sham group, p =1On 3 POD a significantly higher percentage of BNC was observed in ALPPS group (1.5 ± 0.3 %) as well as in PVL (1.6 ± 0.2%) group, compared to sham group (0.7 ± 0.1 %) p: 0.01. Nevertheless, the difference lost significance on 7 POD (1.1 ± 0.3 %, 0.8 ± 0.2 % and 0.8 ± 0,2 %) and on 14 POD (0.5 ± 0.3 %, 0.6 ± 0.3 % and 1.3 ± 0.1 %) in ALPPS, PVL, and sham groups, p=1.

Histological examination

The liver damage score was slightly higher in ALPPS group than in PVL group on 3 POD (Figure 5). More damage was observed on 7 POD and on 14 POD in ALPPS and PVL groups, but without significant difference.

Discussion

The need to obtain and adequate FLR to sustain life after a major liver resection has led to develop a novel surgical technique named the ALPPS approach. Currently, there is a general discussion in the field whether ALPPS procedure is superior to classic two-staged hepatectomy in patients with small FLR. This discussion has led to new publications with systematic reviews, meta-analysis, letters to the

Table 1: The transaminases and bilirubin values are summarized.

		PVL	ALPPS	PValue
	POD	Mean ± SD	Mean ± SD	
	1	660 ± 360	1422 ± 808	0.01
AST(UI/ml)	3	275 ± 92	280 ± 113	0.86
	7	226 ± 135	214 ± 79	0.75
	14	240 ± 181	164 ± 71	0.22
ALT(UI/ml)	1	334 ± 207	888 ± 700	0.01
	3	130 ± 58	114 ± 69	0.80
	7	67 ± 44	64 ± 26	0.10
	14	170 ± 189	64 ± 32	0.31
TB(md/ml)	1	0.10 ± 0	0.10 ± 0.02	0.31
	3	0.16 ± 0.05	0.10 ± 0.06	0.41
	7	0.10 ± 0.00	0.10 ± 0.04	0.03
	14	0.15 ± 0.05	0.10 ± 0.05	1.00

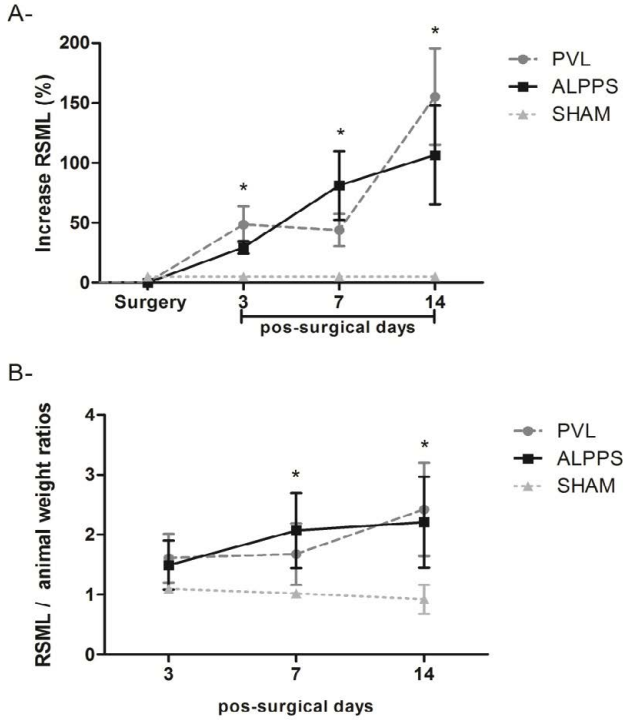

Figure 2A: Percentage of increase of RSML. Note the increased liver volumes after PVL or ALPPS on 3, 7 and 14 POD vs sham group (*p <0,05) . There were no statistical differences when compared PVL vs ALPPS. PVL **(B)**Weight ratio of RSML. There were no statistical differences in Weight ratio of RSML when compared PVL vs ALPPS. Statistical differences were observed between both groups vs sham group on 7 and 14 POD (*p<0,05) . PVL: Portal Vein Ligation Group, ALPPS: ALPPS Group, POD: Postoperative days.

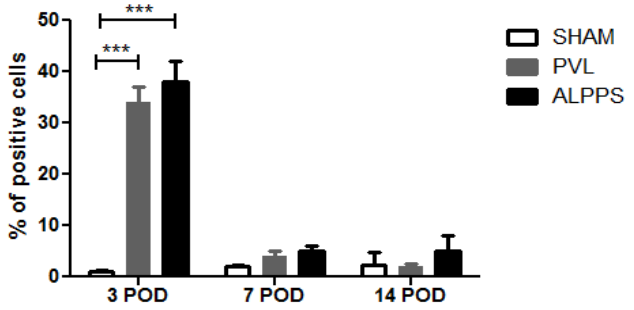

Figure 3: Quantification of LRI by Ki-67 in PVL and ALPPS groups

Note: the percentage of positive cells in both groups on 3 POD. Significant differences was observed in Sham group vs PVL and ALPPS groups (*p<0.001), in the following days decreases significantly and statistical diferences between groups were not observed.

LRI: Liver regeneration index, PVL: Portal Vein Ligation Group, ALPPS: ALPPS Group, POD: Postoperative days.

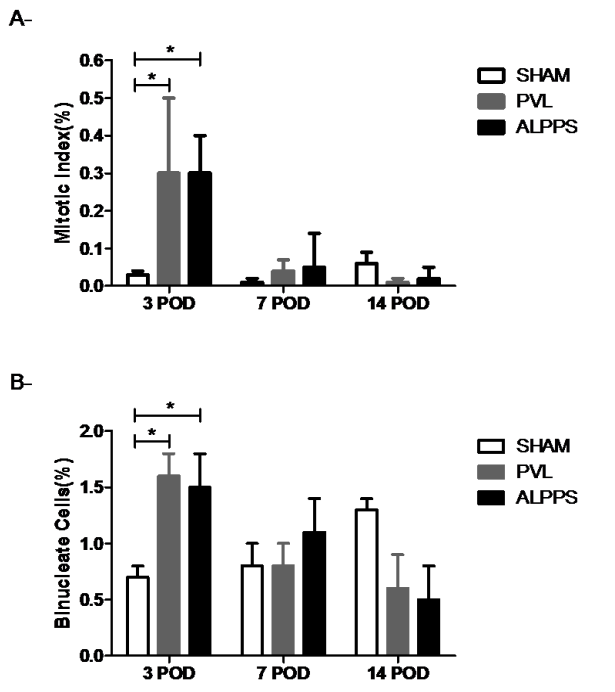

Figure 4: Mitotic Index (top graphic) and Binucleate Cells (below graphic) of RSML in PVL and ALPPS groups.

PVL: Portal Vein Ligation Group, ALPPS: ALPPS Group, POD: Postoperative days.

editors, most of them trying to look for safety, in order to evaluate how to reduce both peri-operative mortality and oncological progression [4,15-17]. One of the criticisms reported after the massive application of ALPPS was the lack of experimental studies, carried out to build a scientific background to understand the mechanisms behind it. In this manuscript, we present an experimental model for Step I of ALPPS and PVL in rats. In contrast to the technique used by Schlegel et al. in this model we performed exclusively Step I of ALPPS.10 The main reason was to assess what happened beyond the first week, especially in ALPPS group. Completion of the second step might have increased the risk of perioperative mortality of the animal affecting the sample size for analysis. Regarding liver volume, we observed that ALPPS increased FLR faster than PVL. However, after 14 days, the liver volume was similar in both groups [11,18,19]. None of these published papers tells us the results regarding FLR, beyond the first week. This was one of the goals of our paper, to show that after the first week, the growth is greater in PVL, achieving equal FLR.

Similar results can be seen when Ki-67 positive hepatocytes are analyzed. There was a significant increase in the number of Ki-67 positive cells during the first three POD in ALPPS and PVL groups, whereas, on 7 and 14 POD, it was similar in all groups. In terms of liver regeneration, hepatocytes are the first hepatic cells to proliferate after partial hepatectomy and the peak of DNA synthesis is between 24 and 48 hours [20,21]. During the first three days the peak of Ki-67 activation occurs, decreasing later [19,22]. These findings suggest that all procedures are associated with the ischaemic damage and increase in portal flow, will produce a stimulation and activation of hepatocytes. Chan et al., in clinical setting, showed an up-regulation of hepatic cell proliferation and growth factor production in biopsies of the remnant liver on the first and second surgery. They detected an increase in positive cells from 1% to 20% for Ki-67 and from 10% to 100% for VEGF in liver biopsies [23,24].

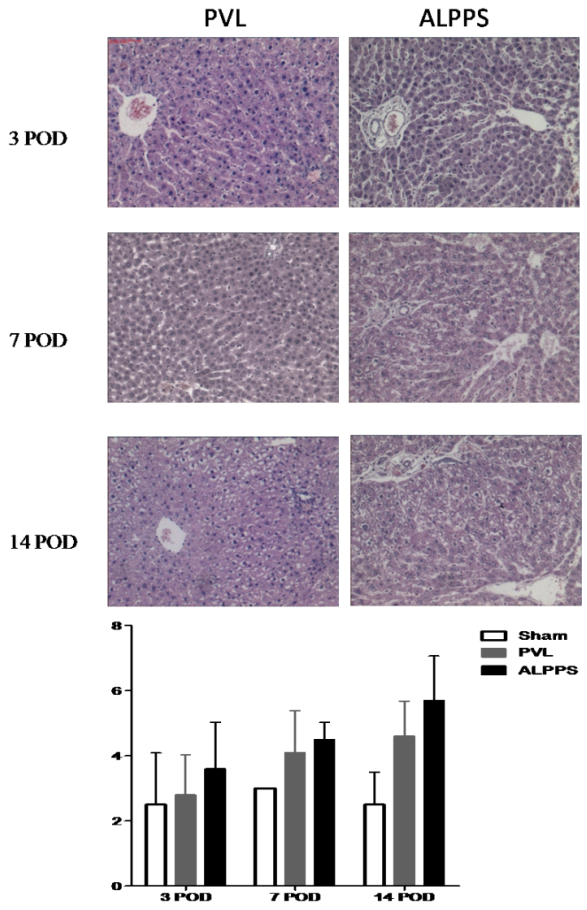

Figure 5: Histological Examination performed by H&E 200 X and modified Daghmen Score. There were no statistical differences between groups.

PVL: Portal Vein Ligation Group, ALPPS: ALPPS Group, POD: Postoperative days

An explanation for the high postoperative morbidity in ALPPS patients might be the presence of small for size syndrome, characterized by liver failure including different degrees of coagulopathy, ascites, cholestasis and encephalopathy. Tanaka and colleagues described that the presence of portal hypertension is responsible for a transient small for size syndrome [25]. There are no typical histopathologic criteria to identify small for size syndrome. In our study, histological liver damage was analyzed as it was proposed by Dahmen et al. [14] Samples were analyzed concerning hepatocellular necrosis, eosinophilic globuli, sinusoidal damage, activated Kupffer cells and cholestasis due to the fact that there are no clear histopathologic criteria to assess liver damage after PVL or ALPPS. We observed that liver damage was similar between ALPPS and PVL and all of them are signs of portal hyperperfusion. In liver samples from rats with ALPPS, there was edema in the sinusoidal space on 3 POD. It might have been due to the increase in portal flow since, over the following days, the edema decreased. Matsuo published the histologyc features after step II in ALPPS and portal vein embolization (PVE) in humans. In that paper the kinetic growth in FLR for ALPPS was significantly major than PVE (14,4 ml/d vs 3,6 ml/d). However, in ALPPS, regenerative hepatocytes were less mature compared with PVE.22. This data demonstrates that faster does not mean more functional.

Schlegel A. et al. published a model of ALPPS in mice, showing that ALPPS is superior to PVL to induce hypertrophy of the liver remnant [10]. They demonstrated that, the presence of circulating proliferating factors related to liver transection could contribute to rapid hepatic growth, which is another factor we are in process to elucidate. A possible cause of this may be that our experimental design extends for 14 POD, whereas, Schlegel for just 7 POD. Another possibility is, regarding the sample size, it has been underpowered to detect meaningful differences between ALPPS and PVL groups or generate a type 1 statistical error. We agree with Schlegel et al, there must be circulatory growth factors that are responsible for liver regeneration (as in any process where Ischemia reperfusion is involved).

We conquer that in ALPPS, the transection of the liver parenchyma might add a contributing factor to the rapid growth, because part of the portal inflow might be redirected within the no ligated lobe, causing some degree of liver "swelling". The same concept applies in several cases of hepatic resections (after liver donation and resections), when the portal flow is redirected. The total portal flow increases throughout a reduced liver parenchyma and consequently, the liver size might be forced to grow as a result of a relative flow increase. Croome et al. have demonstrated that kinetic growth rates in ALPPS and living donors are similar and correlate directly to the size of the FLR [26].

In conclusion, our findings support the existence of similar mechanisms of liver regeneration between classic two stage hepatectomy and ALPPS. FLR growth is faster in ALPPS than classic two stage hepatectomy. However, after the first week, the classic two stage hepatectomy reaches the degree of hypertrophy obtained by ALPPS. That study proves, in an experimental model, that both techniques are useful to achieve the hypertrophy of the FLR, therefore, faster is not always better. Surgeons now can understand better what happens after ALPPS; therefore, based on the best oncological recommendations (type of tumor, response to chemotherapy) and the recently described risk factors (age>than 60 years), they can choose the appropriate technique (ALPPS or PVL) for each patient [27].

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