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Establishment of a novel rat model of different degrees of portal vein stenosis following 70% partial hepatectomy

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Abstract: Liver transplantation may fail due to complications of insufficient portal vein (PV) flow such as portal vein stenosis (PVS). Therefore, establishing a model to explore the effect of PV flow on liver regeneration is crucial and essential. Rats were randomly divided into 6 groups: sham operation rats group; 70% partial hepatectomy (PH) group (group A); PVS groups with mild, moderate, or severe stenosis (group B–D) and portal vein ligation (PVL) group. PVS was produced by ligating PV with parallelly placed needles of different gauges. Ultrasound was performed to validate the stenosis ratio (SR) and velocity ratio (VR) at the prestenotic and stenotic site. Rats were sacrificed on day 1, 3, 7, and 14 after surgery, and liver regeneration rate (LRR) was calculated. We successfully established rat models of different degrees of PVS following 70%PH in 72 rats. The SRs of each PVS group were $44.8 \pm 5.23\%$, $59.3 \pm 4.07\%$ and $69.5 \pm 2.17\%$, which showed no statistical differences compared with those measured by stenosis ratio measured by ultrasound. The survival rate in groups A–D were 100%, 83.3%, 66.7% and 50% respectively. Differences were demonstrated between groups A and C, as well as groups A and D (both $P < 0.05$). Moreover, LRR negatively correlated with SR_u and VR, and the correlation coefficients were -0.534 and -0.522 , respectively. The rat model we established has the potential to be applied in most conditions of liver regeneration with reduced PV inflow, and it provides a foundation for further exploring the relationship between PV hemodynamic changes and liver regeneration.

Key words: partial hepatectomy, portal vein stenosis, rat model

Introductions

Living donor liver transplantation (LDLT) has been widely accepted as an effective therapeutic modality for a variety of end-stage liver diseases [24]. The success of LDLT has increased steadily over decades due to improvements in immunosuppressive therapy and postoperative care [20]. However, for patients requiring intraoperative portal vein (PV) reconstruction, one major challenge of LDLT is the portal vein stenosis (PVS), with the incidence remaining at 0.6–4.5% in recipients of a

living-donor allograft, especially in children [11, 12, 23].

As we know, survival depends on the regeneration capacity of hepatocytes. It has been well documented that approximately 70–80% of hepatic blood flow in normal people is derived from the PV, and the PV has been reported to influence the impairment, regeneration, and function of the transplanted liver [17, 19]. Theoretically, a minimal change in the blood supply of the PV scarcely affects the graft's regeneration until the deprivation in flow of the PV reaches a certain level. Nevertheless, the tolerated limitation of PV deprivation

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and the optimal moment for intervention remain unknown. Recently, lots of clinical and animal studies have been performed to investigate the relationship between PV flow and liver regeneration [2, 16]. However, the blood supply of the PVs in these studies was almost normal. This is different from clinical practices in which PVS and PV deprivation are observed in patients with LDLT. To date, few studies has been reported to study the clinical impact of PV blood deprivation on liver regeneration. There is also a lack of related fundamental studies.

It is considered that intensive hepatocyte division could be triggered by liver resection and that the liver would then present powerful regeneration and compensation abilities allowing it to recuperate structurally and functionally [3, 9, 15]. Based on this theory, an animal model was developed in rats with 70% partial hepatectomy (PH) by attaching needles of different gauges to the PVs to induce PVS and PV blood deprivation of different degrees. Based on this model, the effects of PVS complication on liver regeneration were investigated.

Materials and Methods

Study subjects

All animals and procedures were approved by the Animal Ethics Committee of West China Hospital, Sichuan University. One hundred and eight healthy male SpragueDawley rats (200–400 g, 7–14 weeks of age) were purchased from Dashuo Biotechnology Co., Ltd. and acclimatized for at least 7 days to laboratory conditions. Animals were maintained under constant temperature and humidity conditions with a 12-h light-dark cycle at the animal experiment center of West China Hospital. They had access to standard rodent chow and water ad libitum throughout the experiment.

The rats were randomly divided into 6 groups: sham operation rats group (SOR); PH group (group A); and PVS groups with mild, moderate, or severe stenosis (group B-D) and portal vein ligation group (PVL). After surgery, all subjects were fed food and water at a constant temperature of 25°C. In each experimental group, 6 rats were sacrificed on days 1, 3, 7 and 14 after surgery, respectively.

Surgical procedures

All rats were anaesthetized under ether inhalation and fixed on a plank in the supine position. After skin preparation, the surgical zone was sterilized with iodine, and

the abdominal cavity was exposed after median laparotomy with a 2.5 cm incision. Then the median lobe (ML) and left lateral lobe (LLL) were freed from the ligaments. Generally, after laparotomy and ligament resection, the portal trunk was dissociated. After that, the different surgical procedures were performed on the rats in different groups. Finally, the abdominal cavity was closed followed by intraperitoneal injections of 32 000 units penicillin and 5 ml NaCl (0.9%).

For the sham-operated rats (n=6), neither liver resection nor ligature was performed during surgery.

For the PH group (group A, n=24), only 70% PH was conducted by removing the ML and LLL according to the method reported by Higgins and Anderson [6] (Fig. 1a).

According to the stenosis ratio (SR), PVS was classified into mild ($0% < SR \leq 50%$), moderate ($50% < SR \leq 65%$), sever ($SR > 65%$), and occlusion ($SR = 100%$) in this study. For the PVS groups (groups B-D, n=24 for each group), models were established for mild, moderate and sever PVS. After 70% PH, the portal vein diameter (PVD) of each rat was measured by a vernier caliper at the point 3 mm above the joint of the splenic vein and superior mesenteric vein (Fig. 1b). The corresponding gauge of medical needle to induce PVS, which equaled the diameter of the stenotic site (SS), could be calculated from the formula $SR = (1 - SS/PVD) \times 100%$. During surgery, when the PV was separated from surrounding tissues, a 3–0 silk thread was put around the PV together with the corresponding angulated needle (Fig. 1c). After the ligature was secured, the needle was removed slowly, which yielded a fixed partial stenosis corresponding to the specific diameter of the needle (Fig. 1d).

For the PVL group (n=6), after 70% PH, the portal trunk was ligated with a 3–0 silk suture allowing no portal vein blood to the liver.

In the case of portal thrombosis, all rats received subcutaneous injection of 15 IU/100 g body weight low molecular heparin sodium within an hour after surgery. Postoperative analgesia was achieved by subcutaneous injection of buprenorphine at a dose of 0.1 mg/kg body weight.

Ultrasound examination

Ultrasound was applied 24 h after surgery, to validate the stenosis degree. Animals in PVS groups were ether anesthetized and placed in supine positions. The abdomen was shaved with an electric hair remover to minimize ultrasound attenuation. Ultrasonography was per-

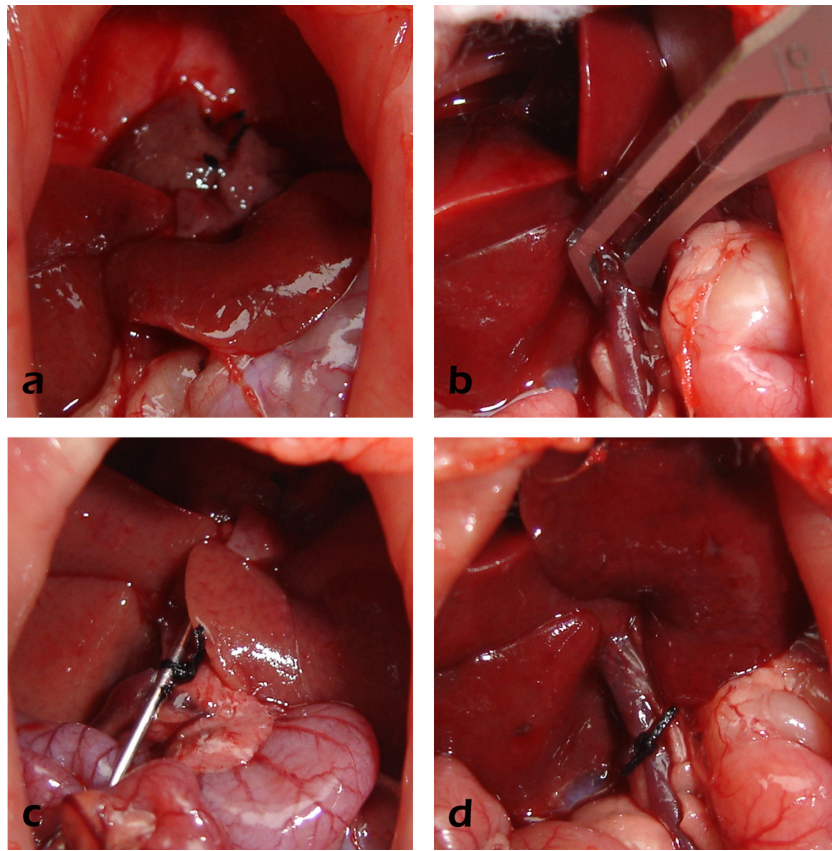


Fig. 1. Intraoperative steps of PVS based on PH: after 70% of the liver is removed (a), the portal vein diameter is measured by a vernier caliper (b), ligation is secured around the portal vein and angulated medical needle (c), and this needle is then removed slowly, which yields a defined lumen corresponding to the specific diameter of the needle (d).

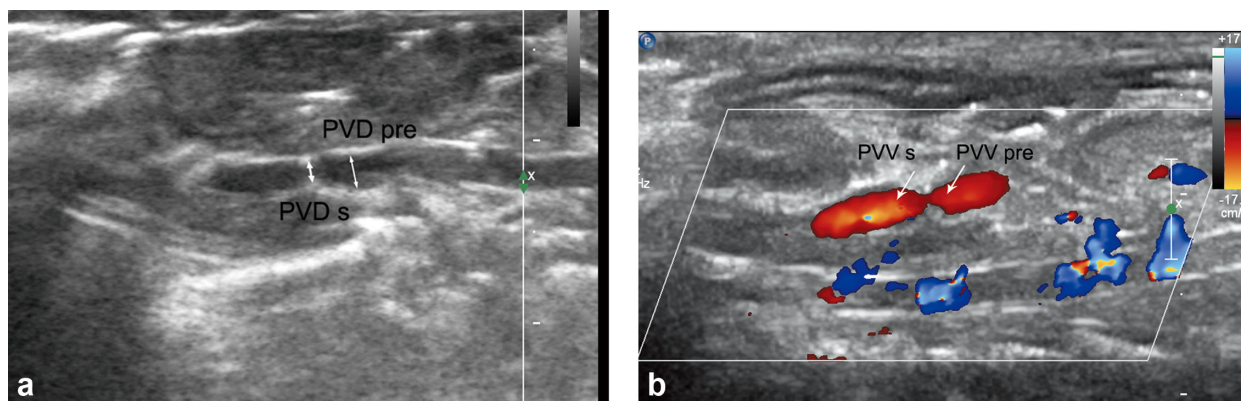


Fig. 2. (a) Diameter of the PV at the prestenotic site (PVD_{pre}) and the stenotic (PVD_s) site measured by B-mode ultrasound. (b) Velocity of the PV at the prestenotic (PVV_{pre}) and stenotic (PVV_s) site detected by color Doppler ultrasound.

formed by the same experienced ultrasound physician, using a Philips iU22 ultrasound machine with a 5.0–12.0 MHz linear transducer.

The diameter of the PV at the prestenotic site (PVD_{pre})

and the stenotic site (PVD_s) was measured by B-mode ultrasound scanning (Fig. 2a). We calculated the stenosis ratio measured by ultrasound (SR_u) according to the formula $SR_u (\%) = 1 - PVD_s / PVD_{pre}$, where PVD_{pre} was

Table 1. The characteristics of the study subjects in each group

Group	Liver weight (g)	Surgical PVD (mm)	B-mode PVDpre (mm)	P value	Needles (count, %)					Surgical SR (%)	Ultrasound SR _u (%)	P value	Velocity ratio (VR)
					18G	19G	20G	21G	22G				
SOR	352.50 ± 88.60	1.82 ± 0.20	–	–	–	–	–	–	–	0	0	–	–
A	324.21 ± 69.22	1.93 ± 0.37	–	–	–	–	–	–	–	0	0	–	–
B	333.46 ± 70.84	2.14 ± 0.24	2.03 ± 0.38	0.245	91.7	0	4.17	4.17	0	44.8 ± 5.23	44.1 ± 13.59	0.799	4.03 ± 1.91
C	337.71 ± 74.33	2.49 ± 0.39	2.58 ± 0.63	0.537	37.5	8.33	41.7	8.33	4.17	59.3 ± 4.07	59.8 ± 12.22	0.852	7.07 ± 5.09
D	317.42 ± 66.98	2.62 ± 0.23	2.60 ± 0.35	0.859	0	0	8.33	79.17	12.5	69.5 ± 2.17	69.4 ± 6.11	0.937	10.7 ± 6.58
PVL	341.83 ± 35.69	2.00 ± 0.38	–	–	–	–	–	–	–	100	–	–	–

Statistical data are expressed as the mean ± SD.

approximated as the portal venous caliber at the ligature site before ligation [8].

Doppler ultrasonography was then employed in observing the portal flow direction, as well as in detecting the portal velocities at the prestenotic (PVV_{pre}) and stenotic (PVV_s) sites (Fig. 2b), which were measured at the stenotic sites where the jet flow could be detected. The length of the sample volume must be adjusted based on the vessel diameter to 0.5 mm, and the angle of insolation must remain constant at less than 60°. Velocity ratio (VR) was defined as VR = PVV_s / PVV_{pre}. All observation data were measured three times and averaged as the resultant values.

Survival status recording

All rats surviving and living longer than 7 days were counted except for those selected for sacrifice in each group. Meanwhile, postmortem examinations were conducted on rats that died to determine the causes of death, examining whether hemorrhage, abdominal adhesion, vascular embolism, or intestinal obstruction had happened.

Liver regeneration estimation

Rats in experimental groups (group A, B, C and D) were sacrificed on days 1, 3, 7 and 14 post operation. The liver was excised and weighed instantly for the calculation of liver regeneration rate (LRR), referring to the formula LRR = (D/E) × 100%, in which D represents the liver weight per 100 g of body weight on the day sacrifice, and E represents the estimated liver weight per 100 g of body weight before hepatectomy, which was calculated from the excised liver weight [10].

Statistical analysis

The *t*-test was utilized to study the difference between surgical PVD and ultrasound measured PVD_{pre} and the

difference between the actual stenosis ratio after surgery (SR_u) and the targeted stenosis ratio (SR). The 7-day survival rates were calculated and compared using the Kaplan-meier survival test and chi-square test. The analysis of variance (ANOVA) test was employed to study the differences in VR and LRR between pairs of groups. All *P* values were two sided. Differences were considered significant if the *P* value < 0.05. Linear correlation analysis was utilized to evaluate the relationship between the regeneration rate of the liver (LRR) and the ultrasound measured SR_u and velocity ratio (VR). All statistical analyses were performed utilizing SPSS 16.0 and GraphPad Prism 6.

Results

Characteristics of the subjects

We successfully established rat models of PVS based on 70% PH in 72 rats. The characteristics for all rats are presented in Table 1. The average surgical PVDs of the rats in the 3 groups with mild, moderate, and severe PVS were 2.14 ± 0.24 mm, 2.49 ± 0.39 mm and 2.62 ± 0.23 mm respectively. The average PVD_{pre} values measured by ultrasound were 2.03 ± 0.38 mm, 2.58 ± 0.63 mm and 2.60 ± 0.35 mm respectively. No significant difference was found between the surgical PVD and PVD_{pre} measured by ultrasound (all *P* < 0.05). The most frequently used sizes of needle in groups B and D were 18G and 21G respectively. As for group C, the more frequently used sizes of needles were 18 G and 20G.

The stenotic site of the PV could be seen in two-dimensional B-mode ultrasound images, and the morphological PVS could be seen clearly. Meanwhile, strictures could be seen in color images in the PVS rats as well. For the rats with severe PVS, prestenotic flow retardation and stenotic flow acceleration with an area of color turbulence were also observed. The targeted surgical SRs

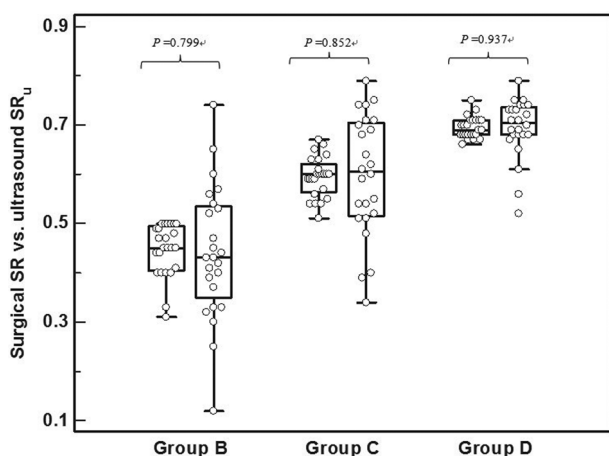


Fig. 3. Box plot of the surgical stenotic ratio (SR left) and ultrasound measured stenotic ratio (SR_u right).

in each group were $44.8 \pm 5.23\%$, $59.3 \pm 4.07\%$, $69.5 \pm 2.17\%$ respectively. In addition, the B-mode ultrasound measured SR_u values in each group was $44.1 \pm 13.59\%$, $59.8 \pm 12.22\%$ and $69.4 \pm 6.11\%$ respectively (Fig. 3). No statistical differences were observed (all $P > 0.05$). The ultrasound measured VRs in the PVS groups were 4.03 ± 1.91 , 7.07 ± 5.09 and 10.7 ± 6.58 respectively, and the VRs of group C and D were significantly higher than that of group B (both $P < 0.05$).

Postoperative conditions

In the sham operation group, rats gradually recovered and fed themselves within 24 h after surgery; none died and no apparent complications occurred. However, rats in the PVS groups presented poor conditions and lack of activities and eating within 24 h; most of the rats that survived did not behave normally until 48 h after surgery.

Complications observed in the experimental groups were as follows: all rats (6/6, 100%) in the PVL group succumbed to acute mesenteric hypertension and clotting manifesting apparent ascites, as well as distension and cyanosis of the gut. Most of the sacrificed rats in the severe PVS group suffered severe congestion of the mesenteric and splenic veins, as well as cyanosis of the gut, mesenteric clotting only occurred in one rat (1/6, 16.7%). The sacrificed rats in group C manifested different degrees of ascites and cyanosis of the gut, but this phenomenon did not occur in the rats died in group B.

Seven-day survival rate

Sixty rats were included in the survival analysis, and

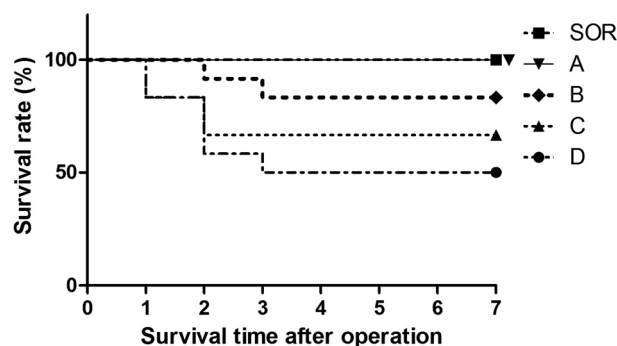


Fig. 4. Survival curve of rats in the different groups.

a total of 70% (42/60) survived to 7 days after surgery. The survival curve of rats in different groups showed a decreased number of surviving rats with aggravation of the PVS degree (Fig. 4). The survival rates in group A-D were 100%, 83.3%, 66.7% and 50%, respectively (Table 2). A death rate comparable to that in group B was found in group A, and one comparable to that in group D was found in group C (both $P > 0.05$). However, significantly higher death rates were found in groups C and D as compared with those in groups A and B, respectively ($P = 0.0049$). More precisely, significant differences were detected between groups C and A ($P = 0.032$) and between groups D and A ($P = 0.006$). Unfortunately, no rats survived after 90 mins in the PVL group.

Liver regeneration rate and its association with SR_u and VR

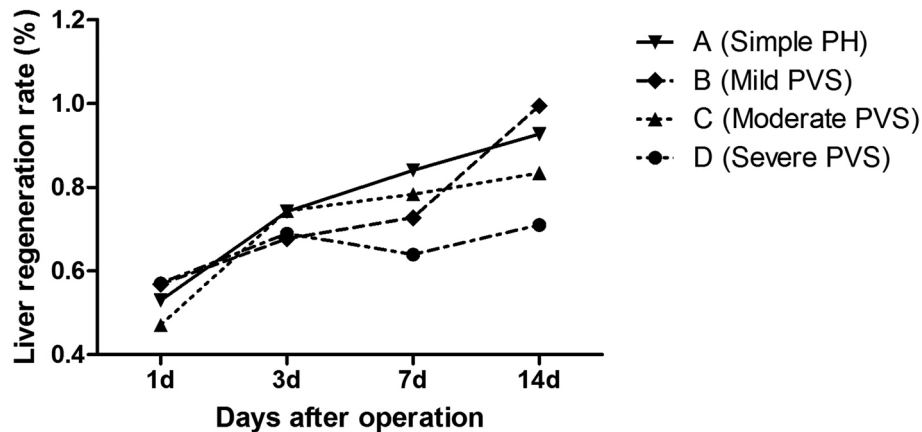
Generally, the liver weight per 100 g body weight increased with time after operation (Fig. 5, Table 3). Regeneration of the liver in groups A and B on the 14th day reached above 90%, and the liver weight had almost recovered. As for group C, liver weight increased steadily, resulting in a relatively lower LRR, but no statistical differences were detected with group A. On the other hand, the gained liver weight in severe PVS rats lagged behind, and the LRR remained below 80%, which was significantly lower than the LRRs of groups A and B ($P < 0.05$) (Table 3). Furthermore, the LRR on the 14th day decreased in conjunction with the increase of SR_u and VR we detected by ultrasound. The results showed that the LRR negatively correlated with the SR_u (Fig. 6a) and VR (Fig. 6b), the correlation coefficients of which were -0.534 and -0.522 , respectively, which demonstrated a significant difference (both $P < 0.05$).

Table 2. The survival conditions in the different groups

Group	Total subjects	Surviving rats					Survival rate (%)
		Day 1	Day 2	Day 3	Day 5	Day 7	
SOR	6	6	6	6	6	6	100
A	12	12	12	12	12	12	100
B	12	12	11	10	10	10	83.3
C	12	10	8	8	8	8	66.7*
D	12	9	7	6	6	6	50*
PVL	6	0	0	0	0	0	0

* $P < 0.05$ vs. group A.**Table 3.** The liver regeneration rates (LRRs) of the different group at the same time point

Group	Day 1	Day 3	Day 7	Day 14
A (simple PH)	52.97 ± 5.55	74.19 ± 8.63	84.06 ± 19.94	92.70 ± 17.34
B (mild PVS)	56.80 ± 6.95 ^c	67.66 ± 11.28	72.69 ± 7.65	99.44 ± 13.58
C (moderate PVS)	47.04 ± 4.25	74.28 ± 8.74	78.31 ± 24.85	83.36 ± 27.32
D (severe PVS)	57.05 ± 6.03 ^c	68.90 ± 6.28	63.91 ± 6.18	70.99 ± 5.71 ^{a,b}

^a $P < 0.05$ vs. group A; ^b $P < 0.05$ vs. group B; ^c $P < 0.05$ vs. group C.**Fig. 5.** Liver regeneration rate (LRR) in the different groups.

Discussion

Portal vein deprivation has been considered one of the major reasons leading to failure in liver transplantations, as the blood supply of the portal vein has been regarded to correlate with regeneration of the liver [3, 9, 15]. However, the tolerated limitation of portal vein deprivation is still unclear, and the optimal time for intervention is still unknown. Limited by the ethics and complicated pathogenesis of human liver diseases, related studies can only be conducted on animals. In this study, a stable and reproducible animal model was established to induce PVS of different degrees in rats, and a pilot study of the relationship between PVS and liver regeneration was

performed. As there is still no standard for classifying PVS degree, referring to the most common classifying system in carotid artery stenosis [4] and considering the practicability of the severe PVS model in further study, the PVS degree was classified into four levels: mild ($0\% < SR \leq 50\%$), moderate ($50\% < SR \leq 65\%$), severe ($SR > 65\%$) and occlusion ($SR = 100\%$).

The classic 70% PH liver regeneration rat model is famous for its regeneration induction without causing fulminant hepatic failure [6]. It can be well performed based on the anatomy of the rat liver, the lobes of which have an independent hilum which makes it easier to block the portal influx for further resection en bloc without causing any tissue damage in residual lobes. The

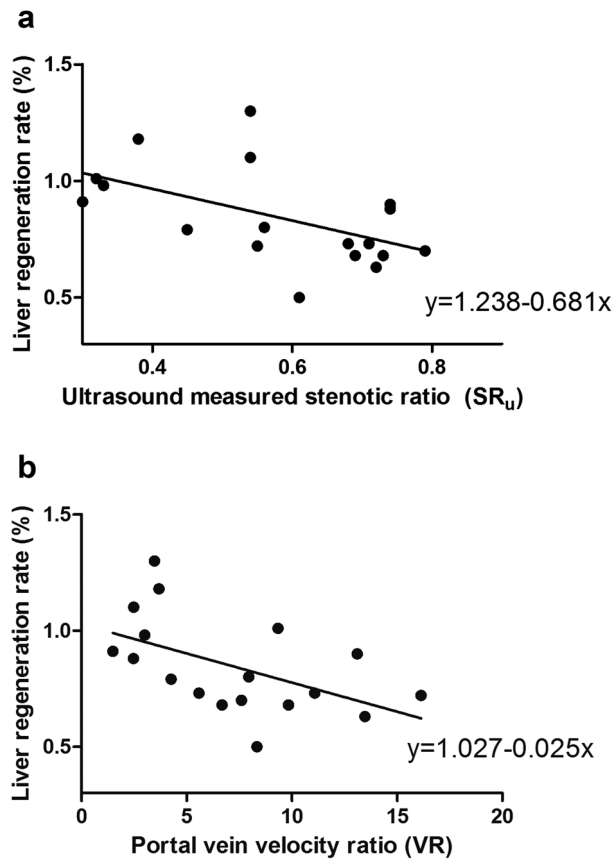


Fig. 6. (a) Linear correlation graph of the LRR with the ultrasound measured SR_u. (b) Linear correlation graph of the LRR with the velocity ratio (VR).

reported survival rate of this model is above 95% [6, 13, 21]. Our results demonstrated that the survival rate of the 70% PH rats was 100% and that the LRR on the 14th day reached above 90%, which was in agreement with the reported results [1]. Furthermore, for the PVS groups, the survival rate decreased with aggravation of the stenosis degree, and the surviving rats with an SR > 50% demonstrated significant differences compared with the control PH group. The survival rate sharply decreased to 50% when the SR > 65%. This also verified the hypothesis that regeneration may be affected when PV flow deprivation reaches a certain level.

As a noninvasive examination method, ultrasound is optimal for determining the diameter and velocity of the PV, which can be further applied in assessing PVS degree [7, 18, 21]. In this experiment, ultrasound was used for the first time in assessing PVS establishment, which was intuitive and convenient. Firstly, the ultrasound measured PVD_{pre} presented no statistical differences com-

pared with the surgical PVD, which demonstrated that approximation of the PVD with the PVD_{pre} at the ligature site is feasible. Subsequently, no statistical differences were found between the surgical SR and B-mode ultrasound measured SR_u, which directly demonstrated the success of model establishment. On the other hand, another index, VR, used to assess vascular stenosis in ultrasound [8] also utilized to assist in grading. Moreover, SR_u and VR both showed negative association with LRR, which was in accordance with the stenosis degree grading.

Nobuoka *et al* [16] recently created a model that likewise could be used in controlling PV blood by partially ligating the portal trunk by suture under microscopy. Apart from the complicated surgical procedures, the constriction induced by suture can only last for a short time, and the suturing operation carries a much higher risk of portal vein damage, bleeding, and secondary thrombus. In this experiment, PV flow deprivation was realized by parallel ligaturing needles in the PV, which was less vascularly injured and relatively stable compared with that in the case of the suturing method [22]. Other surgical models employed in exploring the effect of PV blood on liver regeneration are mainly portosystemic shunting models including the Eck fistula, side-to-side portalcaval shunt [19], and portohepatic shunt [14]. Unlike these shunting models, our model controls portal flow quantitatively as required, as it uses various gauges of needle with a specific diameter.

In the results, comparable rates of survival were found in groups C and D, although significantly higher death were found in groups C and D compared with those in groups A and B. Meanwhile, we found the LRR of group D decreased significantly compared with those of groups A and B on the 14th day after operation. For the moderate PVS group on the other hand, the LRR presented small changes that showed no statistical differences compared with group A. These two phenomena may be attributed to the hepatic artery compensation. Henderson found that in liver transplantation, the hepatic artery of the receptor increased 26% when portal flow decreased 50% [5]. Animal experiments have also proved that “hepatic artery buffer response” is activated when the portal vein influx reduces by more than 50% [25]. For the moderate PVS group, the hepatic artery, which carries more oxygen in comparison with the PV, may have increase the oxygen pressure per unit volume of hepatocytes as a compensatory mechanism. This “hepatic artery

buffer response” might be a reason for the comparable survival rates in groups C and D. However, from the LRR results, we inferred that this compensation mechanism could not meet the nutrient need when PV flow decreased by more than 65%, which showed the limitation of hepatic artery compensation.

In conclusion, we produced a novel model by rebuilding the classic regeneration model in combination with PVS, which has been scarcely reported, and standardized the whole procedures as well. This model is characterized by simplicity, reproducibility, and controllability. Although this model does not reflect a real status of LDLT recipients with vascular complication who may be complicated with some underlying diseases, the data obtained can still be transposed to most conditions of liver regeneration with reduced portal vein inflow. This model can also be applied for further investigations in exploring the effect of therapy on liver regeneration in recipients with portal flow deprivation. Nevertheless, there still remains an abundance of studies that need to be completed before this model can be applied in clinic.

Acknowledgments

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