Hepatic parenchymal transection increases liver volume but not function after portal vein embolization in rabbits

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Background. *Associating liver partition with portal vein ligation for staged hepatectomy induces more extensive liver hypertrophy than ligation alone; however, the mechanisms underlying the accelerated liver regrowth and the functional quality of the hypertrophic liver are presently elusive. This study, therefore, investigated the effect of parenchymal transection on liver volume and function after portal vein embolization in a standardized rabbit model.*

Methods. *Twelve rabbits were subjected to portal vein embolization of the cranial liver lobes and randomized between parenchymal transection of the left lateral liver lobe versus no transection (portal vein embolization only). Liver volume of the nonembolized liver lobe was assessed using computed tomography–volumetry, and liver uptake function was determined by ^{99m}Tc-mebrofenin hepatobiliary scintigraphy before and 3 and 7 days after portal vein embolization.*

Results. *The increase in nonembolized liver volume 3 days after portal vein embolization was 2.7-fold greater in the transected group compared with the portal vein embolization only group (56 ± 16% vs 21 ± 12%, respectively, P < .01) and 1.7-fold greater 7 days after portal vein embolization (113 ± 34% vs 68 ± 24%, P < .01). Liver uptake function did not differ between groups before portal vein embolization (8.4 ± 3.7%/min in the transection group vs 8.9 ± 1.6%/min) on day 3 (33.2 ± 4.7% after transection vs 30.3 ± 4.6%/min, respectively) and day 7 after portal vein embolization (42.6 ± 8.4% vs 39.1 ± 5.3%/min, respectively).*

Conclusion. *Parenchymal transection after portal vein embolization increases liver growth in terms of volume but not function. These results indicate that the rapid volume increase observed after associating liver partition with portal vein ligation for staged hepatectomy does not coincide with the clinically more relevant functional increase. Quantitative liver function tests might be essential in associating liver partition with portal vein ligation for staged hepatectomy to better assess the hypertrophy response and improve clinical decision-making. (Surgery 2016;■:■-■.)*

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Portal vein embolization (PVE) is the gold standard procedure to preoperatively enhance the future liver remnant (FLR) in patients scheduled for major liver resection.[1,2] Recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was introduced, which induces rapid hypertrophy of the FLR, thereby allowing more extended liver resections in a shorter period of time.[3] The hypertrophy induced by ALPPS is greater and faster compared with other conventional techniques, such as PVE[2] or the "standard" 2-stage hepatectomy.[4]

ALPPS is associated with substantial morbidity and mortality, however, which has led to controversy in the literature regarding its safety and its

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indications.[5,6] Although mortality has declined from the initially reported 12% to 9% in major series,[7,8] morbidity remains substantial and postoperative liver failure is the most common cause of death after resection despite the rapid hypertrophy.[8,9]

Interestingly, the hypertrophied liver volume did not correlate to mortality in 320 patients collected from the ALPPS registry.[4] This observation called into question the accuracy and relevance of liver volume assessment as the main parameter to time the second stage. Indeed, histologic assessment of the hypertrophied FLR demonstrated that hepatocytes were smaller and more immature in patients after ALPPS compared with PVE.[10] These preliminary results suggest that the observed liver volume increase after ALPPS might not reflect a proportional increase in liver function.

Several hypotheses have been postulated to explain the increased hypertrophy seen in ALPPS. These include induction of proliferation by an inflammatory response triggered by the parenchymal transection and the more complete portal occlusion by preventing collateral perfusion by the parenchymal division.[11,12] Several animal models have been developed to study the hypertrophy response induced by ALPPS, mostly in small rodents.[13-17]

These models, however, likely lack translational value due to discrepancies in the observed response versus the response in humans. In rats, extensive necrosis of the ligated liver lobes is observed,[13] and the increase in liver weight gain of ALPPS over portal vein ligation is less pronounced compared with humans.[14,16] It was shown recently that the hypertrophy response in a rabbit model of portal vein occlusion resembles the response seen in patients, which most likely yields more reliable experimental results compared with other rodent models.[18]

This study aimed to examine the effect of parenchymal transection on both liver volume and function after PVE in a standardized rabbit model using ^{99m}Tc hepatobiliary scintigraphy for functional assessment. The main findings were that the addition of parenchymal transection to PVE indeed induced rapid hypertrophy. Liver function, however, was not increased by parenchymal transection and was similar to PVE alone.

It was concluded that rapid hypertrophy leads to immature liver tissue that may not sustain patients after resection despite the impressive volume increase. Due to the important clinical implications of the data, ALPPS should be used with caution and with functional monitoring of the FLR.

METHODS

Animals. Twelve New Zealand White rabbits (female, mean ± standard deviation [SD] weight of 2,887 ± 231 kg) were obtained from Charles River (Saint-Germain-sur-l'Arbresle, France). Animals were housed individually with ad libitum access to water and standard chow in a temperature-controlled room with a 12-hour, dark-light cycle. Rabbits were allowed to acclimatize for at least 7 days before inclusion in the experiments. All experimental protocols were approved by the Animal Ethics and Welfare committee of the Academic Medical Center (BEX35). Experiments were reported in accordance with the Animal Research: Reporting of In Vivo Experiment (ARRIVE) guidelines.

Experimental design. Rabbits were randomized in 2 groups of 6 animals. Six were planned for PVE of the cranial liver lobes (PVE group), and 6 rabbits underwent PVE of the cranial liver lobes combined with partial transection of the left lateral liver lobe (PVE with transection group). The primary outcome was regional hepatic mebrofenin uptake measured using ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS)[19] and increase in liver volume measured on contrast-enhanced computed tomography (CT) images.[20] Both scans were performed the day before PVE as well as 3 and 7 days after PVE. All rabbits were killed 7 days after PVE.

Portal vein embolization. PVE of the cranial liver lobes was performed as described previously.[20-22] In brief, rabbits were anesthetized by subcutaneous (SC) injection with ketamine (25 mg/kg; Nimatek, Eurovet, Bladel, The Netherlands) and medetomidine (0.2 mg/kg; Dexdomitor, Orian, Espoo, Finland) and maintained under anesthesia with isoflurane (2%; Forene, Abbott, Kent, United Kingdom). Analgesic care was given by SC injection of buprenorphine (0.03 mg/kg; Temgesic, Reckitt Benckiser, Hull, United Kingdom). Enrofloxacin (0.2 mg/kg SC; Bayrtril, Bayer, Berlin, Germany) was administered daily, starting at PVE and continuing for 3 days.

A branch of the inferior mesenteric vein was used to catheterize the portal system with an 18G catheter. Using a microcatheter (Renegade 3F; Boston Scientific, Natick, MA) and 0.36-mm diameter and 182-cm long guidewire (Transend-ex; Boston Scientific), the cranial lobes were embolized with polyvinyl alcohol particles (PVA 300–500 μm; Cook, Bloomington, IN) and platinum fibered coils (5 and 4 mm; Boston Scientific)