Comparable liver function and volume increase after portal vein embolization in rabbits and humans

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Background. *Portal vein embolization is the gold standard approach to preoperatively enhance the future liver remnant before liver resection. Portal vein embolization is studied in several experimental animal models; however, clinical translation of results is often difficult. We aimed to examine the translational value of the portal vein embolization response in a standardized rabbit model by comparing the volume and function increase with the response seen in patients.*

Methods. *Six rabbits were subjected to embolization of the cranial liver lobes, and the hypertrophy response of the caudal liver lobe was studied using computed tomography volumetry and Technetium-99m-labeled-mebrofenin hepatobiliary scintigraphy. Results were compared to those from patients who underwent portal vein embolization between 2005 and 2014. All patients were subjected to computed tomography volumetry and hepatobiliary scintigraphy before and after portal vein embolization.*

Results. *The increase in liver function of the caudal liver lobe in rabbits was faster compared to the increase in liver volume. There was no decrease in total liver function after portal vein embolization. Results in patients were similar to rabbits, with a faster increase in liver function compared to patients and no decrease in total liver function after portal vein embolization.*

Conclusion. *The portal vein embolization response in terms of liver volume and function is similar between rabbits and humans. Accordingly, the rabbit model is a suitable tool to study portal vein embolization–related parameters that cannot be investigated in patients. (Surgery 2016;■:■-■.)*

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Portal vein occlusion techniques, such as embolization or ligation, are the current standard to increase future liver remnant (FLR) volume before major liver resection to prevent posthepatectomy liver failure.[1,2] Preoperative selection of patients who require portal vein embolization (PVE) is usually based on volumetric assessment of the liver by computed tomography (CT) or magnetic resonance imaging.[3,4] However, liver function is the most important postoperative parameter in liver operation patients, because the remnant liver must sustain the patient with sufficient functional capacity. Moreover, liver volume does not necessarily reflect liver function, and several techniques have consequently been developed to measure liver function.[5]

Technetium-99m-labeled (^{99m}Tc) mebrofenin hepatobiliary scintigraphy (HBS) holds the greatest potential,[6] because it can measure basolateral uptake[7,8] and excretory function[9]—2 important components of liver function[10]—in a single session. Accordingly, ^{99m}Tc-mebrofenin HBS is standardly employed in patients scheduled for liver resection at our center.[11] ^{99m}Tc-mebrofenin HBS has high predictive value for posthepatectomy liver failure and aids in the selection of patients scheduled for major liver resection for PVE.[11] In terms of hepatic uptake and excretion function, an increase in function precedes an increase in volume after PVE in patients.[12]

At this point, it is unclear whether the volumetric and functional dynamics in humans are mimicked in standardized animal models, which include mice,[13]

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rats,[14,15] rabbits,[16-18] and pigs.[19] These models are used to study many topics, such as the difference between PVE and portal vein ligation,[20,21] absorbable embolization materials,[15,16,22] and the effect of combined occlusion of hepatic veins,[17] arteries,[23,24] or bile ducts[14] on liver regeneration. In addition, drugs that potentially enhance or modulate liver growth can be tested using these models.

Our laboratory prefers to use the rabbit model, because the size of the animals allows the use of similar embolization materials as in humans, and the anatomy of the rabbit liver, with complete separation of the cranial and caudal liver lobes, allows rapid and reproducible embolization of the cranial liver and facilitates imaging with reliable volume calculation of the caudal liver lobe (Fig 1).

In light of the volume-versus-function issue, the first aim of this study was to determine the volumetric and functional dynamics of the future remnant liver after PVE in rabbits using routine clinical techniques to assess both parameters. As such, CT was used to measure volume and ^{99m}Tc-mebrofenin HBS was used to measure function. The second aim was to assess the translatability of the rabbit model to the clinical situation. Consequently, the results were compared to volumetric and functional dynamics in 42 patients subjected to PVE where the same techniques had been employed.

The main findings are that (1) the increase in function was more pronounced compared to volume after PVE in rabbits and (2) the liver volume and function response after PVE in rabbits shows similar kinetics compared to the response in patients subjected to PVE. Accordingly, the rabbit PVE model is representative of the clinical situation in terms of post-PVE liver volume and function and therefore constitutes a useful tool for translational PVE research.

METHODS

Rabbit model of PVE. Six New Zealand White rabbits (female) were obtained from Charles River (Saint-Germain-Nuelles, France). Rabbits were individually housed under conditions with a 12-hour dark-light cycle and ad libitum access to standard chow and water. Animals were acclimated for 7 days before inclusion in the experiments. All experiments were approved by the animal ethics and welfare committee of the Academic Medical Center (BEX 35).

The methods of anesthesia and PVE were described in detail previously.[22,25] Rabbits underwent embolization of the cranial liver lobes with polyvinyl alcohol particles (diameter: 300–500 μm; Cook, Bloomington, IN) followed by fibred platinum coils (5.0 and 6.0 mm; Boston Scientific, Natick, MA).

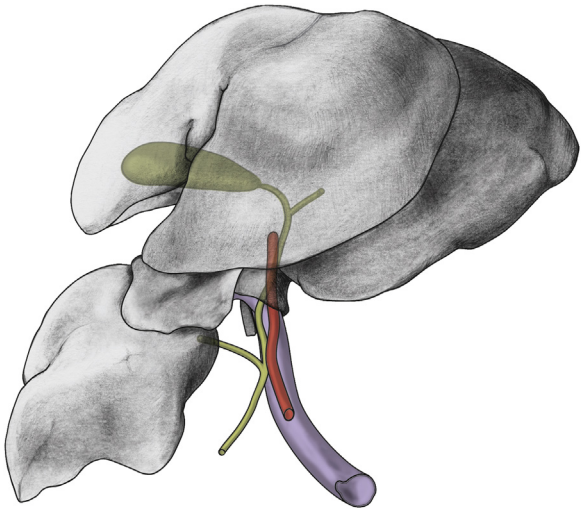

Fig 1. Rabbit liver anatomy with the cranial liver lobes completely separated from the caudal liver lobe. Courtesy of Libuse Markvart. (Color version of this figure is available online).

Quantification of liver regeneration. Rabbits were subjected to ^{99m}Tc-mebrofenin HBS 1 day before PVE and 3 and 7 days thereafter. The animals were placed in the supine position with the heart and liver under a large field of view. HBS was performed with a single photon emission CT camera (SPECT-CT; Siemens, Symbia T16, Munich, Germany). Rabbits were injected with 50 mBq of ^{99m}Tc-mebrofenin (Bridatec; GE Healthcare, Little Chalfont, United Kingdom), and image acquisition was immediately started for 5 minutes at a frequency of 12 min^{-1}. The scanning protocol was optimized based on scans in a pilot experiment (data not shown).

For data analysis, the geometric mean of the anterior and posterior camera was used, and regions of interest (ROI) were drawn around the left ventricle, total liver, and caudal liver lobe for the generation of time-activity curves. The hepatic ^{99m}Tc-mebrofenin uptake rate was calculated as the increase in ^{99m}Tc-mebrofenin uptake over 120 seconds, corrected for perfusion using the time-activity curve generated from ROI around the left ventricle. Total liver function (TLF) was defined and the total hepatic ^{99m}Tc-mebrofenin uptake rate calculated as a percentage of the injected dose per minute. The uptake rate of ^{99m}Tc-mebrofenin was calculated in the caudal liver lobe based on the ROI surrounding the caudal liver lobe. The same was done to calculate the function of the cranial liver lobes (Fig 2).

Directly after HBS, contrast-enhanced CT scans were made in each rabbit at each time point on the