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ORIGINAL ARTICLE

Assessment of liver regeneration after associating liver partition and portal vein ligation for staged hepatectomy: a comparative study with portal vein ligation

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Abstract

Background: To investigate the diagnostic value of diffusion kurtosis imaging (DKI) and diffusion-weighted imaging (DWI) in assessing liver regeneration after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) compared with portal vein ligation (PVL).

Methods: Thirty rats were divided into the ALPPS, PVL, and control groups. DKI and DWI were performed before and 7 days after surgery. Corrected apparent diffusion (D), kurtosis (K) and apparent diffusion coefficient (ADC) were calculated and compared, radiologic–pathologic correlations were evaluated.

Results: The volume of the right median lobe increased significantly after ALPPS. There were larger cellular diameters after ALPPS and PVL (P = 0.0003). The proliferative indexes of Ki-67 and hepatocyte growth factor were higher after ALPPS (P = 0.0024/0.0433). D, K and ADC values differed between the groups (P = 0.021/0.0015/0.0008). A significant correlation existed between D and the hepatocyte size (r = −0.523), no correlations existed in ADC and K (P = 0.159/0.111). The proliferative indexes showed moderate negative correlations with ADC (r = −0.484/−0.537) and no correlations with D and K (P = 0.100–0.877).

Discussion: Liver regeneration after ALPPS was effective and superior to PVL. DKI, especially the D map, may provide added value in evaluating the microstructure of liver regeneration after ALPPS, but this model alone may perform no better than the standard monoexponential model of DWI.

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Introduction

The main limiting factor for hepatic resection to treat liver tumors is the amount of the future liver remnant (FLR) to maintain sufficient liver function.[1] Portal vein ligation (PVL) remains the gold standard strategy to guarantee a sufficient FLR,[2,3] but insufficient hypertrophy (generally 10–50% of the total liver volume within 2–8 weeks) may increase the waiting time, inducing risk of tumor progression and ultimately loss of resectability.[4–6] Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has recently been described as a promising strategy to induce a rapid and marked increase in the FLR volume, allowing for greater FLR growth (40–160%) in only a week (6–9 days).[7–10] However, the amount of volumetric liver increase might not necessarily reflect a true increase in the liver tissue; and functional hepatocellular regeneration, not just a volumetric increase of FLR has become a priority.

Diffusion-weighted imaging (DWI) has been demonstrated as a promising technique for visualizing the cellular density and properties of the extracellular matrix.[11] However, apparent diffusion coefficient (ADC) is calculated using a monoexponential

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Ruo-fan Sheng and Li Yang contribute the same to the article.

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analysis, which assumes Gaussian behavior of water diffusion.[12] Diffusion kurtosis imaging (DKI) is an advanced DWI model that quantifies non-Gaussian behavior of diffusion and provides both a corrected ADC and the excess kurtosis of tissue.[13] It may provide an opportunity to gain further insights into the states of liver diffusivities and tissue microstructural complexity compared to standard DWI;[12] but its application in the liver is scarce and mostly limited in vitro studies.[12,14,15]

Until now, whether ALPPS can achieve sufficient liver regeneration with a true increase in the liver tissue and functional hepatocellular proliferation has remained controversial.[1,2,5,16,17] Additionally, there remain many uncertainties about the biological substrate of the volumetric changes;[2] and few studies have reported on the imaging analysis. The purpose of this study was to evaluate the diagnostic value of DKI and conventional DWI in assessing liver regeneration as well as the underlying histological and molecular features after ALPPS using rat models, in comparison with PVL.

Materials and methods

Animal model

The animal care and use committee of our institution approved this study. All animals received humane care and the study protocols complied with the institution's guidelines. Thirty male, 8-week-old, Sprague-Dawley rats (ca. 250–280 g) were divided into 3 groups, each of the following groups consisted of 10 rats: (i) ALPPS group: selective portal vein ligation of all branches except the branch to the right median lobe (RML) and liver parenchymal partitioning between the right/left median lobes; (ii) PVL group: selective portal vein ligation only; and (iii) Sham (control) group: abdomen opened and closed after manipulation of the liver hilum.[18]

Anesthesia was induced by intraperitoneal injection of 4% Pelltobarbitalum (0.1 ml/100 g). Operations were performed with care under an operating microscope (Carl Zeiss, Jena, Germany; ×10). As lobular architecture of the rat liver is different from patients,[19] the ALPPS model was developed with the goal of making the rat liver anatomy a similar variant to that of the human liver. In PVL, occlusion of 70% of the liver mass was achieved via ligation (7-0 silk string) of the portal vein branches feeding the left median, left lateral, right lateral and caudate lobes. In the ALPPS group, the right median lobe was completely split via stepwise placement of a clamp along the ischemic demarcation line after ligation of the portal vein branches, and sutured using 4-0 silk string, no hepatic pedicle clamping was used. All animals recovered on a heating pad after surgery.

Image acquisition

All rats were scanned by MR the day before surgery and seven days after surgery. MRI was performed using a 3.0-T scanner (Verio, Siemens, Erlangen, Germany) with a delicated phased-array animal coil. DKI was performed with a single-shot spin-echo echoplanar sequence using tridirectional motion-probing gradients (3-scan Trace mode) with 6 b-values (0, 200, 500, 1000, 1500 and 2000 s/mm^2) and the following parameters: TR/TE = 5100/96.8 ms, slice thickness = 2.0 mm, interslice gap = 0.5 mm, field of view = 138 × 138 mm, scan matrix = 148 × 148, half Fourier factor = 7/8, GRAPPA accelerated factor = 2, average = 4, and total scan time = 5 min 52 s. DWI was acquired with the same single-shot spin-echo echoplanar sequence and parameters as DKI sequence's except that b = 0, 800 s/mm^2 and total scan time = 1 min 30 s.

A three-dimensional T1-weighted volumetric interpolated breath-hold examination sequence with fat suppression for volumetric analysis was obtained with the following parameters: TR/TE = 4.43/1.53 ms, slice thickness = 2.0 mm, no interslice gap, and field of view = 100 × 100 mm, following the administration of gadoxetic acid (0.1 ml/kg; Primovist; Bayer Healthcare, Berlin, Germany). Hepatobiliary phase images were obtained 20 min after contrast administration.

Imaging analysis

DICOM images from the DKI sequence were post-processed using in-house software programmed in MeVisLab (Version 1.2.0; MeVis Medical Solutions AG, Bremen, Germany). This program performed voxel-by-voxel analysis, fitting diffusion-weighted signal intensities as a function of the b-value using the following equation: $S = S_0 \times \exp(-b \times D + b^2 \times D^2 \times K/6)$, in which b represents the b-value, D represents the corrected apparent diffusion, and K represents the excess kurtosis.[12] Through this calculation, the program output maps for each explant of D and K, and then automatically output the values using the region of interest (ROI) measurements. Three ROIs measuring 0.15 cm^2 were drawn on the RML, avoiding large vessels, lesions, artefacts and the liver border, to measure the D, K coefficients as well as ADC (Fig. 1a–c). The average values were used. All images were analyzed by two radiologists (H.Q.W. and L.Y. with 16 and 10 years of experience, respectively, in abdominal imaging) in a blinded manner. A randomized order of studies was provided. The readers were blinded to the animal groupings and pathology reports.

MR liver volumetry

As demonstrated by Lee *et al.*,[20] semi-automated liver MR volumetry using HBP gadoxetic acid-enhanced MRI was a reliable, fast tool to measure the liver volume, comparable to CT volumetry. A computer-aided semiautomatic liver volumetry software IQQA-liver (Version 2.0; EDDA technology, Princeton, USA) was employed running on the hepatobiliary phase T1-weighted 3D VIBE images. The total liver and RML were manually outlined in every slice, excluding the major vascular structures; volumes both before and 7 days after surgery were recorded. The procedure was performed by one radiologist (R.F.S. with 6 years of experience in abdominal imaging).

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