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Original contribution

# Comparison of microvascular perfusion evaluation among IVIM-DWI, CT perfusion imaging and histological microvessel density in rabbit liver VX2 tumors

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ABSTRACT

*Object:* To explore microcirculation features with intravoxel incoherent motion (IVIM) and to compare IVIM with CT perfusion imaging (CTPI) and microvessel density (MVD).

*Materials and methods:* Hepatic CTPI and IVIM were performed in 16 rabbit liver VX2 tumor models. Hepatic arterial perfusion (HAP), hepatic arterial perfusion index (HPI), Blood flow (BF), and blood volume (BV) from CTPI were measured. Apparent diffusion coefficient (ADC), true diffusion coefficient (D), perfusion fraction (f), and pseudo-diffusion coefficient (D*) from IVIM were measured. MVD was counted with CD34 stain. The microcirculation features with IVIM were compared with CTPI parameters and MVD.

*Results:* Strong linear correlations were found between D value ($0.89 \pm 0.21 \times 10^{-3}$ $mm^2/s$) and HAP ($15.83 \pm 6.97$ ml/min/100 mg) ($r = 0.755$, $P = 0.001$) and between f value ($12.64 \pm 6.66\%$) and BV ($9.74 \pm 5.04$ ml/100 mg) ($r = 0.693$, $P = 0.004$). Moderate linear correlations were observed between ADC ($1.07 \pm 0.32 \times 10^{-3}$ $mm^2/s$) and HAP ($r = 0.538$, $P = 0.039$), respectively; and between D value and MVD ($9.31 \pm 2.57$ vessels at 400 × magnification) ($r = 0.509$, $P = 0.044$). No correlations were found between D* ($119.90 \pm 37.67 \times 10^{-3}$ $mm^2/s$) and HAP, HPI ($68.34 \pm 12.91\%$), BF ($4.95 \pm 2.16$ ml/min/100 mg), BV.

*Conclusion:* IVIM parameters can characterize microcirculation to certain extent and separate it from pure water molecular diffusion. There is fair correlation between D or ADC value and CTPI parameters or MVD, but no correlation between D* or f value and CTPI parameters or MVD except f value and BV, which is still unclear and need further clinical studies to validate.

## 1. Introduction

Since the introduction of diffusion-weighted imaging (DWI), great success has been achieved in quantitative research with apparent diffusion coefficient (ADC), especially in differentiating malignant and benign tumors, such as hepatic cellular carcinoma and breast cancer [1–4]. However, previous studies showed that ADC could not fully reflect the physiological behaviors based on a simple exponential relationship between DWI signal and b value [5–7]. With recent advances in magnetic resonance imaging (MRI) techniques, intravoxel incoherent motion (IVIM) diffusion weighted imaging, which is based on a biexponential model between DWI signal and multiple b values, has been applied in noninvasive characterization and follow-up of focal or diffuse lesions in liver [8–11], through the derived parameters, including true diffusion coefficient (D value, which characterizes the pure Brownian motion of the water molecules), pseudo-diffusion coefficient (D* value, pseudo-random motion of the microcirculation caused by pseudo-random distribution of the capillary network within the voxels) and perfusion fraction (f value) [12,13]. IVIM-DWI has showed a promising prospect in providing microcirculatory information without contrast agents and has attracted researchers' great interests. However, there are still some limits about IVIM-DWI, such as the interpretable number and range of b values, rational scientific acquisition methods, and advanced scientific mathematical analysis models [14,15]. Moreover, the relationship between quantitative parameters in microcirculatory perfusion derived from IVIM-DWI and perfusion parameters derived from other imaging techniques remains unclear [16–18].

Dynamic contrast-enhanced MRI (DCE-MRI) is another MRI method that allows for estimation of tissue perfusion and permeability. By implementing a pharmacokinetic model described by Materne et al. [19], DCE-MRI can be used to determine arterial flow (Fa), portal flow (Fp), arterial fraction (ART), mean transit time (MTT), and distribution volume (DV) of the gadolinium-based contrast agent. Multiple research groups have assessed the correlation between DCE-MRI and IVIM-DWI

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in head and neck cancer [16], lung cancer [20], and liver cirrhosis [15]. Nevertheless, controversial results were found from these studies, ranging from no correlation to moderate to strong correlation between DCE-MRI and IVIM-DWI [16,21,15,20].

As a quantitative imaging modality, computed tomography perfusion imaging (CTPI) can noninvasively evaluate the microcirculatory perfusion process of living tissues or organs. Previous studies showed that quantitative hepatic perfusion parameters derived from CTPI have a high accuracy, repeatability and consistency [22–24]. CTPI also is valuable in early detection of hepatic tumors and in individual monitoring of the therapeutic effect and prognosis assessment. However, concerns about high radiation exposure in CTPI have hindered its widespread use.

The aim of our study is to quantitatively investigate the correlation between parameters derived from IVIM-DWI and those from CTPI, and to compare these parameters with the microvessel density (MVD) on histological examination, based on an animal model.

## 2. Materials and methods

This study was approved by the local institutional animal care and use committee.

### 2.1. Experimental animal models

Twenty-one New Zealand white rabbits (weight 2.0–3.0 kg, 5–6 months old, with no constriction on gender) were used in this study. Each animal was anesthetized with 3% pentobarbital sodium (1 ml/kg) via an ear vein injection, followed by a midline abdominal incision, to expose liver tissue. The implantation of VX2 tumor was performed by injecting 0.2–0.3 ml of suspension of the tumor tissue into the liver with a syringe (1 ml). The incision was sutured layer by layer after liver bleeding ceased. Ultrasonography was performed 3 to 4 weeks later to confirm the location and size of the tumors. Animals with tumors ranging from 1 to 3 cm in diameter in the liver parenchyma were preliminarily included for unenhanced CT scanning as well as $T_1$WI and $T_2$WI MRI scanning.

Based on the findings from unenhanced CT and MRI scanning, the inclusion criteria of the subsequent study were: 1) a single tumor in the liver parenchyma; 2) with a diameter larger than 1 cm, but less than or equal to 3 cm; and 3) no prominent necrotic area. The exclusion criteria were: 1) multiple tumors; 2) tumors outside the liver parenchyma; 3) tumors larger than 3 cm in diameter; or 4) prominent necrotic area.

### 2.2. CT perfusion imaging protocol

The animals were anesthetized with 20% urethane (first dose: 10 ml; then an additional 5 ml each time depending on anesthesia degree) injected via the abdominal cavity. The animals were fixed in a supine position with free breathing during the scan.

CT perfusion imaging studies were performed with a 256-slice Brilliance iCT scanner (Philips Healthcare, Cleveland, Ohio, USA). Initially, a plain helical CT scan was performed to determine the scan range. The parameters for the plain scan were set at: tube voltage 120 kV, tube current 80mAs, collimation 128 × 0.625, slice thickness 2.5 mm, slice increment 2.5 mm, pitch 0.99, focal spot resolution: STANDARD, rotation time 1.50 s, field of view 136.0 mm, and image matrix 512 × 512. Later on, hepatic CTPI was performed using a stationary axial scan model (NON-JOG). A bolus of 5 ml of contrast medium (Iohexol injection, 350 mgI/ml) was injected at a flow rate of 1.0 ml/s followed by 5 ml of saline solution into an ear vein through a 24-gauge catheter using double tube high-pressure syringe (Ulrich medical, Germany). One and half second after the contrast medium injection, CTPI scans were performed with a scan time of 0.58 s and interval time of 1.5 s and repeated 40 times. The parameters of the CTPI scans were set at tube voltage 80 kV, tube current 80 mA, fixed scan length 40 mm (covering the VX2 tumor and at least part of the spleen), and the other parameters were the same as those of the plain scan.

The raw data of CTPI were reconstructed with filtered back projection, then transferred to an Extended Brilliance™ Workspace 4.0.2.144 (Philips) and analyzed with Functional CT software package (General Perfusion Type and Liver Perfusion Type). The aorta at the level of 12th thoracic vertebra was defined as the input artery while the main portal vein was defined as the input vein, with a region of interest (ROI, as large as possible within the lumen) placed on the relevant areas, respectively. The most obvious enhanced parenchyma in the spleen also was placed with an ROI. Subsequently, the time density curve (TDC) was automatically obtained through the maximum slope method. Two independent radiologists placed ROI on three consecutive images with the maximum area of VX2 tumors to measure hepatic arterial perfusion (HAP), hepatic perfusion index (HPI), Blood flow (BF), and blood volume (BV). ROI should be as large as possible, but should not cover the adjacent normal parenchyma, obvious vessels and prominent necrosis. The average values of the above parameters were calculated.

### 2.3. MR imaging protocol

The IVIM-DWI was performed with Achieva 1.5 T (Philips Healthcare, Best, Netherlands). Anesthetized following the same protocol as described in the CTPI, the animals were fixed in a supine position and then placed in an 8-channel phased-array coil specialized for rabbits (Product model: CG-RBC18-H150-AP, Shanghai Chenguang Medical Technologies Co., Ltd., Shanghai, China) with free breathing during the scan. Axial T1-weighted turbo spin echo sequence (TR/TE: 413/10 ms; FOV, AP/PL/FH: 100/100/50 mm; ACQ matrix M × P: 148 × 120; slice thickness: 2.5 mm; NSA: 2), T2-weighted turbo spin echo sequence (TR/TE: 2110/80 ms; FOV, AP/PL/FH: 100/100/50 mm; ACQ matrix M × P: 148 × 115; slice thickness: 2.5 mm; NSA: 2), and axial and coronary T2-weighted spectral presaturation attenuated inversion recovery (SPAIR) (TR/TE: 2660/80 ms; FOV, AP/PL/FH: 100/100/50 mm; ACQ matrix M × P: 120 × 120; slice thickness: 2.5 mm; NSA: 2) were obtained to determine the liver VX2 tumors. Axial IVIM-DWI was performed by using a single-shot spin echo-planar imaging sequence combined with SPAIR, with 12 b values (0, 10, 20, 30, 40, 50, 75, 100, 150, 300, 500 and 800 s/mm$^2$). The diffusion gradients were applied along the x, y and z-axis for a bi-exponential model fitting of the signal intensities.

The raw data of IVIM-DWI were transferred to a vendor-supplied workstation (Extended Workspace, Philips Healthcare), where a software program (PRIDE DWI Tool, version 1.5, Philips Healthcare) was used to extract the IVIM parametric maps, and then Image J software (National institute of Health, Bethesda, MD) was used to further process the data. Conventional $T_2$-weighted MR images (Fig. 1a) and DW images (b = 100 s/mm$^2$) (Fig. 1b) were used as references to determine

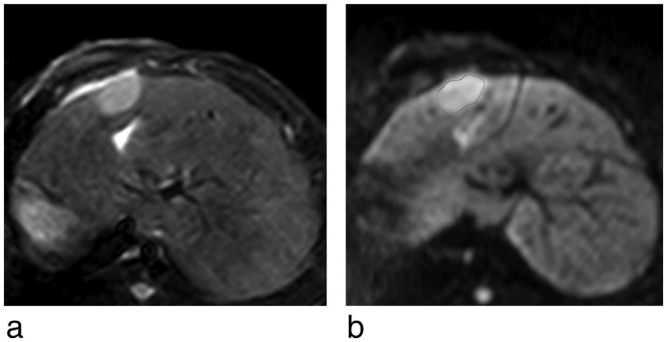


**Fig. 1.** A rabbit model with liver VX2 tumor. (a) Conventional $T_2$WI showed the VX2 tumor located in the left lobe. (b) Axial DWI map (b = 100 s/mm$^2$) showed region of interest (ROI) covered most of the VX2 tumor as large as possible.