In-vivo evaluation of hepatic function using dynamic Gd-EOB-DTPA enhanced MRI with a dual-input one output two-compartment pharmacokinetics model

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Introduction: Liver disease is a serious threat to public health with a high prevalence caused by hepatitis, obesity, and alcohol abuse, et al. If not treated in time, repeated/continuous liver damage can lead to cirrhosis and finally end up with hepatic carcinoma that has high mortality [1]. Advanced cirrhosis is widely regarded as being irreversible. Thus, early diagnosis of liver damage is critical. Liver function is an important and sensitive indicator for liver damage. However, current serum based liver function evaluation can only evaluate the whole liver, and may underestimate the local damage due to the strong functional compensation of liver. Recently, dynamic Gd-EOB-DTPA enhanced MRI together with pharmacokinetic modeling was proposed to characterize the liver perfusion and function [2]. By binding with hepatocytes, and excreted through the hepatic vein and biliary, pharmacokinetic model can be used to estimate the intracellular uptake rate of Gd-EOB-DTPA, which may reflect the liver function [3]. However, previous proposed pharmacokinetic model may not be accurate due to the assumption of contrast excretion from hepatic vein. More importantly, the relationship between intracellular uptake rate and traditional serum liver function parameters has been investigated. **In this study, we proposed a new hemodynamic model to better describe the behavior of the Gd-EOB-DTPA by adding a directly measured contrast excretion term from hepatic vein. Further validations with serum liver functional parameters were carried out for the proposed model and original model[2].**

Material and methods:

Theory: After injection of Gd-EOB-DTPA, blood carries Gd-EOB-DTPA from hepatic artery and portal vein into hepatic parenchyma. Gd-EOB-DTPA transfers to extravascular and extracellular space (EES) and into hepatocytes. Part of the contrast will be excreted via hepatic vein and the remaining part through the biliary. Because the excretion time from biliary is longer than the usual DCE-MRI acquisition time used, this outlet is assumed negligible. So we proposed a two-compartment, two-input and one output model to describe the behavior of Gd-EOB-DTPA in liver, as shown in **Fig. 1**. The contrast concentrations of two compartments have equations:

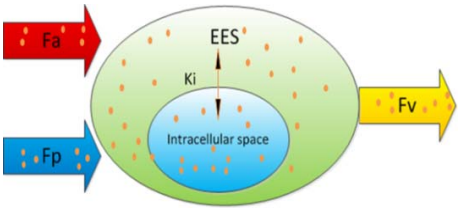

Fig.1: Schematic diagram of perfusion model, orange dots are Gd-EOB-DTPA

EES concentration: $Ve \cdot dCe(t)/dt = FaCa(t) + FpCp(t) - FvCv(t+Tv) - KiCe(t)$ (Eq.1);

Intracellular space concentration: $Vi \cdot dCi(t)/dt = KiCe(t)$ (Eq.2);

Thus, the contrast concentration of hepatic parenchyma C_t: $Ct(t) = ViCi(t) + VeCe(t)$ (Eq.3);

derived: $Ct(t) = [\delta(t) + Ki] * \exp(-Ki \cdot t/Ve) * [FaCa(t) + FpCp(t) - FvCv(t+Tv)]$ (Eq.4);

where C_a, C_p, C_v, C_e, and C_i are the contrast concentrations in the hepatic artery, portal vein, hepatic vein, EES, and intracellular space, respectively; F_a, F_p and F_v are the plasma flow of hepatic artery, portal vein and hepatic vein. K_i is the intracellular uptake rate; V_e, V_i are the fraction of EES and intracellular space in hepatic parenchyma, respectively; T_v is the hepatic vein delay. C_a, C_p, C_v, and C_t can be directly measured from images. The parameters directly derived from model fitting are F_a, F_p, F_v, K_i and V_e. *Data acquisition:* Twenty-five patients with hepatitis history (10 males, mean age 48.8 ± 11.2) were recruited in our study after informed consent. Dynamic contrast enhanced MR acquisition was performed on a 3.0 T scanner (Discovery MR750, GE, US). LAVA sequence was employed with 8ch HDMR2 torso array coil (RX). Scan parameters were: TR/TE=2.084/0.82ms, flip angel=12°, temporal resolution=2s, FOV=400*400mm², resolution=3*3mm², 40 slices. After the scan started, 0.025mmol/kg Gd-EOB-DTPA was injected intravenously at 2 mL/sec and followed by a 15 mL saline flush administered at the same injection rate coincident with first scan. A total of 200 frames were acquired. Routine serum tests including albumin (ALB) and prealbumin (preALB) were performed for all patients to evaluate their liver function. *Imaging analysis:* ROIs were carefully selected to avoid surface of liver with partial volume artifacts and regions contaminated by motion artifacts for hepatic artery, portal vein, hepatic vein and hepatic parenchyma (**Fig. 2a-d**). A clustering algorithm were used to reduce the noise: first, select one pixel as a seed point, and extract the enhancement profiles of the seed point and its nearest 11*11 pixels; then, the 121 curves were classified into 10 sets with fuzzy c-means cluster algorithm, and select the clustering center most correlated with the seed point profile as the enhancement profile *S(t)* of the ROI. By assuming a linear relationship between image intensity and contrast concentration, *S(t)/S(0)*-1 were used in pharmacokinetic models, where *S(0)* is the base line intensity, and the average intensity of first 5 time points was set for this value. For model fitting, we use non-linear least square curve fitting function with a fitting boundaries (F_a, F_p, F_v: 0~200, K_i: 0~1, V_e: 0~1). As a comparison, the published model [2] was also used with same ROIs and fitting boundaries. SPSS was used to calculate the 2-tail Pearson correlation between the pharmacokinetic parameters generated by two models and serum parameters.

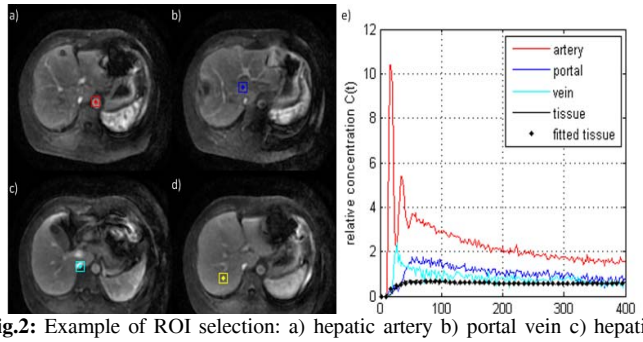

Fig.2: Example of ROI selection: a) hepatic artery b) portal vein c) hepatic vein d) tissue; and e) the concentration profiles and fitted result.

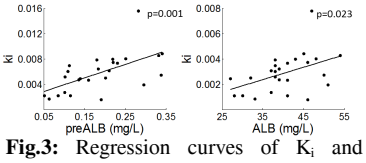

Fig.3: Regression curves of K_i and preALB and ALB of proposed model.

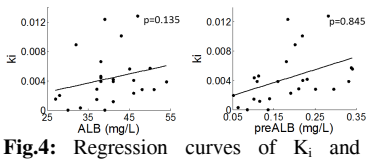

Fig.4: Regression curves of K_i and preALB and ALB of published model.

Results: A typical fitting result of the proposed model was shown in **Fig.2e**. The intracellular uptake rate K_i generated from the proposed model was found to be significantly correlated with preALB ($p < 0.005$) and ALB ($p<0.05$), as shown in **Fig. 3**. On the other hand, the K_i generated from the published model [4] has no significant correlation with preALB (p=0.135) and ALB (p=0.845) (**Fig. 4**).

Discussion and conclusion: In this study, a new model was proposed for pharmacokinetic analysis of dynamic Gd-EOB-DTPA enhanced liver MR imaging. The significant association found between K_i and preALB, ALB proven the feasibility of our model to evaluate localized liver function, since protein metabolism is one of the main functions of liver [4]. Moreover, the insignificant correlations between K_i generated from the published model [2] and serum parameters suggest the proposed model has better accuracy than previously published model. **In conclusion, the proposed dual-input one output two-compartment pharmacokinetics model for dynamic Gd-EOB-DTPA enhanced liver MRI is capable of localized liver function evaluation in-vivo.**

Reference:

[1] Detlef Schuppan et al. Lancet2008; 371: 838–51; [2] Steven S et al. Radiology 2012; 263:874-883; [3] G Schuhmann-Giampieri et al. Radiology 1992; 183:59-64; [4] Frederick K. Beck. American Family Physician 2002; 65:1975-1978.