Pharmakokinetic modeling and quantification of the liver function using DCE-MRI with contrast agent Gd-EOB-DTPA

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Purpose: We evaluate the possibility to establish a mathematical model which is able to describe liver function parameters noninvasive and space-resolved by magnetic resonance imaging (DCE-MRI). In contrast to other liver function tests, not only the overall hepatic function but even the function of hepatocytes in specific liver areas is supposed to be determined. We analyze and compare embolized and healthy liver areas regarding metabolism of arterial and portal venous blood using Gd-EOB-DTPA as liver specific contrast agent.

Introduction: All patients included in the present study had malignant liver indications which lead to an operation in order to occlude the portalvenous blood flow in the specific area. The aim of this embolization is to achieve an undersupply of the malicious area, causing it to shrink whereas the healthy liver parts start to grow. The overall blood supply of the occluded areas is reduced only to arterial blood flow while the sinusoidal blood flow with an amount of about 75% is completely suppressed. Non-embolized areas still maintain both arterial and portal venous supplies, thus a good comparison of flow and metabolism in the specific areas is possible. A continuous acquisition of the concentration-time-curve of the applied liver-specific contrast agent Gd-EOB-DTPA can be used to asses liver function expressed by the metabolism rate of the contrast medium (CM). The applied contrast agent distributes in the bloodstream and gets transported actively into healthy hepatocytes. Using a two compartment model [Fig. 1] based on the indicator dilution theory [Ref. 2, 4], it is possible to determine six relevant liver parameters.

Material and Methods: The state of the research covers the processed data of five. All MR-data were acquired in an at 1.5T MRI (Siemens MAGNETOM Avanto). Receiving coils were a standard Siemens 6-channel body coil as well as a 6-channel table coil. To record the contrast agent behavior up to 30 minutes after bolus injection, a 3D gradient-echo-keyhole-sequence with a time resolution of 3.4s (Siemens, syngo TWIST) and parallel acquisition was used. Sequence parameters were the repetition time TR=2.33ms, echo time TE=0.84ms, 24 k-space rows, central space 20%, 20% read out rate of the peripheral k-space, PAT-factor 3, no. of average 1, FoV 400x400mm, acquisition matrix 205x256, reconstruction matrix 256x72x265, slice thickness 2.5mm and flip angle α=30°. Acquisition of the dynamic data was performed over approx. 30 minutes. Within this time frame, dynamic and anatomic images were recorded in turns, resulting in gaps of the dynamic data as demonstrated [Fig. 3]. The breaks in the dynamic sequence were used for anatomic image acquisition. As the sequence was designed to allow free breathing for the patient throughout the whole data acquisition, a subsequent movement correction of the liver was performed. Motion correction was performed locally for the liver exploring the "normalized mutual information" routine by dint of a high-resolution reference image [Fig. 2, left]. The computation was performed by the visualization software Amira (FEI Visualization Sciences Group). To be able to identify the concentration information from the MR data, we use the method from Li et al. [Ref. 1], equations (1) and (2), implemented in Amira to convert signal intensities to relaxation rates. The change of relaxation rates is directly proportional to the contrast agent concentration. S(α) equals the acquired MR-Signal of a static image with defined flip angle α. TR is the time of repetition and R1 as well as M0 are identified experimentally with several measurements with different flip angles. All of these variables are used in eq. (2) to compute the relaxation rates successive for every voxel. S(0) equals the signal without contrast agent and S(t) the signal at a specific time t after the bolus injection. Subtracting the base relaxation rate, the converted relaxation maps are proportional to the contrast agent concentration with a proportionality factor 1/K (equ. 3).

$$S(\alpha) = sin(\alpha) \cdot M_0 \frac{1-e^{-T_R \cdot R1_0}}{1-cos(\alpha) \cdot e^{-T_R \cdot R1_0}} \quad (1) \qquad R1(t) = \frac{-1}{T_R} \cdot ln\left(\frac{1-(A+B)}{1-cos(\alpha)\cdot(A+B)}\right) \quad (2)$$

$$A = \frac{S(t)-S(0)}{M_0 \cdot \sin(\alpha)} \qquad B = \frac{1-e^{-T_R \cdot R1_0}}{1-\cos(\alpha)\cdot e^{-T_R \cdot R1_0}} \qquad C_T(t) = \frac{R1(t)-R_0}{K} \quad (3)$$

The resulting motion-corrected concentration maps [Fig. 2, right] were used to extract the concentration-time-curves of ROIs placed in the aorta (C_{AIF}), the Vena portae (C_{PVIF}) as well as the examined liver area (C_T). The used rate equations include two enhancing compartments and two inputs. One first compartment represents the sinusoids whereas the other compartment represents the hepatocytes. The simplex optimization algorithm is used to fit the following parameters: *overall sinusoidal flow* (F_G), *sinusoidal mean transit time* (MTT), *hepatic uptake / extraction rate* (K_I / K_E) as well as the *compartment volumes* (v_S / v_H) [Fig. 1]. To reduce the number of free parameters, two parameters were fixed: The arterial time delay between aorta and liver was fixed between 3-9 seconds depending on the data. Additionally, the overall sinusoid flow was separated into 25% of arterial and 75% of portal venous blood flow in case of non-occluded liver areas.

Results and Discussion: The computations resulted in stable regressions for all patients in healthy liver areas. The means and standard deviation of the determined parameters over all five patients are shown in table 1. All calculated parameters are within the range of expected physiological parameters and additionally to other published work [Ref. 4]. The contrast agent's uptake is at about 5%/s whereas the extraction rate is just at about 0.8%/s, resulting in the hepatic enrichment. The mean transit time of the sinusoids amounts to 5-8s. In agreement with the technical literature, the hepatocytes volume takes about 70% of the overall liver volume whereas the sinusoids take less than 10%. Although the means show coherent values with technical literature, averaging data of patients with different malignant indications results in high deviations of up to 40% (F_G, K_E). The low SNR in the dynamic sequence is most likely due to the patient's ability for free breathing throughout the whole examination. The accuracy of the regression might depend on the fixed values used in rate equation for fitting. In contrast to other published work regarding the pharmacokinetic modeling of Gd-EOB-DTPA [Ref. 3, 4], we used both liver inlets for describing a measurement duration of up to 30 minutes. This results in an accurate fitting of the contrast agent's behavior up to the point of maximum enrichment. Additionally using a two compartment approach was especially important for a proper description of the contrast agent's arterial and portal venous phase.

Conclusion: We successfully created a model to quantify space-resolved the hepatocytes function via metabolism rate of Gd-EOB-DTPA in the liver based on patient data in healthy liver segments, being an opportunity for liver function analysis. The computation provides stable regressions for all patients with physiological coherent parameters

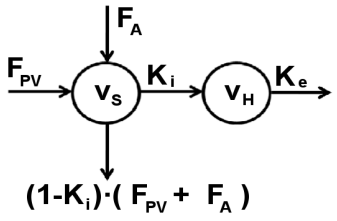

Fig. 1: Two-compartment liver model of contrast agent Gd-EOB-DTPA

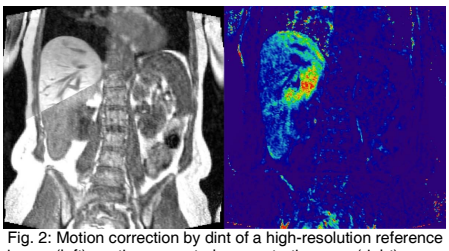

Fig. 2: Motion correction by dint of a high-resolution reference image (left), motion-corrected concentration map (right)

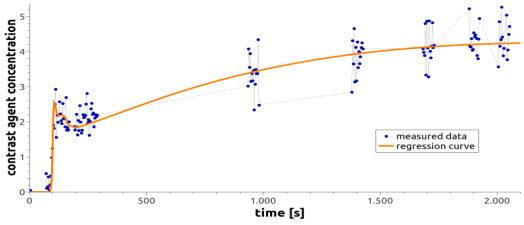

Fig. 3: Using a simplex-algorithm, the regression curve gets fitted to the measured data, thus identifying the model's unknown parameters

	$\frac{1}{K} \cdot F_G$	v_S [%]	v_H [%]	K_I [%/s]	K_E [%/s]	MTT [s]
means	$4{,}43 \cdot 10^{-4}$	3,20	66,20	5,09	0,82	6,79
st. dev.	$1{,}92 \cdot 10^{-4}$	0,94	4,55	1,18	0,32	1,17

Table 1: Means and standard deviations of the free parameters over all five patients, ROI in healthy liver areas

References:

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