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DCE-MRI of the liver: effect of linear and non linear conversions on hepatic perfusion quantification and reproducibility

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Abstract

Purpose—To evaluate the effect of different methods to convert MR signal intensity (SI) to gadolinium concentration ([Gd]) on estimation and reproducibility of model-free and modeled hepatic perfusion parameters measured with DCE-MRI.

Materials and Methods—In this IRB-approved prospective study, 23 DCE-MRI examinations of the liver were performed on 17 patients. SI was converted to [Gd] using linearity vs. non linearity assumptions (using SPGR signal equations). [Gd] vs. time curves were analyzed using model-free parameters and a dual-input single compartment model. Perfusion parameters obtained with the two conversion methods were compared using paired Wilcoxon test. Test-retest and inter-observer reproducibility of perfusion parameters were assessed in 6 patients.

Results—There were significant differences between the two conversion methods for the following parameters: AUC60 (area under the curve at 60 seconds, $p < 0.001$), peak gadolinium concentration (C_{peak} , $p < 0.001$), upslope ($p < 0.001$), F_p (portal flow, $p = 0.04$), total hepatic flow (F_t , $p = 0.007$), and MTT (mean transit time, $p < 0.001$). Our preliminary results showed acceptable to good reproducibility for all model-free parameters for both methods [mean coefficient of variation (CV) range, 11.87–23.7%], except for upslope (CV = 37%). Among modeled parameters, DV (distribution volume) had CV <22% with both methods, PV and MTT showed CV <21% and <29% using SPGR equations, respectively. Other modeled parameters had CV >30% with both methods.

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Conclusion—Linearity assumption is acceptable for quantification of model-free hepatic perfusion parameters while the use of SPGR equations and T1 mapping may be recommended for the quantification of modeled hepatic perfusion parameters.

Keywords

Liver; perfusion quantification; fibrosis

INTRODUCTION

Dynamic contrast-enhanced (DCE)-MRI allows for the quantitative characterization of tissue microvasculature in physiological and pathological conditions (1). It consists in the intravenous injection of gadolinium (Gd) based contrast agents while images are acquired with high temporal resolution, to capture changes in MR signal intensity (SI) as a function of time, due to contrast agent uptake in a tissue of interest. Tracer kinetic modeling of DCE-MRI has been used to quantify perfusion changes for the assessment of tumor angiogenesis (2, 3) and, more recently, for the diagnosis of liver fibrosis and cirrhosis (4–9). Accurate and reproducible quantification of hepatic perfusion parameters depends on the ability to reliably determine gadolinium concentration ([Gd]) from the acquired SI for both the liver parenchyma and the vascular input functions (VIF, which includes hepatic artery and portal vein in the liver). While the relationship between Hounsfield Units and iodine concentration in CT is linear (10, 11), in MRI the relationship between SI and [Gd] approaches linearity for certain ranges of image acquisition parameters, such as a short repetition time (TR) for an appropriately chosen flip angle (FA) (4, 6, 7, 9). The assumption of linearity has been used to convert MR signal to [Gd] concentration for liver perfusion quantification (4, 7, 9). Alternatively, the MR signal equations (12–15) assuming non linearity can be used to convert SI to [Gd]. Here we refer to the equations describing the behavior of the MR signal as the spoiled gradient recalled echo (SPGR) equations, as indicated in the Quantitative Imaging Biomarker Alliance (QIBA) guidelines (16). This requires knowledge of the imaging parameters and a pre-contrast T1 measurement of tissue of interest. The latter can be either calculated using T1 mapping techniques or assumed using published values (17).

As recent review papers (18–20) have pointed out, there is a lack of consensus on the methodology to be followed when analyzing DCE-MRI data in the liver. While some authors assume linearity between MR signal and [Gd] (7, 9, 21), some do not (22). The lack of homogeneity in image analysis methods may lead to difficulties in comparing results generated from different research groups and may hinder the widespread clinical application of this technique.

In this study, we aim to evaluate the impact of the method used to convert MR signal to [Gd] on the calculation of model-free and modeled hepatic perfusion metrics using a dual-input single compartment kinetic model (4, 7, 9). To our knowledge there is no published data addressing this important issue. We use inter-scan and inter-observer reproducibility of hepatic perfusion parameters using both conversion techniques as endpoints to provide guidelines for the use of either conversion method. Although there are published studies assessing reproducibility of CT (23, 24) and MR perfusion metrics in liver tumors (25–31),

there is limited knowledge on the reproducibility of perfusion metrics in liver parenchyma (25, 26). In line with the recently published QIBA guidelines on the acquisition and analysis of DCE-MRI data (16), we hope that this study can clarify and provide some guidelines for DCE-MRI of the liver by evaluating the effect of the linear and SPGR methods to convert MR signal intensity to gadolinium concentration on estimation and reproducibility of hepatic perfusion parameters.

MATERIALS AND METHODS

Patient population

This was a HIPAA compliant single center prospective study funded by NIH and approved by our local institutional review board. Informed signed consent was obtained from all patients. Seventeen patients (M/F 11/6, mean age 56 y, range 45–67 y) with untreated chronic hepatitis C virus (HCV) infection were enrolled consecutively in the study during a 12-month period from January to December 2011. These patients were recruited from the local Hepatology clinic after undergoing percutaneous liver biopsy for the assessment of fibrosis stage and inflammation grade (average delay between biopsy and MRI: 41 days, range 7–148 days). METAVIR fibrosis stages were: F2 (n=5), F3 (n=8) and F4 (n=4). Six patients underwent repeat DCE-MRI during two visits that were 2 to 30 days apart (mean delay 10 d) to assess test-retest reproducibility of hepatic perfusion parameters. All patients had eGFR (estimated Glomerular Filtration Rate) higher or equal to 60 ml/min/1.73 m².

Phantom experiments

Before in vivo imaging, the sequence used for T1 mapping of the liver parenchyma was validated using a phantom consisting of 13 tubes filled with different concentrations of gadobenate dimeglumine (Multihance, Bracco Diagnostics, Princeton, NJ), with a range of 0–5 mM, which is higher than the contrast agent concentrations normally achieved in the liver tissue during a dynamic scan. The phantom was imaged using a Look-Locker (used for T1 mapping in vivo) and an inversion recovery turbo spin echo sequence (IR-TSE). The latter was used as the reference for T1 calculations (32). Sequence parameters are listed in Table 1.

In vivo image acquisition

All examinations were performed on a 1.5T clinical system (Magnetom Avanto, Siemens AG, Erlangen, Germany) with a multichannel spine and body matrix coil and 45 mT/m maximum gradient strength. Since portal venous flow can increase after eating, all patients were asked to fast for 6 hours before the study. Patients were positioned arms up in a supine position. After routine scout scans to localize the liver, the following was acquired:

- T1 mapping, using a breath-hold Look-Locker sequence (see Table 1 for imaging parameters) before the injection of contrast so as to obtain a baseline hepatic T1 value (33, 34). T1 maps were acquired twice (during 2 separate MR exams) in 3 patients to assess reproducibility of T1 measurement.
- Whole liver DCE-MRI, using a 3D Fast Low Angle Shot (FLASH) sequence in the coronal plane (to minimize flow artifacts in the aorta). Imaging parameters are

detailed in Table 1. Similarly to a previous study from our group (9), 64 coronal volumes were acquired after contrast injection with an average temporal resolution of 2.7 sec (range, 2.4–4.0 sec) for approximately 2.5 to 4.2 minutes, after 3 pre-contrast acquisitions. Patients were instructed to take an initial 40 s breath-hold followed by a series of 24 s breath-holds separated by short periods (6.6 s) of quick breathing. Patients who could not maintain long breath-holds were instructed to breath shallowly. Images were acquired before and after injection of 0.05 mmol/Kg of gadobenate dimeglumine (Multihance) followed by a 25 ml saline flush injected at a rate of 5 ml/second with an MR-compatible power injector.

Image processing

Images were analyzed by two different observers (observer 1, 4th year medical student who underwent training using a set of 5 MRI studies under the supervision of observer 2, an experienced body MR radiologist, with 8 years experience).

T1 mapping—T1 maps were generated using MRmap (<http://sourceforge.net/projects/mrmap>) (Fig. 1) (17), for both phantom and in vivo experiments. For phantom experiments, the relationship between R1 values (1/T1) obtained from Look-Locker and IR-TSE sequence, and between these and known [Gd] values were assessed. For in vivo imaging, pre-contrast liver T1 was measured with the validated Look-Locker sequence using a single large region of interest (ROI) in the right hepatic lobe (276 ± 50 voxels). For vascular input function (VIF), blood T1 was assumed to be 1500 ms as described previously (35).

Image segmentation and registration of DCE-MRI—Image segmentation and registration was performed using software (FireVoxel) developed at New York University running on a Windows PC. A rigid registration algorithm was used, using the gallbladder, the dome of the liver and the portal vein as landmarks. SI versus time curves were obtained by placing ROIs spanning 2–5 slices in the abdominal aorta (at the level of the celiac artery, average of 187 ± 84 voxels), portal vein (at the level of the porta hepatis, 110 ± 23 voxels) and within the right hepatic lobe (4795 ± 2158 voxels) by observer 1 (Fig. 2, 3). The same landmarks were used when analyzing repeat scans by observer 3 (a physicist with 6 years' experience in MR processing, see below), to ensure ROI correspondence for the evaluation of inter-scan and inter-observer variability. Large vascular structures and liver lesions were avoided. The abdominal aorta at the level of the celiac artery was used as a surrogate for hepatic blood flow due to the small size of the hepatic artery. ROIs were propagated through all time frames using the software package.

Conversion of SI to Gd Concentration ([Gd])—SI was converted to [Gd] using two different methods (Fig. 3):

1. Assuming linearity between SI and [Gd], based on the following approximation, according to the method described by Schabel et al (36) and as used previously (7, 9, 37):

$$[Gd] = k \cdot (S - S_0) / S_0 \quad [1]$$

where S_0 is the pre-contrast SI, S is the post-contrast SI and k is a scaling parameter given by

$$k = \frac{1}{T1_{pre} \cdot r} \quad [2]$$

with $T1_{pre}$ being the pre-contrast T1 value and r being the contrast agent relaxivity. Assuming a relaxivity $r = 6.5 \text{ l s}^{-1} \text{ mM}^{-1}$, a value of 1500 ms for the $T1_{pre}$ for the vessels and a value of 500 ms for the $T1_{pre}$ of the liver parenchyma, the resulting constants were $k(\text{liver}) = 0.31 \text{ mmol/L}$ and $k(\text{blood}) = 0.1 \text{ mmol/L}$.

2. Using the SPGR signal equation without assuming linearity, which allows estimation of post-contrast T1 if the pre-contrast T1 and imaging parameters are known (14, 15). Post-contrast T1 was found by inverting the following equation:

$$SI(t) = \sin(\alpha) \cdot M_0 \cdot \frac{1 - \exp\left(-\frac{TR}{T1(t)}\right)}{1 - \cos(\alpha) \cdot \exp\left(\frac{TR}{T1(t)}\right)} \quad [3]$$

where SI is the signal intensity, α is the flip angle, t is time, and M_0 is proportional to the spin density and scanner calibration factors. [Gd] can be then calculated from obtained T1 values using the widely accepted linear relationship below.

$$[Gd] = \frac{1}{r} \cdot \left(\frac{1}{T1(t)} - \frac{1}{T1_{pre}} \right) \quad [4]$$

For this SPGR conversion, the values of $T1_{pre}$ of the liver parenchyma were estimated for each patient using the Look-Locker sequence. A fixed $T1_{pre}$ of 1500 ms was used for blood.

Calculation of model-free hepatic perfusion parameters—The following 4 parameters, time to peak (TTP, in s), peak concentration (Cpeak, in mmol/L), upslope (in mmol/L.s), and area under the curve at 60 seconds (AUC60, in mmol/L.s) were calculated using model-free computations that did not require information about VIF.

- TTP was calculated as $T_{peak} - T_{rise}$, where T_{peak} is the time point at which SI reached its maximum and T_{rise} is the time point at which SI exceeded the baseline threshold (user determined).
- Cpeak was calculated as the [Gd] at T_{peak} .
- Upslope was calculated as C_{peak}/TTP .
- AUC60 was defined as the area under the time activity curve of gadolinium contrast over 60 seconds from the start of contrast enhancement (T_{rise}).

Calculation of modeled hepatic perfusion parameters—A dual-input single compartment model (4, 6) was implemented using MATLAB (The MathWorks, Inc., Natick, MA). This model takes into account the dual blood supply of the liver and assumes

an instantaneous mixing or equilibrium of contrast medium along the course of a vessel, and was previously validated with radiolabeled microspheres in rabbits. Non linear least-squares fittings were implemented in MATLAB to fit the model curve to the measured liver concentration curve. Estimated perfusion parameters included: arterial flow (F_a , ml/min/100g), portal venous flow (F_p , ml/min/100g), total liver blood flow ($F_t = F_a + F_p$, ml/min/100g), arterial fraction [$ART = (F_a/F_t) \times 100$, %], portal venous fraction [$PV = (F_p/F_t) \times 100$, %], distribution volume (DV , %), and mean transit time (MTT , s). DV is the distribution volume of Gd-contrast through the liver compartment and MTT is the average time it takes a Gd molecule to traverse the liver from the arterial or portal inputs to the venous output.

Test-retest assessment and inter-observer variability

Six subjects underwent repeat studies 2 to 30 days apart (mean delay 10 d), which were analyzed by observer 1 to assess the inter-scan reproducibility of estimated model-free and modeled perfusion parameters using the two conversion methods described above. In addition, inter-observer variability was assessed for both conversion methods in a set of 6 random MRI studies assessed by observers 1 and 3.

Statistical analysis

MATLAB program was used for statistical analysis. Estimated perfusion parameters obtained with different signal conversion methods were compared using a paired Wilcoxon test. Inter-scan and inter-observer reproducibility of estimated perfusion parameters were assessed by calculating the coefficients of variation ($CV = SD/Mean \times 100\%$). We defined parameter reproducibility as excellent when $CV < 10\%$, good when CV was between 10–20%, acceptable when CV was between 20–30%, and poor when $CV > 30\%$.

RESULTS

Performance of in vitro and in vivo T1 mapping

$R1$ values ($1/T1$, s^{-1}) calculated using the IR-TSE sequence were linearly correlated with $[Gd]$ over the whole range of tested concentrations in phantoms ($r = 0.998$, $p < 0.0001$). $R1$ values calculated using the Look-Locker sequence were linearly correlated with $[Gd]$ for a range of concentrations between 0 and 5 mM ($r^2 = 0.998$, $p < 0.0001$) (Fig. 4). In this range, $T1$ values calculated from the Look-Locker acquisition showed very good agreement with $T1$ values calculated using the IRTSE sequence (slope = 0.96 and $r^2 = 0.99$, $p < 0.001$). This range corresponds to $T1$ values between 34.2 and 676.1 msec. In our in vivo dataset, the mean calculated pre-contrast liver $T1$ values obtained from the Look-Locker sequence was 555 ± 65 ms (range 417–648 ms), which fell within the validated linear range for the Look-Locker sequence. There was excellent reproducibility of liver $T1$ values, with CV of $T1$ values ranging from 0.9 to 2.5% as assessed in 3 patients (Table 2).

Estimated model-free and modeled hepatic perfusion parameters

23 DCE-MRI examinations of the liver were analyzed in 17 patients. The parameter TTP does not depend on the $[Gd]$ conversion method and therefore was calculated only once. There was a significant difference between the two $[Gd]$ conversion techniques for all perfusion parameters ($p < 0.05$) except for the flow fractions (ART and PV), F_a and DV .

Hepatic flow parameters were significantly lower when using the SPGR equation, while MTT and model-free parameters were significantly higher ($p < 0.05$, Table 3).

Hepatic perfusion parameter test-retest reproducibility

CVs for model-free parameters AUC and Cpeak showed good test-retest reproducibility when assuming linearity (mean CV 12.9% and 11.8%, respectively), and good to acceptable reproducibility when not assuming linearity (mean CV 19.1% and 23.7%, respectively). Reproducibility of upslope was poor for both methods (mean CV =36.6%), while reproducibility for TTP was good (mean CV 16.5%). Regarding modeled parameters, DV showed acceptable to good reproducibility with both methods (mean CV=15.2% with the linearity assumption; and 21.3% using the SPGR equation), while PV and MTT showed good/acceptable reproducibility only when using SPGR equation (mean CV=20.6% and mean CV=28.4%, respectively). The other modeled parameters had poor reproducibility (CV higher than 30%) with both methods, with ART and Fa being the least reproducible parameters (Table 4).

Inter-observer variability (Table 5)

Inter-observer variability was compared by calculating the CV between perfusion parameters obtained by two different observers. CVs were less than 24% for all parameters except for Fa, ART and upslope.

DISCUSSION

In this study, we calculated model-free and modeled liver perfusion parameters as well as their test-retest/inter-observer reproducibility using 1) the assumption of linearity between MR signal and [Gd], and 2) the SPGR MR signal equations without assuming linearity.

It is essential to determine the reproducibility of estimated liver perfusion parameters, in order to interpret data aimed at stratifying subjects with liver disease or evaluate tumor response to treatment and plan future clinical studies (9, 38). Prior published results of perfusion parameters in liver fibrosis and cirrhosis, liver metastases, and tumor angiogenesis have differed (39). These differences may stem from the fact that different studies have used different analysis methods, and both the acquisition and post-processing of liver perfusion data are not standardized.

In this study, we investigated the effect of different methods to convert MR signal to [Gd] on the estimated liver perfusion metrics. Additionally we assessed inter-scan, and inter-observer reproducibility of liver perfusion parameters. Our results indicate that the estimated hepatic perfusion parameters are all significantly different between the two conversion methods, except for Fa, ART, PV and DV. Most estimated parameters values we report using the assumption of linearity are similar to previously published values of hepatic perfusion parameters calculated with MRI (5, 7, 9). Conversely, to our knowledge there is no published study using the SPGR signal equation and the single compartment dual input model used here (4).

Using CVs as a measure of reproducibility, we found that AUC60, Cpeak, TTP, and DV are the most reproducible liver perfusion parameters when using the linearity assumption. PV also shows acceptable to good reproducibility when calculated under no linearity assumption. This may have important clinical implications, since TTP and DV have been shown to differentiate normal liver from cirrhosis (9), with DV allowing also to discriminate advanced fibrosis in a prior study (7). Furthermore, our results indicate that the reproducibility of perfusion parameters is affected by the method of [Gd] calculation. While the reproducibility of model-free parameters tended to be better with the linearity assumption (except for upslope), the reproducibility of certain modeled parameters (Fa, ART and PV) was slightly improved without linearity assumption. The reproducibility of all model-free parameters was good to acceptable (except for upslope), while the reproducibility of modeled parameters varied significantly. ART, Fa and Fp had poor reproducibility while PV, DV and MTT had acceptable reproducibility without the linearity assumption and DV had good reproducibility with the linear conversion. As for inter-observer variability, there was good agreement between the two observers for all perfusion parameters, with the exception of upslope, flow parameters and ART. We attribute the poor inter-scan and inter-observer reproducibility of ART and Fa to the small contribution of arterial flow to liver perfusion, which makes it challenging to accurately estimate these quantities. This is not the case for hypervascular tumors such as hepatocellular carcinoma (HCC), which have higher arterial contribution (40, 41). Miyazaki et al (25) evaluated the reproducibility of ART (named also hepatic perfusion index) in the whole liver and in liver metastases (in 8 patients) using model-free parameters. They compared the VIF gradients from the initial rise to the splenic and hepatic peaks. The reported CVs for ART were 5.1% and 13% for liver and metastases, respectively. While their study used whole liver ROI, including lesions and vascular structures, our ROIs were localized in normal appearing liver, excluding all major vascular structures. We believe that this would generate a more homogeneous ROI with less variation per voxel. Another study by Ng et al (27) looked at the reproducibility of the volume transfer constant between blood plasma and the extravascular space (CV= 8.9%) and AUC at 90 seconds (CV= 9.9%) using DCE-MRI in liver tumors, but not in liver parenchyma. Importantly, this group used a single input model that only characterizes the arterial input and assumed linearity of [Gd]. Several other studies have assessed the reproducibility of liver perfusion parameters using CT (23, 24) and showed excellent parameter reliability. Recently, Ng et al (24) assessed the reproducibility of CT perfusion parameters in normal liver and liver tumors in 7 patients and the effects of motion and data acquisition time on reproducibility and found the within-patient CVs of blood flow, blood volume and MTT to be 11.2%, 14.4% and 5.5%, respectively, using a single-input model.

There are several limitations to our study. First, the number of patients was relatively small. Although a total of 17 patients were scanned, only 6 patients were scanned twice to evaluate reproducibility. Despite the small number of patients, certain perfusion parameters displayed good to acceptable reproducibility. The poor reproducibility of flow parameters in our study could be due to multiple factors. Our temporal resolution (~2.7 sec) may have been insufficient to prevent under-sampling of the arterial input function peak. Furthermore, the time course of contrast agent concentration in the vessel lumen is notoriously difficult to

sample, because of the high concentrations (and therefore short T1 values) reached in the blood plasma. This may be resolved with the use of a low dose, high temporal resolution pre-bolus acquisition (42), or alternatively by slowing down the injection rate of the contrast agent. The requirement of baseline T1 mapping can also have limitations, adding a degree of complexity and potential source of error to the analysis. Many different models have been proposed for liver perfusion modeling (39). Our study used a minimally complex model. Other models while being closer to physiological processes, are more complex, which may add variability. Comparison to a quantitative gold-standard perfusion technique such as radioactive microspheres was not performed. A future study with a larger number of cases will be needed to further investigate whether the accuracy of DCE-MRI for liver fibrosis detection is affected by the method of [Gd] calculation. Finally, we did not assess reproducibility of perfusion metrics in focal liver lesions such as HCC.

In conclusion, we found that there are significant differences in most estimated model-free and modeled (using dual-input single compartment kinetic model) hepatic perfusion parameters obtained with DCE-MRI and two different methods of converting SI to [Gd]. Due to the observed reproducibility values, we recommend the use of the linearity assumption for evaluating model-free parameters, while no linearity assumption about the MR signal should be made when calculating modeled parameters. Furthermore, we recommend only using the most reproducible parameters for clinical DCE-MRI analysis in diffuse liver disease (model-free parameters, such as AUC60, Cpeak, TTP and modeled parameters DV and PV). With a better understanding of the reproducibility of DCE-MRI, the modality can now be more reliably applied as a clinical imaging tool for the diagnosis of liver pathology and for prospective drug trials. Future studies need to examine the accuracy of both conversion methods for detection of liver fibrosis, and the reproducibility of tumor perfusion metrics.

Acknowledgments

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Abbreviations

ART	arterial fraction (%)
AUC60	area under the time activity curve of gadolinium contrast over 60 s from the start of contrast enhancement (mmol/L.s)
Cpeak	peak concentration (mmol/L)
DCE-MRI	dynamic contrast-enhanced MRI
DV	distribution volume (%)
Fa	hepatic arterial blood flow (ml/min/100g)
Fp	hepatic portal blood flow (ml/min/100g)
Ft	total hepatic blood flow (ml/min/100g)
[Gd]	gadolinium concentration (mmol/L)

HCV	hepatitis C virus
IRTSE	inversion recovery turbo spin echo
MTT	mean transit time (s)
PV	portal venous fraction (%)
SI	signal intensity
SPGR	spoiled gradient recalled echo
TTP	time to peak (s)
VIF	vascular input function

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Figure 1.
64 year-old man with chronic HCV. Liver T1 map obtained with breath-hold Look-Locker sequence (see parameters in Table 1). T1 value in right hepatic lobe was 510.6 msec.

Figure 2.

64 year old man with chronic HCV (same as in Fig. 1). Select images (16.2, 24.3 and 32.4 sec after gadolinium contrast injection) shown from DCE-MRI acquisition (temporal resolution of 2.7 s, other parameters listed in Table 1) show ROI placement for perfusion processing over the abdominal aorta (in red), portal vein (PV in blue) and liver parenchyma (in green).

Figure 3.

64 year old man with chronic HCV (same as in Fig. 1, 2). Signal intensity (SI) versus time curves for abdominal aorta (in red), portal vein (in blue) and liver parenchyma (in green) shown on top. Concentration vs. time curves for the aorta, portal vein and liver parenchyma using linear and SPGR conversion methods shown on the bottom. Both the SI and [Gd] (Gadolinium concentration) curves appear as expected. The arterial curves portray a sharp first pass peak with secondary recirculation peaks. Aortic signal saturation is observed on the linear conversion curve, with clear differences in gadolinium concentrations ([Gd]) seen in the 3 tissues of interest (aorta, portal vein and liver) when comparing the two conversion methods.

Figure 4.

Phantom data using the IRTSE and Look-Locker sequences for measuring pre-contrast T1. $R1$ ($1/T1$ in sec^{-1}) vs. concentration for the Look-Locker sequence correlated well with the IRTSE sequence in a concentration range of 0 to 5 mM. This corresponded to T1 values up to 676.1 msec, which fell in the range of calculated in vivo hepatic T1 values.

Table 1

Sequence parameters of the Look-Locker and IRTSE sequences used for T1 mapping, and the 3D FLASH sequence used for liver DCE-MRI.

	Look-Locker	IRTSE	3D FLASH
Acquisition Plane	Axial	Axial	Coronal
TR	23.49	5000	2.67
TE	1.12	4.7	0.94
Flip angle	10	180	12
TI	-	50,100,250,500,750,1000,1250,1500,1750,2000,2500,3000	-
FOV Read (mm)	430	300	400
FOV Phase (%)	75	79.7	100
Slice thickness (mm)	10	3	3 (interpolated)
Acquisition matrix	192×144	128 × 102	192×121
Number of slices	1	1	36
Parallel imaging factor	1	1	GRAPPA 3
Scan time	20 s	2:15 min per TI (27 min)	2.5–3.5 min
Temporal resolution	-	-	2.7 s (average)
Number of volumes	-	-	64

Table 2

Test-retest reproducibility (expressed as coefficient of variation: CV) of liver T1 values (in ms) assessed in 3 patients using the Look-Locker sequence. This shows excellent inter-scan reproducibility of T1 calculations.

	Patient #1	Patient #2	Patient #3
Liver T1 baseline	432.8	566.8	625.3
Liver T1 repeat	417.2	574.2	647.6
CV (%)	2.5	0.9	2.4

Table 3

Estimated model-free and modeled hepatic perfusion parameters (mean $\pm$ SD) obtained with linear and non linear conversion methods (17 patients with 23 DCE-MRI acquisitions). All parameters were different between the two methods, except for Fa, ART, PV and DV.

Model free parameters	Linear conversion	Non linear conversion	p [*]
AUC60	0.15 $\pm$ 0.05	0.24 $\pm$ 0.15	0.00004
TTP	57.53 $\pm$ 18.58		NA
Cpeak	0.26 $\pm$ 0.06	0.39 $\pm$ 0.17	0.00002
Upslope	0.005 $\pm$ 0.002	0.01 $\pm$ 0.01	0.00003
Modeled parameters	Linear conversion	Non linear conversion	p [*]
Fa	70.78 $\pm$ 75.30	57.71 $\pm$ 61.07	0.06
Fp	316.55 $\pm$ 1248.12	212.55 $\pm$ 160.08	0.04
Ft	387.33 $\pm$ 290.43	270.27 $\pm$ 177.19	0.007
ART	24.29 $\pm$ 25.83	25.60 $\pm$ 30.50	0.18
PV	75.71 $\pm$ 25.83	74.40 $\pm$ 30.50	0.18
DV	60.97 $\pm$ 24.28	61.50 $\pm$ 41.61	0.9
MTT	20.43 $\pm$ 0.43	25.42 $\pm$ 10.05	0.00006

AUC60: area under the time activity curve of gadolinium contrast over 60 s from the start of contrast enhancement (mmol/L.s), TTP: time to peak (s), Cpeak: peak concentration (mmol/L), Upslope: Cpeak/TTP [mmol/(L.s)], Fa: hepatic arterial blood flow (ml/100g/min), Fp: hepatic portal blood flow (ml/100g/min), Ft: total hepatic blood flow (ml/100g/min), ART: arterial fraction (%), PV: portal venous fraction (%), DV: distribution volume (%), MTT: mean transit time (s)

* Paired Wilcoxon test (significant p-values are bolded)

Table 4

Coefficients of variation (mean and range, in %) for estimated model-free perfusion parameters and modeled liver perfusion parameters measured in 6 patients. Parameters (TTP, DV and MTT) that have been previously shown to discriminate normal from cirrhotic livers all have good to acceptable reproducibility. The reproducibility of most modeled parameters was improved using the SPGR equation, except for DV.

Model free parameters	Linear conversion	Non linear conversion
AUC60	12.97 (1.36–38.84)	19.07 (6.58–45.75)
TTP	16.48 (3.21–64.93)	16.48 (3.21–64.93)
Cpeak	11.87 (0.47–22.64)	23.70 (1.66–64.16)
Upslope	36.66 (2.51–81.58)	36.77 (4.87–84.04)
Modeled parameters	Linear conversion	Non linear conversion
Fa	73.16 (0.21–139.47)	52.94 (0.79–140.13)
Fp	58.42 (4.88–136.36)	52.44 (0.01–113.59)
Ft	38.86 (4.86–99.28)	37.32 (0.01–78.20)
ART	73.16 (6.05–140.42)	64.14 (0.77–140.48)
PV	34.03 (0.02–114.78)	20.57 (0.00–63.67)
DV	15.21 (4.12–25.74)	21.25 (12.13–35.70)
MTT	33.12 (9.73–92.93)	28.44 (8.49–67.34)

AUC60: area under the time activity curve of gadolinium contrast over 60 s from the start of contrast enhancement (mmol/L.s), TTP: time to peak (s), Cpeak: peak concentration (mmol/L), Upslope: Cpeak/TTP [mmol/(L.s)], Fa: hepatic arterial blood flow (ml/100g/min), Fp: hepatic portal blood flow (ml/100g/min), Ft: total hepatic blood flow (ml/100g/min), ART: arterial fraction (%), PV: portal venous fraction (%), DV: distribution volume (%), MTT: mean transit time (s)

Table 5

Inter-observer variability. Coefficients of variation (mean and range, in %) of estimated hepatic perfusion parameters obtained by two independent observers using the two conversion methods. Reproducibility was acceptable to excellent, except for Fa and ART and upslope (with the nonlinear conversion).

Model-free parameters	Linear	Non linear conversion
AUC60	8.91 (2.50–19.02)	9.91 (3.03–20.63)
TTP	16.40 (3.20–64.90)	16.41 (3.20–64.90)
Cpeak	11.80 (0.40–22.61)	23.60 (1.60–64.10)
Upslope	24.42 (0.72–85.94)	36.60 (4.82–84.00)
Modeled parameters	Linear	Non linear conversion
Fa	62.24 (0.40–136.40)	55.29 (0.39–133.75)
Fp	20.83 (4.54–45.86)	17.66 (3.27–47.58)
Ft	17.31 (5.40–32.67)	18.74 (4.73–40.86)
ART	68.04 (21.89–137.83)	61.12 (21.96–133.23)
PV	8.67 (0.04–21.66)	3.74 (0.02–12.65)
DV	9.06 (0.64–14.70)	10.20 (1.12–17.72)
MTT	11.23 (0.00–19.14)	12.66 (2.71–24.01)

AUC60: area under the time activity curve of gadolinium contrast over 60 s from the start of contrast enhancement (mmol/L.s), TTP: time to peak (s), Cpeak: peak concentration (mmol/L), Upslope: Cpeak/TTP [mmol/(L.s)], Fa: hepatic arterial blood flow (ml/100g/min), Fp: hepatic portal blood flow (ml/100g/min), Ft: total hepatic blood flow (ml/100g/min), ART: arterial fraction (%), PV: portal venous fraction (%), DV: distribution volume (%), MTT: mean transit time (s)