Chapter 8

PERFUSION MRI OF THE WHOLE LIVER AT HIGH TEMPORAL AND SPATIAL RESOLUTION WITH 4D THRIVE: FEASIBILITY OF FOCAL LESION CHARACTERIZATION USING PARAMETRIC MAPS.

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ABSTRACT

**Objective:** To prospectively evaluate a new imaging sequence (4D THRIVE) for whole liver perfusion in high temporal and spatial resolution. Feasibility of parametric mapping and its potential for characterizing focal liver lesions (FLLs) are investigated.

**Methods:** Fifteen patients suspected for colorectal liver metastases (LMs) were included. Parametric maps were evaluated qualitatively (ring enhancement and lesion heterogeneity) and compared to three-phased contrast-enhanced MRI. Quantitative analysis was based on average perfusion values of entire FLLs. Reference standard comprised surgery with histopathology or follow-up imaging. Fisher’s exact test was used for qualitative and Kruskal-Wallis test for quantitative analysis.

**Results:** In total 29 LMs, 17 hemangiomas and 4 focal nodular hyperplasias were evaluated. FLLs could be differentiated by qualitative assessment of parametric maps respectively three-phased contrast-enhanced MRI (Fisher’s p < 0.001 for comparisons between LMs and hemangiomas and LMs and FNHs for both ring-enhancement and lesion heterogeneity) rather than by quantitative analysis of parametric maps (Chi-square for Kep = 0.33 (p=0.847) and chi-square for Kel = 1.35 (p=0.509)).

**Conclusion:** This preliminary study shows potential of 4D THRIVE for whole liver imaging enabling calculation of parametric maps. Qualitative rather than quantitative analysis was accurate for differentiating malignant and benign FLLs.
INTRODUCTION

For detecting and characterizing tumours in abdominal organs like the liver, the hepatic purely arterial phase is important [1-3]. For conventional contrast-enhanced dynamic liver imaging, the period of the hepatic phase will overlap with enhancement of blood coming from the portal vein in the duration of a 20-second acquisition time [3]. Also, imaging of the portal-venous phase is crucial for characterizing focal liver lesions (FLLs) (e.g. ring-enhancement being a useful sign to differentiate hemangiomas and metastases)[4]. Hence for contrast-enhanced Magnetic Resonance Imaging (MRI) of abdominal organs, a precise timing of contrast-enhancement, short acquisition times and accurate sampling are crucial.

To date, reports of liver perfusion at MRI are limited in number and vary considerably [5]. Pharmacokinetic analysis of DCE MRI has been used in literature to provide a non-invasive assessment of hepatic perfusion [6, 7]. DCE MRI has also been used for imaging one or some slices throughout the liver parenchyma [8].

The presented study introduces a new technique using keyhole imaging based T1w CE-MRI of the whole liver in high temporal and spatial resolution including automated calculation of parametric maps. In a group of patients suspected of colorectal Liver Metastases (LMs), the new 4D THRIVE sequence is compared with standard three-phased DCE MRI. Implications for the characterization of FLLs are examined qualitatively and quantitatively.

MATERIALS AND METHODS

Patients

From May 2007 till September 2007, 15 consecutive patients (10 female; 5 male, mean age 55.7 ± 10.3 years) suspected for
metachronous LMs from colorectal carcinoma at a tertiary referral center were included in this study. Patients were included in this study when at follow-up for a primary tumour, a new non-cystic FLL was detected at ultrasound (US) and/or laboratory results showed elevated Carcino-Embryonic Antigen > 3.4 ng/ml for non-smokers, >4.3 ng/ml for smokers in combination with elevated transaminase levels (ALT >41 U/l for male, >31 U/l female patients), elevated alkaline phosphatase >129 U/l, and elevated bilirubin (total bilirubin > 1.2 mg/dl). All patients fasted for 4 hours prior to each MRI examination. Patients were excluded when there were contraindications for intravenous injection of gadolinium-BOPTA (Multihance®, Bracco, Milan, Italy) or for MRI. This prospective study was approved by the hospital ethics committee and written informed consent was obtained from all patients.

**MRI technique**

All images were acquired using a 3.0T Achieva X-series scanner (Philips Medical Systems, Best, The Netherlands) and a 6-element Torso coil. Perfusion imaging was part of a conventional MRI examination including T2w TSE with fat-suppression (TR/TE: 777ms/60ms; matrix: 256mm; slice thickness: 6mm) and in-and-out-of-phase imaging (TR/TE: 177ms/2.3ms and 4.6ms; matrix: 256mm; slice thickness: 6mm).

Perfusion imaging was performed using Four-Dimensional T1-weighted High Resolution Imaging with Volume Excitation (4D THRIVE) as described by Beck [9] was used. This method is based on a 3D fat-saturated spoiled turbo gradient echo sequence where a fat saturation pre-pulse followed by the acquisition of several profiles is combined with 3D dynamic elliptical centric Keyhole, Half Scan (partial Fourier acquisition) and Sensitivity Encoding (SENSE) to
accelerate the acquisition. The elliptical centric Keyhole method consists of dynamically acquiring a limited number of central ky-kz-space profiles (disk), and sharing the high spatial resolution information from a single full data set called reference. To further accelerate the technique, an alternating viewsharing technique as described in [10] was applied. The central ky-kz disk defined by the keyhole percentage hereby is subdivided in three regions, $P^+$, $C$ and $P^-$, where $P^+$ and $P^-$ cover positive and negative peripheral regions in this central disk and $C$ the central region as shown in Fig. 1. The central region $C$ is acquired every dynamic scan while regions $P^+$ and $P^-$ are shared with subsequent dynamic scans according to an alternating viewsharing scheme: $P^+ - C - P^- - C - P^+ - C - P^- - C - P^+ - P^- - C - P^+ - Ref$. The $P^-$ and $P^+$ parts from subsequent keyhole scans are shared in the reconstruction process.

The perfusion sequence parameters were TR/TE=2.9ms/1.4ms, turbo factor = 46, FOV 375mm x 280 mm, in-plane resolution 2mm, acquisition slice thickness 3mm, reconstruction of 133 slices of 1.5 mm thickness. Acquisition was transverse, Sense factor was 2 in the anterior-posterior direction. The keyhole factor was 45% (spatial resolution in phase and slice encoding direction was 3.7 mm) and the viewsharing percentage $(P^+ + C)/(P^+ + C + P^-)$ was 55% leading to a total acquisition time of 24.8 % with respect to the reference acquisition.

A first 3D scan of the whole liver was obtained during breath-hold before injection of contrast agent. During the first four breath-holds after injection, 3 dynamic scans were performed per breath-hold - with 2 keyhole acquisitions acquiring only the central alternating ky-kz parts, $P^- - C$ and $P^+ - C$, as shown in Figure 1, concluded by a reference acquisition, $P^- - C - P^+ - Ref$, that acquires both central and peripheral ky-kz parts. During the last two breath-holds
1 dynamic scan, P- C-P+ -Ref, was performed. This resulted in 15 dynamic scans in total. The acquisition time of the central part of k-space was 2.7 seconds and the acquisition time of the reference acquisition was 10.8 seconds (10.8s x 45/100 (Keyhole percentage) = 4.9s; 4.9s x 0.55 (viewsharing) = 2.7s). This results in an acquisition time of 16.2 seconds per breath-hold for the first four post-contrast breath-holds, and an acquisition time of 10.8 seconds for the remaining two post-contrast breath-holds.

Figure 1. A schematic depiction of the alternating viewsharing technique. The central ky-kz disk defined by the keyhole percentage is subdivided in three regions, P+ , C and P-, where P+ and P- cover positive and negative peripheral regions in this central disk and C the central region as shown in fig. 1. The central region C is acquired every dynamic scan while regions P+ and P- are shared with subsequent dynamic scans according to an alternating viewsharing scheme: P+ -C-P'-C-P+ -C-P+ -C-P+ -Ref. The P- and P+ parts from subsequent keyhole scans are shared in the reconstruction process.

One respiration was allowed between the first two post-contrast breath-holds and two respirations before the third to fifth
post-contrast breath-hold. A longer free breathing period was allowed before the last breath-hold.

One ml/10 kg (0.05 mmol/kg) body weight of gadolinium-BOPTA (MultiHance®, Bracco, Milan, Italy) was injected as a bolus via the cubital vein immediately followed by 20ml of physiologic saline (NaCl 0.9%) both at 3ml/s using Spectris MR injector (Medrad, Maastricht, The Netherlands). Fluoroscopic imaging was used for bolus tracking. Scanning was started when the contrast agent was filling the right atrium.

**Calculation of parametric maps**

After the MRI examination, anonymous patient labels were assigned to each patient for blinded image interpretation. To correct for possible misregistration due to non-reproducible breath-hold levels, a registration procedure was applied to align all dynamic scans to the first one, using the IRTK toolbox [11]. The registration procedure was applied selectively in the smallest possible box containing the whole liver and the allowed geometrical transformations were restricted to rigid body motion (rotations/translations). Perfusion quantification was based on the two-compartment model initially proposed by Brix G. et al. [12], slightly modified for breast [13] and liver [14] applications, and simplified by Tofts P. [15] for the case of extremely short bolus injection. In this model, tissue is composed of two compartments, plasma and interstitial space (or extravascular extracellular space, EES). The concentration of contrast agent in plasma is described by a mono-exponential decay with a time constant Kel, and the rate of contrast agent exchange between plasma and EES is called Kep (Kep=Ktrans/ve, [16]). The relative signal increase is assumed to be linearly related to the concentration of contrast agent. By fitting
equation [17] in reference [15] to our data, we could estimate for each voxel $K_{ep}$, $K_{el}$, and an amplitude factor $AH$ which is proportional to $ve$ (EES volume fraction) and to the concentration of contrast agent in the plasma just after the bolus [15]. Pharmacokinetic modeling was implemented on the PRIDE workstation (Philips Research Imaging Development Environment) based on IDL (Interactive Data Language, ITT Visual Solutions, Boulder, CO, USA).

**Qualitative analysis of parametric maps; comparison with three-phase CE-MRI**

Image analysis was performed by one abdominal radiologist (7 years of experience in abdominal MRI). The radiologist did not have any other information about patient history, laboratory results, findings of other imaging techniques, or final diagnosis during this evaluation session. This radiologist first evaluated the routine MRI sequences for FLLs. The detected FLLs were assigned a specific liver segment using Couinaud’s segmental anatomy. Only FLLs which were detected on these sequences were further evaluated. Liver cysts were not evaluated in this study as they (almost) never pose any diagnostic problem using MRI.

$K_{ep}$ maps are most suitable for evaluating the arterial status of FLLs, therefore they were selected for qualitative analysis. The parametric maps were evaluated for the presence or absence of ring-enhancement surrounding FLLs and for the presence or absence of heterogeneity throughout each entire FLL. Fisher’s exact test was used to test for differences between LMs and hemangiomas and LMs and FNHs for both ring-enhancement and lesion heterogeneity. Calculation of intra-observer variability was performed by kappa-analysis.
To compare the performance of 4D THRIVE-based parametric maps with standard three-phased contrast-enhanced MRI (3D THRIVE), the same qualitative analysis (ring enhancement and lesion heterogeneity) was applied to a subset of the native 4D THRIVE series, obtained by keeping only the reference scan (P^-C-P^+-Ref) acquired at the end of breath-holds, while removing the fast keyhole scans obtained at the beginning of breath-holds.

**Quantitative analysis of parametric maps**

Quantitative evaluation of parametric maps was also performed: the above mentioned radiologist drew ROI’s including entirely each detected FLL, and the mean Kep and Kel were computed in each ROI. Kruskal-Wallis analysis was used for quantitative analysis (Kep and Kel) using the lesion type as grouping variable. Calculation of intra-observer variability was performed by Pearson correlation (no normal distribution of FLLs for Kep and Kel). Differences were considered statistically significant when p<0.05.

**Reference standard for lesion characterization**

For evaluating LMs, in patients eligible for surgery, intraoperative US findings during surgery and histopathologic findings were used as reference standard. In all other patients the final diagnosis was established by independent reading of all available imaging examinations (retrospective and prospective analysis of all available imaging studies (US, Computed Tomography (CT), MRI) by two radiologists (7 and 14 years of experience in abdominal MRI), and follow-up imaging were used.

For hemangiomas, diagnosis was based on typical findings on US, CT, or MRI. Typical lesion characteristics had to be present on at least two of three imaging modalities.
For Focal Nodular Hyperplasias (FNHs), diagnosis also was based on typical findings on US, CT, or MRI. All patients eligible for surgery were operated on if indicated.

RESULTS

All examinations were performed without any adverse events. In all cases a complete registration and alignment of all dynamic scans to the first one could be performed (see example in fig.2). Parametric maps including the whole liver were obtained for all patients.

**Figure 2.** The perfusion data before (upper row) and after (lower row) co-registration to the first dynamic scan of the series. From left to right, same slice in dynamic scans 1, 2, 5, 8, 11 and 14., i.e. first dynamic scan of each breath-hold excluding the delayed breath-hold scan. Before co-registration, slice positions are clearly different due to different breath-hold levels. After registration, pixel positions in different dynamic scans become comparable, hereby allowing calculation of parametric maps.

In total 29 LMs (diameter range: 7mm-50mm, mean diameter: 19.2mm ± 12.7mm), 17 hemangiomas (diameter range: 6mm-29mm, mean diameter: 17.6mm ± 7.3mm) and 4 FNHs (diameter range: 8mm-80mm, mean diameter: 34.5mm ± 33.1mm) were detected (fig. 3-5).
Figure 3. A liver metastasis in a 68-year-old woman using transverse contrast-enhanced 4D THRIVE. The reference image using 4D THRIVE in delayed phase (on the left) is shown with corresponding automatically calculated Kep map (on the right). The parametric map shows the liver metastasis (white arrow) as a heterogenous lesion with ring enhancement. Portal vein is indicated with white arrowhead.

Figure 4. A liver hemangioma in a 56-year-old man using transverse contrast-enhanced 4D THRIVE. The reference image using 4D THRIVE in the delayed phase (on the left) is shown with corresponding automatically calculated Kep map (on the right). The parametric map shows the liver hemangioma (white arrow) with absent ring enhancement (white arrow).

Five patients were operated on, 7 patients were diagnosed having liver hemangiomas on follow-up imaging and 3 patients were diagnosed having LMs showing progressive disease on follow-up imaging (table 1).
4D THRIVE for whole liver imaging

Figure 5. An FNH in a 30-year-old woman using transverse contrast-enhanced 4D THRIVE. The reference image using 4D THRIVE in the delayed phase (on the left) is shown with corresponding automatically calculated Kep map (on the right). The parametric map shows the FNH as a homogenous focal liver lesion with central scar and feeding artery.

Table 1. Patient overview giving details on operated lesions, lesions diagnosed during follow-up (and lesions showing progressive disease)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Metastasis</th>
<th>Hemangioma</th>
<th>FNH</th>
<th>Surgery and IOUS</th>
<th>Follow-up</th>
<th>Progressive disease</th>
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The numbers in columns 2-7 refer to the number of lesions detected (columns 2-4) and the number of lesions diagnosed via surgery and IOUS or follow-up imaging. IOUS: intraoperative ultrasound.
Examples of time-intensity curves in normal liver and LM in patient 15 are shown in figure 6.

**Qualitative analysis of parametric maps; comparison with three-phased CE-MRI**

The results of qualitative evaluation of FLLs using parametric maps are given in table 2. Fisher’s $p < 0.001$ for the comparison between LMs and hemangiomas and LMs and FNHs for both ring-enhancement and lesion heterogeneity. Kappa = 1 for the two readings of ring-enhancement and lesion heterogeneity with $p < 0.001$. The qualitative analysis of standard three-phased contrast-enhanced MRI gave the same results as parametric maps (see table 2).

![Figure 6. Time-intensity curves for normal liver (left) and liver metastasis (right). Signal intensities are presented as percentage of the local pre-contrast signal intensity.](image)
4D THRIVE for whole liver imaging

**Table 2.** Number of lesions with or without ring enhancement and heterogeneity using parametric maps, respectively three-phased contrast-enhanced MRI images.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Ring enhancement</th>
<th>Heterogenous lesion</th>
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<tbody>
<tr>
<td></td>
<td>present</td>
<td>absent</td>
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<tr>
<td>Metastasis</td>
<td>27</td>
<td>2</td>
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<tr>
<td>Hemangioma</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>FNH</td>
<td>0</td>
<td>4</td>
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</table>

**Quantitative analysis of parametric maps**

The result of quantitative evaluation of FLLs using parametric maps (ROI including each lesion entirely) is given in table 3. Chi-square for Kep = 0.33 (p=0.847) and chi-square for Kel = 1.35 (p=0.509). Pearson correlation is 0.995 for Kep and 0.991 for Kel both with p<0.001.

**Table 3.** Kep and Kel values (in s\(^{-1}\))

<table>
<thead>
<tr>
<th>Kep</th>
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<th>Kel</th>
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<td>FNH</td>
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SD: Standard Deviation.

**DISCUSSION**

Our study demonstrated the feasibility of whole liver perfusion imaging at high temporal and spatial resolution with 4D THRIVE, including parametric maps. A statistically significant difference between LMs and benign FLLs (hemangiomas and FNHs)
was found for qualitative analysis of ring-enhancement and lesion heterogeneity using parametric maps. Using whole-lesion ROI placement on parametric maps and calculation of averaged Kep and Kel, we didn’t observe any difference between LMs, hemangiomas or FNHs. A perfect intra-observer variability was found for ring-enhancement and lesion heterogeneity using qualitative analysis of parametric maps. An almost perfect intra-observer variability was found for quantitative analysis of parametric maps.

T1w CE MRI has only rarely been used for liver perfusion imaging [14, 18-20]. In most cases, only one to a few slices within the liver have been used. The study of White M et al. [21] has evaluated the whole liver (3D volume with 36 slices) in humans suffering from colorectal LMs. Voxel-based parametric mapping of hepatic perfusion index (HPI) was calculated. Regions of abnormal perfusion were visualized on HPI maps revealing areas of locally increased HPI around colorectal LMs. Their method for MRI voxel-based parametric mapping of HPI has the potential to demonstrate regional variations in perfusion at segmental and subsegmental level. Using gentle breathing during dynamic imaging caused blurring of HPI maps in a small number of cases. In our study a different approach is used. Qualitative analysis showed that presence of ring-enhancement and lesion heterogeneity is useful in this study to differentiate malignant from benign FLLs. The ring-enhancement detected in this study is concordant with locally increased HPI extending around the visible margins of known colorectal LMs described by White M et al. [21]. In our study the whole liver was scanned in higher temporal and spatial resolution resulting in parametric maps allowing evaluation of all FLLs. Scanning was performed in multiple breath-holds to avoid blurring and phase-encoding artifacts due to respiratory motion, and the differences in
diaphragm level between breath-holds were corrected off-line by image registration.

Jackson A et al. [22] have performed T1w DCE MRI in patients suffering from hepatic malignancies. Typical arterial enhancement was demonstrated. This was comparable with the results of our study, but comparison is difficult as a different perfusion model was used. Only two patients with hemangiomas were evaluated, making accurate comparison with our data impossible. The number of FLLs is not mentioned. 4D THRIVE in our study was performed with higher spatial and temporal resolution. It is surprising in the study of Jackson A et al. that all dynamic series had such a comparable breath-hold level (liver positioning) obviating the use of co-registration procedures in most patients. This was not the case in our study. Like Jackson A et al., we used a pharmacokinetic model with a single vascular input, which is appropriate for lesions showing a strong arterial enhancement, but is not realistic for normal liver which is perfused mainly with portal blood. Unlike Jackson A et al., our model does not rely on measuring the arterial input function (AIF). We make instead the hypothesis that the AIF has the same shape for all patients (mono-exponential decay after bolus) but its decay rate Kel is adjusted individually pixel per pixel, as was also done by Scharf J et al. [19]. This choice was motivated by the fact that, due to the extensive anatomical coverage of our MRI sequence (whole liver), the temporal resolution of our data was not high enough for accurate measurement of individual AIF, which is known to be complicated also by ROI positioning issues and inflow effects [23, 24].

To our knowledge this study is the first MR perfusion imaging of the whole liver in humans with high temporal and spatial resolution allowing calculation of parametric maps. 4D THRIVE offers
potential for assessment of the whole liver as part of a routine MRI examination. An advantage of 4D THRIVE is that the peripheral part is acquired at the end of a breath-hold, with reduced motion artifacts in case of (slight) movement. Another advantage from a clinical point of view was the ability to scan the whole liver for evaluating FLLs.

Currently, parametric maps still require (non-commercially available) specialist software, but they are likely to enter the clinical practice because of a number of advantages: they are able to spatially match tumour vascular characteristics such as blood volume, blood flow, permeability and leakage space, they offer an easy visual evaluation of the liver, their calculation can be automated for optimal workflow, and they can be acquired repeatedly for follow-up studies. Furthermore, parametric maps don’t require time-consuming and observer-dependent ROI placement, and they evaluate perfusion parameters locally rather than calculating mean perfusion changes in the whole lesion or a part of a lesion. Whole-lesion ROI assessment may be inappropriate particularly for evaluating malignant lesions where heterogeneous areas of enhancement are diagnostically important [17, 25-27]. This is concordant with the results of our study where quantitative data using ROI calculations were not (so) useful to characterize FLL’s, while a merely qualitative evaluation of parametric maps was able to differentiating malignant from benign FLLs.

It may appear contradictory that parametric mapping, a fundamentally quantitative method, turns out to be more successful as a visual inspection tool than as a measure of perfusion parameters in this study. However, with further improvements of the perfusion maps (e.g. through higher temporal resolution of the acquisition sequence and more accurate registration procedures),
and more specific ROI placement strategies, parametric maps could become useful also as a quantitative tool, especially in follow-up studies.

In our study we considered that the set of reference scans from the 4D THRIVE sequence was comparable to a regular three-phased CE MRI study (3D THRIVE), which could have been performed in a separate study. However since acquisitions are restricted to breath-holds, compromises need to be made with respect to spatial resolution in the 4D THRIVE technique as compared to a true 3D THRIVE acquisition. Nonetheless, the 4D THRIVE sequence has the advantage of obtaining quantitative data for perfusion calculation which is not the case using three-phased CE MRI.

In conclusion, in this preliminary study we show that the 4D THRIVE sequence is feasible for perfusion-based T1w CE-MRI and allows calculation of parametric maps. The 4D THRIVE sequence seems promising for qualitative differentiation of malignant and benign FLLs using parametric maps. Once the methodology is established, rigorous multi-observer studies including more patients will be required to validate perfusion MRI and determine its impact on the ability to differentiate malignant from benign FLLs.
REFERENCES


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