Magnetic Resonance Imaging of the Hepatobiliary System Using Hepatocyte-Specific Contrast Media

Nils Dahlström

Center for Medical Image Science and Visualization

Division of Radiological Sciences
Department of Medicine and Health Sciences
Faculty of Health Sciences
Linköping University, Sweden

Linköping 2009
Cover pictures
Left: MRI overview of the upper abdomen in the coronal plane.
Right: Contrast-enhanced MRI of the biliary system using Gd-EOB-DTPA.

Published articles have been reprinted with the permission of the copyright holder.


ISBN 978-91-7393-653-8
ISSN 1100-6013
To Linda and Gustav

“Never worry about theory as long as the machinery does what it’s supposed to do.”

Robert A. Heinlein
CONTENTS

1. INTRODUCTION 1

2. BACKGROUND 2
   2.1. Hepatic and Biliary Disease 2
   2.2. Imaging Modalities 4
      2.2.1. Ultrasound (US) 4
      2.2.2. Computed Tomography (CT) 4
      2.2.3. Nuclear Medicine (NM) 5
      2.2.4. Magnetic Resonance Imaging (MRI)
         2.2.4.1. Nuclear Magnetic Resonance 6
         2.2.4.2. MRI technique 7
         2.2.4.3. Basic layout of a MRI sequence 7
         2.2.4.4. T1 and T2 Relaxation 8
         2.2.4.5. MRI Sequences 9
   2.3. Contrast Media in Liver MRI 10
      2.3.1. Gd-BOPTA (MultiHance®) 10
      2.3.2. Gd-EOB-DTPA (Primovist®) 11
      2.3.3. Gadolinium Contrast Media and Relaxivity 11
      2.3.4. Contrast Administration and Bolus Timing 12
      2.3.5. Safety of Gadolinium-Based Contrast Media 14

3. AIMS 15
   3.1. Paper I 15
   3.2. Paper II 15

4. MATERIAL AND METHODS 16
   4.1. Subjects 16
   4.2. Contrast Media 16
   4.3. MRI Technique 16
   4.4. Image and Signal Intensity Analysis, Statistical Analysis 17
      4.4.1. Paper I 17
      4.4.2. Paper II 17
ABSTRACT

There are two Gadolinium-based liver-specific contrast media for Magnetic Resonance Imaging on the market, Gd-BOPTA (MultiHance®, Bracco Imaging, Milan, Italy) and Gd-EOB-DTPA (Primovist®, Bayer Schering Pharma, Berlin, Germany). The aim of this study in two parts was to evaluate the dynamics of biliary, parenchymal and vascular enhancement using these contrast media in healthy subjects.

Ten healthy volunteers were examined in a 1.5 T magnetic resonance system using three-dimensional Volumetric Interpolated Breath-Hold (VIBE) sequences for dynamic imaging with both contrast media – at two different occasions – until five hours after injection. The doses given were 0.025 mmol/kg for Gd-EOB-DTPA and 0.1 mmol/kg for Gd-BOPTA. The enhancement over time of the common biliary duct in contrast to the liver parenchyma was analyzed in the first study. This was followed by a study of the image contrasts of the hepatic artery, portal vein and middle hepatic vein versus the liver parenchyma.

While Gd-EOB-DTPA gave an earlier and more prolonged enhancement of the biliary duct, Gd-BOPTA achieved higher image contrast for all vessels studied, during the arterial and portal venous phases. There was no significant difference in the maximal enhancement obtained in the liver parenchyma.

At the obtained time-points and at the dosage used, the high contrast between the common biliary duct and liver parenchyma had an earlier onset and longer duration for Gd-EOB-DTPA, while Gd-BOPTA achieved higher maximal enhancement of the hepatic artery, portal vein and middle hepatic vein than Gd-EOB-DTPA.

Diseases of the liver and biliary system may affect the vasculature, parenchyma, biliary excretion or a combination of these. The clinical context regarding the relative importance of vascular, hepatic parenchymal and biliary processes should determine the choice of contrast media for each patient and examination.
LIST OF PAPERS

This thesis is based on the following two papers, which are referred to by their Roman numerals (I and II).


# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
</tr>
<tr>
<td>B₀</td>
<td>The static magnetic field</td>
</tr>
<tr>
<td>B₁</td>
<td>The varying radiofrequency magnetic field produced by the RF-coil</td>
</tr>
<tr>
<td>CCC</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>CHD</td>
<td>Common Hepatic Duct</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
</tr>
<tr>
<td>FOV</td>
<td>Field Of View</td>
</tr>
<tr>
<td>GRE</td>
<td>Gradient (Recalled) Echo</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular Carcinoma</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>HIDA</td>
<td>Hepatobiliary Iminodiacetic Acid</td>
</tr>
<tr>
<td>In vitro</td>
<td>In phantoms or tubes</td>
</tr>
<tr>
<td>In vivo</td>
<td>In the living body</td>
</tr>
<tr>
<td>MDCT</td>
<td>Multi-Detector Computed Tomography</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRCP</td>
<td>Magnetic Resonance Cholangiopancreatography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>Mᵋ</td>
<td>Longitudinal magnetisation</td>
</tr>
<tr>
<td>Mᵧ</td>
<td>Transverse magnetisation</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Non-Alcoholic Fatty Liver Disease</td>
</tr>
<tr>
<td>NASH</td>
<td>Non-Alcoholic Steatohepatitis</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NSF</td>
<td>Nephrogenic Systemic Fibrosis</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>R₁</td>
<td>Longitudinal relaxation rate [s⁻¹]</td>
</tr>
<tr>
<td>R₂</td>
<td>Transverse relaxation rate [s⁻¹]</td>
</tr>
<tr>
<td>r₁</td>
<td>Longitudinal relaxivity [s⁻¹mM⁻¹]</td>
</tr>
<tr>
<td>r₂</td>
<td>Transverse relaxivity [s⁻¹mM⁻¹]</td>
</tr>
<tr>
<td>RF</td>
<td>Radio Frequency [MHz]</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SE</td>
<td>Spin Echo</td>
</tr>
<tr>
<td>SPIO</td>
<td>Small Superparamagnetic Iron Oxide particles</td>
</tr>
<tr>
<td>T</td>
<td>Tesla</td>
</tr>
<tr>
<td>T₁</td>
<td>Longitudinal relaxation time [s]</td>
</tr>
<tr>
<td>T₂</td>
<td>Transversal relaxation time [s]</td>
</tr>
<tr>
<td>T₂*</td>
<td>Transversal relaxation time including B₀ inhomogeneities effects [s]</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time [s]</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time [s]</td>
</tr>
<tr>
<td>USPIO</td>
<td>Ultrasmall Superparamagnetic Iron Oxide particles</td>
</tr>
<tr>
<td>VIBE</td>
<td>Volumetric Interpolated Breath-hold Examination</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

The non-invasive methods for discovering and characterizing disease processes in the liver and the biliary system have improved greatly over the last decades due to the continuing development of computed tomography (CT), sonography or ultrasound (US), nuclear medicine (NM) and magnetic resonance imaging (MRI). Contrary to CT and NM, Magnetic Resonance imaging does not expose the patient to any ionizing radiation, and compared to US there are other advantages such as greater volume coverage and less operator dependence. When body MRI was introduced in the early 1980’s, its superior soft-tissue contrast was believed to provide enough diagnostic information for most needs, without the use of contrast media. Gadolinium-based and other contrast media were, however, soon shown to be of importance in disease detection and characterization. Liver-specific substances have also been developed and are now commonly used in various clinical situations. There is a continuous need for comparative studies to validate the choice of contrast medium and imaging strategy in different settings. With the introduction of Gd-EOB-DTPA (Primovist® 0.25 mmol/ml, Bayer Schering Pharma, Berlin, Germany) in 2004, there were two similar Gadolinium-based liver-specific compounds on the market, the other being Gd-BOPTA (MultiHance® 0.5 mmol/ml; Bracco Imaging, Milan, Italy). The aim of this study in two parts was to evaluate the dynamics of biliary, parenchymal and vascular enhancement using these contrast media in healthy subjects.
2. BACKGROUND

2.1. Hepatic and Biliary Disease

The liver is a large and complex organ with diverse functions, many of them critical for survival. When the liver is affected by disease, its considerable regenerative capacity makes many pathological processes stay undetected for a long time. Diseases initially arising in the biliary system can cause secondary or associated liver disease. Moreover, many cancer types, e.g. colorectal and breast cancer, spread metastases to the liver. Metastatic disease can also stay subclinical for a long time since a considerable portion of the liver has to be affected before liver function begins to fail (13).

Hepatobiliary diseases can be classified in several ways, e.g. diffuse versus focal disease. Diffuse liver disease encompasses many different processes such as infection, autoimmune inflammation, fatty infiltration, metabolic disorders, and certain genetic diseases. The dominant diffuse liver process in the population of the industrialized regions is fatty infiltration, which can be caused by alcohol consumption but is also present without association with alcohol, named Non-Alcoholic Fatty Liver Disease, NAFLD (58). The latter is considered the hepatic aspect of insulin resistance and represents a spectrum from slight, diffuse fat accumulation (steatosis) via Non-Alcoholic Steatohepatitis (NASH) where there is also an inflammation (33), to the formation of liver cirrhosis (53). In many parts of the world, infection with hepatitis virus B (HBV) and C (HCV) is very common and is there the leading cause of cirrhosis (57). When detected early, before cirrhosis has developed, many of these conditions can be successfully treated and sometimes cured. Cirrhosis predisposes, however, to hepatocellular cancer (HCC), especially in chronic hepatitis B and C (71). Steatosis and NASH, i.e. without cirrhosis, have also been discussed as possible predisposing conditions to HCC (7, 26).

Focal or multifocal malignant liver disease is in Europe and the United States most commonly caused by metastases from various cancer types, whereas in many regions of Asia and Africa the primary liver cancers, primarily HCC, are more common than secondary metastases (2, 57).

Diseases affecting the gallbladder, especially cholelithiasis and cholecystitis, are more common than biliary duct stones and cholangitis (66). Cancer of the gallbladder, intra- or extrahepatic biliary ducts is less common than malignant disease arising in the liver (39). However, biliary duct malignancy poses a significant
Background

clinical problem, since it may spread inconspicuously along the duct walls before it produces a mass large enough to produce symptoms of biliary obstruction.

Primary Sclerosing Cholangitis, a chronic diffuse inflammatory biliary disease of unknown origin and suspected to have a autoimmune component, produces long-standing inflammation of the duct walls and surroundings, fibrosis with biliary duct strictures and an increased risk of cholangiocarcinoma (CCC) (6). At present, no curative treatment of PSC exists, except liver transplantation, and an important goal of clinical observation is to detect CCC, which is an indication of liver transplantation, if detected early. Following the progression of PSC is also important to adjust symptomatic treatment with medications and in some cases with biliary duct dilatation.

Non-invasive imaging methods are of great importance for detection and characterization of liver disease and also for evaluating hepatic vascular and segmental anatomy to provide a basis for surgical planning (47). The clinical surveillance programs of chronic hepatobiliary disease, e.g. HBV/HCV cirrhosis and PSC, rely on regular imaging in combination with other tests. In many cases, biopsy is needed to characterise focal and diffuse liver disease, but since this is an invasive procedure, it is not feasible as a repeated test. In the case of HCC there is agreement on a description of a successive change from benign parenchymal regenerative nodules to clearly malignant lesions, where arterial neovascularization is the most crucial sign of malignant change (73). The capacity of an imaging modality to reliably detect early pathological arterial vascularization is most important also for other hypervascular tumors.

Acute biliary conditions such as biliary colic due to gallstones and/or cholecystitis are nowadays often evaluated with ultrasound, and later with other modalities if necessary, e.g. when percutaneous or endoscopic interventional treatment is required. In biliary imaging, the focus is on outlining the shape of biliary ducts and gallbladder to detect stones, strictures or masses. At the same time, it is necessary to relate these findings to the surrounding structures, primarily the liver.

Some techniques to describe functional aspects of the biliary system also exist and will be briefly outlined in the following sections.

Overall, an optimal imaging modality needs to provide large volume coverage to include the entire liver and biliary system, a dynamic capacity to image changes in blood flow, contrast media enhancement and movement over time, and image contrast and resolution suitable for the clinical situation.
2.2. Imaging Modalities

2.2.1. Ultrasound (US)

Diagnostic ultrasound, also named Sonography, uses high-frequency sound waves and pulses to form images of the body. The speed of sound depends on the tissue type and interfaces between tissues act as partial or total reflectors of the ultrasound waves. The travel time of the ultrasound waves is interpreted as distance to the different interfaces and by using a range of frequencies, directions and pulse amplitudes in combination with advanced signal processing, two-, three- and even four-dimensional image data can be reconstructed. No known health risks are associated with exposure to diagnostic ultrasound. Thanks to its real-time imaging capacity with high spatial and temporal resolution it is used in most areas of the body. Image quality is limited by total reflection by air- or gas-containing organs, skeletal or other calcified structures and by the depth of the object to examine. Diagnostic ultrasound is considered more operator-dependent than other modalities.

In upper abdominal imaging, it is an efficient means of examining the liver, gallbladder, biliary ducts and pancreas. The introduction of ultrasound contrast media in the last decade has increased its accuracy and applications, e.g. in liver lesion detection and characterization, especially where small lesions are undetected by CT or MRI (21, 54, 79). Contrast-enhanced ultrasound (CEUS) adds functional information on normal and pathological vascular structures and on tissue perfusion in real time, which CT and MR cannot provide at equal spatial or temporal resolution (12).

2.2.2. Computed Tomography (CT)

Introduced by Hounsfield in 1971 (30), computed tomography (CT) has developed from producing one 2-dimensional image slice in several minutes to almost instantly delivering time-resolved three-dimensional image datasets amounting to thousands of images. The CT equipment consists of a rotating ring-like frame carrying the x-ray tube which delivers fan-shaped radiation to the opposite side, where an array of small detector elements is located. The frame rotates continuously in its housing (gantry) around the patient table, which moves through the gantry opening. The detector array samples the radiation that has passed through the patient at and this data is then processed to form a three-dimensional representation of the body. The image elements contains an attenuation value corresponding to the density or opacity to x-ray radiation, measured on the Hounsfield (HU) unit scale that defines the attenuation of air as -1000 HU and that of water as 0 HU. Thus, there are typical attenuation values of all tissues and direct comparisons between examinations can
therefore be made. While many organs are well delineated by CT, the contrast between soft tissues is low. Therefore, contrast media based on iodine are frequently used to improve the conspicuity of vessels and parenchymal organs.

Computed tomography is a generally available modality in many parts of the world and is typically the first choice in examinations of the abdomen with focus on malignancies. Modern multi-detector CT (MDCT) equipment (35) combined with contrast medium power injectors provide reliable imaging at high resolution in several phases of vessel enhancement, which makes it possible to image the liver in 1–2 arterial-dominant phases, portal venous phase and later phases if needed. Examinations including several phases can, however, lead to a considerable dose of ionizing radiation, especially for those patients who are referred for regular follow-up, e.g. during or after chemotherapy.

Specifically for biliary imaging purposes, ordinary contrast-enhanced MDCT image data from a portal venous or later phase can be processed with the Minimum Intensity Projection (MinIP) technique. This will highlight the lowest-intensity parts of the image data, which normally corresponds to the bile-filled biliary ducts and gallbladder (17, 40). Although not available in all countries, an intravenous cholangiographic contrast medium that is excreted by the biliary system – meglumine iotroxate (Biliscopin®, Bayer Schering Pharma, Berlin, Germany) – can be used for contrast enhancement of the biliary ducts in MDCT (29, 56).

### 2.2.3. Nuclear Medicine (NM)

Nuclear medicine uses detectors sensitive for ionizing radiation from radioactive isotopes that have been introduced into the body. The isotopes or rather the molecules – tracers – they are part of have different affinity for different organs or tissues. Organs and functions can be targeted by specific tracers to produce image data and quantitative measures of tracer uptake and elimination. In hepatobiliary imaging, the Hepatobiliary Iminodiacetic Acid (HIDA) scan is used to evaluate the elimination of HIDA, which mainly takes place in the liver (34).

Positron Emission Tomography (PET) combined with CT in the same machine – CT/PET or PET-CT – has become more available during recent years. Tracer compounds containing positron-emitting isotopes are introduced into the patient and detected by the PET equipment, which gives higher resolution images than other NM techniques. These are then easily fused with morphological images obtained from the CT part of the CT/PET-machine. The role of CT/PET in hepatobiliary imaging is so far limited. In some cases, it may assist in finding distant metastases of primary liver tumors that have tracer uptake (16).
2.2.4. Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is based on the electromagnetic interactions of the hydrogen nuclei – protons – in the body. All protons exhibit magnetic properties due to their electrical charge and spin. The MRI unit consists of a main superconducting electromagnetic coil producing a very strong stationary magnetic field, gradient coils providing additional and weaker but highly variable magnetic fields and antennas for sending and receiving radiofrequency waves to/from the body being examined. Very simplified, images are formed from weak radio waves emitted from the protons in the body, their frequency and phase representing different locations. To receive the proper signals, a great number of physical parameters need to be defined correctly in the MRI machine, so that the relevant tissues are imaged with the intended characterization or so-called weighting.

The MR imaging process can be tuned to show different tissues with varying contrast, highlighting and suppressing structures in numerous ways. There is, however, no reference tissue or any well-defined range of signals from different tissues. In each experiment or scan, a grayscale image is finally formed but the underlying values in the image pixels lie on a unique scale for that scan. It is possible to perform MRI with a quantitative approach, but the methods used have been time-consuming and difficult to use. With newly developed MRI sequences this is becoming more practical, and quantitative comparison of tissue signals (instead of just visual judgment) can be applied (74, 75).

2.2.4.1. Nuclear Magnetic Resonance

In quantum mechanics, proton spin can be viewed as the sum of the spins of its constituent elementary particles (quarks) but in the following text a simpler model will be used, regarding the proton as a charged rotating particle possessing a magnetic moment, similar to a bar magnet. The proton can also be called a magnetic dipole. When subjected to a strong magnetic field, protons will align along (parallel) or against (antiparallel) this field, in almost equal proportions. There will be a minute net surplus of protons in parallel orientation, which is the lower energy state, resulting in a net magnetization parallel to the external field. The stronger the magnetic field is, the larger the net magnetization becomes.

The protons also exhibit a rotating movement – precession – around the magnetic field axis, similar to how a gyroscope moves. The precession frequency is proportional to the external magnetic field strength according to the Larmor equation:

\[ f = \frac{\gamma}{2\pi}B \]  

(Eq. 1)
Where \( f \) is the Larmor frequency, \( \gamma \) is the *gyromagnetic ratio* (constant for each nucleus), 42.6 MHz/Tesla for the proton, and \( B \) is the external magnetic field strength, measured in Tesla (T).

When the protons receive electromagnetic energy in the form of a radiofrequency (RF) wave or pulse, at the Larmor frequency, the net magnetization vector will tip away from the direction of the external magnetic field. This is an unstable state, so as soon as the RF wave has ended, the net magnetization vector will return to the equilibrium state and at the same time, energy is emitted from the protons in the form of a RF wave. Hence, the system of aligned protons can temporarily absorb RF energy and then emit an RF signal that can be detected. This phenomenon is the foundation of Nuclear Magnetic Resonance, NMR, described in 1946 by Bloch and Purcell (4, 62).

### 2.2.4.2. MRI technique

In Magnetic Resonance Imaging (MRI), certain developments of the NMR technique make it possible to form images of the human body or objects. Lauterbur and Mansfield both described aspects of MRI that still today constitute the basis of the technique (22, 46, 52).

The modern MRI unit uses a constant strong magnetic field, typically with a strength of 1.5 T, produced by a superconducting electromagnet. There are also three additional electromagnets – gradient coils – each designed to produce a transient magnetic field in one of three orthogonal directions, to be used separately or combined. This field can change quickly in amplitude and in any direction. The MRI unit has radiofrequency coils – i.e. antennas – designed to deliver and receive RF energy. Usually a large RF coils is used for delivery and smaller receiving RF coils of various shapes are placed near the patient.

The MRI examination consists of a vast number of parameters defining complex programs – MRI sequences – of how gradient and RF energy will be used, how and when RF signals will be collected and – lastly – how the acquired data will be processed or *reconstructed* to form an image.

### 2.2.4.3. Basic layout of an MRI sequence

If a magnetic gradient field is turned on in the same direction as the external magnetic field, it produces a gradual change in field strength along the head-to-feet direction of the patient, here called the \( z \)-axis. The protons in the patient will thereby precess – resonate – at slightly different RF frequencies depending on their position along the \( z \)-axis. An RF pulse of a specific frequency is then selected to excite all protons at a specific location on the \( z \)-axis, which amounts to selecting a “slice” of protons in the patient.
After this slice-selecting gradient and RF pulse, the protons will start realigning to their equilibrium state. Using gradients perpendicular to the first one, in the $x$ and $y$ direction, the precession of the protons in the selected slice are manipulated so that the emitted RF signals differ in frequency and phase in a regular pattern. This means that the combination of a certain frequency and phase represents a certain position in the $x$-$y$-plane, i.e. in the selected slice. In this way, the signals from different parts of the body can be recorded and used to form an image.

### 2.2.4.4. T1 and T2 Relaxation

Two time constants, $T_1$ and $T_2$, describe the rate at which the net magnetization parallel/longitudinal ($T_1$) with and perpendicular/transversal ($T_2$) to the external field returns to equilibrium.

$T_1$ relaxation is caused by interaction between the excited protons and the local electromagnetic fields in the neighboring structures. One important interaction is the dipole-dipole type, where the proton is affected by another magnetic dipole tumbling in a frequency close to the Larmor frequency. The $T_1$ constant represents the time for the longitudinal magnetization, $M_z$, to reach 63% of its maximal value (Figure 1).

$T_2$ relaxation depends on the continuing dephasing of the precessing protons, the $T_2$ constant being the time for the transversal magnetisation, $M_{xy}$, to fall to 37% of its original level (Figure 2). Dephasing is caused by to local magnetic field inhomogeneities and occurs at a faster rate than $T_1$ relaxation. $T_2$ is thus less than or equal to $T_1$.

![Figure 1. Longitudinal relaxation.](image1)

![Figure 2. Transversal relaxation.](image2)
### 2.2.4.5. MRI Sequences

A vast number of MRI sequences have been developed. They can be classified as Spin Echo (SE) or Gradient Echo (GRE) sequences or hybrids of SE and GRE. Briefly, a SE sequence can be described as using an RF pulse to refocus spins, while a GRE sequence applies varying gradient fields for the same purpose. The data is gathered in many repeated steps, i.e. in a sequential manner, with the repeat interval named Repetition Time (TR). During each TR, gradient changes and RF pulses are synchronized to optimize the echo – acquired at the *Echo Time* (TE) – from longitudinal or transverse relaxation (or a combination of these) of the tissues of interest.

All acquired echoes, i.e. RF energy emitted from the patient, represent small portions of the data necessary for the formation of an image. This information is registered according to its frequency and phase in an abstract data representation called k-space. Information of low frequency lies in the center of k-space, and represents in the final image areas of high contrast, while the periphery of k-space contains the data describing high spatial resolution but low contrast. High contrast information is desirable e.g. when a quickly passing bolus of contrast medium needs to be imaged. Hence, MRI sequences can be designed to acquire the echoes carrying high contrast information in various ways, which makes it possible to time not only the contrast medium delivery but also the acquisition of the most pertinent contrast enhancement.

The amplitude of the echo and its dependence on tissue T1 or T2 is important for image quality. In abdominal imaging the time it takes to acquire a sequence is another important factor, since the abdominal organs move with the patient’s breathing. Imaging of the abdominal organs specifically requires data acquisition either synchronized with breathing movements or fast enough to be completed during one breath-hold. An important improvement is the development of fast T1-weighted GRE sequences that yield image data with isotropic (equal in all three dimensions), high resolution, i.e. three-dimensional image volumes instead of the 2-dimensional several millimeters thick slices from the traditional SE and GRE sequences. One example is the Volumetric Interpolated Breath-hold Examination (VIBE) developed for Siemens MRI units and used in the studies here presented. All MRI equipment vendors offer similar sequences. The VIBE sequence is designed to provide an isotropic resolution of 1–2 mm and T1-weighting optimized for abdominal organs (64). Gradient Echo sequences generally use short TE values, which offers stronger T1 weighting, so that the T1-shortening effects of contrast media can be better appreciated.
2.3. Contrast Media in Liver MRI

In 1988, Gd-DTPA (Magnevist®, Bayer Schering Pharma, Berlin, Germany) was the first Gd-based contrast medium to be introduced in clinical MRI. It was followed by several compounds with similar properties and uses. These are distributed in the extracellular space and eliminated by the kidneys. Because of their extracellular distribution, both Gd-BOPTA and Gd-EOB-DTPA can be used in the same way as the standard extracellular contrast media, but the hepatobiliary uptake and elimination give them also a hepatocyte-specific function. Another contrast agent excreted in the bile is Mangafodipir trisodium (Mn-DPDP, Teslascan®, GE Healthcare AS, Oslo, Norway), introduced in 1997. However, since it is administered as an infusion over 10-20 minutes, it cannot be used in early dynamic imaging. Furthermore, Endorem® (Guerbet, Roissy, France) and Resovist® (Bayer Schering Pharma, Berlin, Germany), based on small (SPIO) or ultra-small (USPIO) iron oxide particles have been introduced as liver-specific agents (63). They show high hepatic uptake, although this occurs in the Kupffer cells of the Reticulo-Endothelial System and not in the hepatocytes. In the following sections, Gd-BOPTA and Gd-EOB-DTPA will be covered in more detail.

2.3.1. Gd-BOPTA (MultiHance®)

Gd-BOPTA (gadolinium benzyloxypropionictetraacetate, MultiHance® 0.5 mmol/ml; Bracco Imaging, Milan, Italy) was introduced on the European market in 1998 and was approved by the United States Food and Drug Administration (FDA) in 2004. Its indications include MRI of the Central Nervous System and of the liver and contrast-enhanced MR angiography. Gd-BOPTA is distributed in the body like ordinary extracellular contrast media such as Gd-DTPA, but in the liver it is taken up by hepatocytes and excreted into the bile in an adenosine triphosphate (ATP)-dependent process involving a multispecific transporter on the canalicular aspect of the hepatocyte (43). This allows extracellular space enhancement in early acquisitions and prolonged hepatocyte enhancement in delayed acquisitions. In humans, the dose fraction that is excreted via the hepatobiliary route is 1–4% (69), which means that the major portion is eliminated by the kidneys. Despite this, enhancement of the biliary system is achieved 60-120 minutes after i.v. injection (78). In Phase I studies, the mean elimination half-life ranged from 1.17 to 2.02 hours (69). Gd-BOPTA has higher relaxivity than standard extracellular Gd-based contrast media (77). For Gd-BOPTA, the recommended dose for liver imaging is 0.05 mmol/kg (51) but in clinical routine the double dose is used in many centers (10, 25, 41, 42).
2.3.2. Gd-EOB-DTPA (Primovist®)

Gd-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid, Primovist® 0.25 mmol/ml, Bayer Schering Pharma, Berlin, Germany) is a more recently approved liver-specific contrast agent, first released in 2004 in Europe and approved (labeled Eovist®) in the USA in 2008. Like Gd-BOPTA, it combines hepatocellular specificity with T1-relaxivity and extracellular behavior (68, 76). After intravenous injection, Gd-EOB-DTPA is first distributed into the extracellular space and then taken up by the hepatocytes. It is excreted unmetabolized in equal proportions by the kidneys and by ATP-dependent active transport in the hepatocytes to the biliary system (28), such that the hepatobiliary excretory proportion is approximately ten times greater than for Gd-BOPTA. Renal excretion can be substituted by the hepatobiliary elimination and vice versa. After bolus injection of 0.025 mmol/kg (the recommended dose), the peak liver enhancement is reached after about 20 minutes, followed by a plateau phase. The agent is cleared from the serum to reach a concentration below the limit of quantification 24 hours after injection and its plasma half-life is one hour (28). In the safety phase I study by Hamm et al (28) four doses of Gd-EOB-DTPA were tested: 0.010, 0.025, 0.05 and 0.1 mmol/kg. While the pharmacokinetic data suggested linear kinetics with no saturation of hepatic uptake at any dose, the highest dose (0.1 mmol/kg) produced susceptibility effects in liver imaging and was therefore considered excessive. Bollow et al (5) also reported susceptibility effects at the highest two doses (0.05 and 0.1 mmol/kg) in a study on contrast-enhanced cholangiography.

2.3.3. Gadolinium Contrast Media and Relaxivity

Contrast media based on Gd are normally used to shorten T1, which is accomplished by dipole-dipole interaction through the great magnetic moment of Gd. Different Gd-based compounds can have different tumbling rates and therefore different capacity in affecting the T1 relaxation rate. This capacity is referred to as the relaxivity of the contrast medium and measured in [s⁻¹mM⁻¹]. It is important to note that the effect on T1 relaxation here depends on the tumbling rate of the contrast medium being close to the Larmor frequency, which depends on the external magnetic field. This means that measurements of T1 relaxivity performed at one magnetic field strength are not directly translatable to another field strength. Relaxivity depends on many other factors, such as temperature, viscosity and protein binding of the contrast medium (50).

Gd-BOPTA has frequently been referenced as having twice the relaxivity of conventional Gd contrast agents such as Gd-DTPA. The underlying measurements were performed at 0.47 T (77) which is a common setup for in vitro relaxivity measurements. As reported by Cavagna et al (9), in vivo measurements used in a
computer model estimated the T1 relaxivity of Gd-BOPTA in rat liver to 30 mM\(^{-1}\)s\(^{-1}\), although data from two different groups of animals were used and the precision of the estimate was not stated. In measurements performed at the clinically more relevant field strength of 1.5 T, the additional relaxivity of Gd-BOPTA was in the order of 50%, rather than 100% as mentioned above (Table 1). The measured relaxivity values are also influenced by the different properties of the solvent or tissue holding the contrast medium. A comprehensive comparison where fourteen MRI contrast media were investigated at up to four different magnetic field strengths (0.47 T, 1.5 T, 3 T, and 4.7 T) and in different solutions has been reported by Rohrer et al, who recommend that comparative measurements be performed in plasma (not water), using primarily clinically relevant field strengths: 1.5 T and 3 T (65). According to these measurements, Gd-EOB-DTPA and Gd-BOPTA have very similar relaxation rates.

Table 1. Reported relaxivity values of Gd-BOPTA and Gd-EOB-DTPA according to results available in the literature. The experiments reported by Rohrer where fourteen MRI contrast media were investigated at up to four different magnetic field strengths (0.47 T, 1.5 T, 3 T, and 4.7 T) and in different solutions confirmed some relaxivity measures at 0.47 T from previously reported studies and provided more relevant measures performed at 1.5 T.

<table>
<thead>
<tr>
<th>Solution:</th>
<th>Water</th>
<th>Plasma</th>
<th>Blood</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast Medium:</td>
<td>Gd-BOPTA</td>
<td>Gd-EOB-DTPA</td>
<td>Gd-BOPTA</td>
<td>Gd-EOB-DTPA</td>
</tr>
<tr>
<td>Rohrer 2005 (65)</td>
<td>4.0 (3.8-4.2)</td>
<td>4.7 (4.5-4.9)</td>
<td>6.3 (6.0-6.6)</td>
<td>6.9 (6.5-7.3)</td>
</tr>
<tr>
<td>Relaxivity [s(^{-1})mM(^{-1})] at 1.5 T (63 MHz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relaxivity [s(^{-1})mM(^{-1})] at 0.47 T (20 MHz)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rohrer 2005 (65)</td>
<td>4.0 (3.8-4.2)</td>
<td>4.7 (4.5-4.9)</td>
<td>9.2 (8.7-9.7)</td>
<td>8.7 (8.3-9.1)</td>
</tr>
<tr>
<td>Vittadini 1988 (77)</td>
<td>4.63 ±0.01</td>
<td>6.88 ±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schulmann-Giampieri 1992 (68)</td>
<td></td>
<td></td>
<td>5.3 ±0.33</td>
<td>8.64 ±0.47</td>
</tr>
<tr>
<td>De Haën 1999 (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bracco 2003 (1)</td>
<td>4.4</td>
<td>10.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3.4. Contrast Administration and Bolus Timing

Dynamic contrast-enhanced imaging aims at obtaining image sets from several successive time-points, requiring some sort of synchronization between imaging and contrast medium delivery. The first image acquisition post injection is normally made to obtain an optimal enhancement of the arteries when the contrast bolus passes for the first time, so-called first-pass imaging. The time-points for the following acquisitions are then planned according to the clinical question, but will in
most cases include a portal venous phase at 45–50 seconds and an equilibrium or interstitial phase at 120–180 seconds post injection.

The simplest way of coordinating contrast media administration with imaging is to set a fixed delay, like 15–20 seconds for the arterial phase, from contrast injection until the start of image acquisition. Due to inter- and intraindividual variations in circulation, imaging will sometimes start too early or too late for optimal arterial enhancement. If the contrast medium is administered by manual injection, even more variation in the arrival time of the bolus can be expected. The quality of the portal venous phase may also be affected, while later phases generally are affected very little by a timing error of 5–10 seconds.

To achieve better synchronization, remotely controlled power injectors are very helpful and practically necessary for routine clinical use.

The timing can be more individualized by using a test bolus of contrast, given at the same injection rate as the main bolus, followed by real-time imaging from which the observer can derive the time elapsed from the start of injection until peak enhancement. The same time-delay is then used for timing the arterial phase acquisition in the dynamic imaging after the main bolus. The amount of contrast in the test bolus is normally considered too small to affect the image quality in the arterial phase, since the test bolus has been greatly diluted in the extracellular fluid volume. The special case of test bolus use with hepatocyte-specific contrast media is discussed later in this chapter.

A technique that is becoming more frequently used, as more powerful MRI equipment capable of fast gradient switching is introduced, is the automated bolus-detection technique. A real-time imaging acquisition runs during injection of the contrast medium by power injector, while a software application on the MRI unit measures the signal intensity continuously in the relevant anatomic region, typically the aorta. When the bolus arrives at that location, the signal increases and the MRI unit automatically triggers the start of the first main image acquisition, i.e. the arterial phase. Alternatively, the MRI operator can start the scan manually while monitoring the bolus progression in the real-time images. This technique has initially been introduced in MR angiography of the abdominal aorta (60) but is now in use in various MR angiography applications and also in MRI of the liver. With the test bolus technique, there may be differences in contrast bolus arrival between the test bolus imaging and the acquisition of the arterial phase due to the imaging being done in different respiratory phases. The automated bolus-detection technique achieves better timing in this regard (31, 45).

Techniques for obtaining more than one arterial phase have been described (36). In contrast-enhanced CT of the liver, the use of two or more early phases has been described since the introduction of multidetector CT equipment. The late arterial phase was considered more important than the early arterial phase when vascular,
parenchymal and tumor enhancement was evaluated (36) and in hypervascular tumor enhancement (19).

Even the use of power injectors has undergone significant development. The single-head injectors used initially have largely been replaced by dual-head injectors, since most MRI protocols use saline as a “flush bolus” immediately after contrast delivery. Various strategies of injecting contrast have been described but in general, for abdominal MRI, the contrast bolus is given at a flow rate of 2–3 ml/s, followed by the saline bolus at the same rate. The choice of injection rate depends primarily on the focus of the MRI exam and the speed of image acquisition.

2.3.5. Safety of Gadolinium-Based Contrast Media

Gadolinium-based contrast media are generally safe and well tolerated. This applies also to Gd-BOPTA and Gd-EOB-DTPA although there is greater experience with the former (3). However, the risk of inducing Nephrogenic Systemic Fibrosis (NSF) in patients with low renal function is considered to be associated with any type of Gd-based contrast medium (14, 20, 72).
3. AIMS

3.1. Paper I

To evaluate the time course of biliary enhancement in T1-weighted imaging with Gd-BOPTA and Gd-EOB-DTPA in normal healthy subjects.

3.2. Paper II

To evaluate the time course of hepatic parenchymal and vascular enhancement in T1-weighted imaging with Gd-BOPTA and Gd-EOB-DTPA during the arterial, portal venous, and hepatobiliary phases in normal healthy subjects.
4. MATERIAL AND METHODS

4.1. Subjects

After approval from the local ethics committee and written informed consent, ten healthy volunteers were examined on two different occasions, during April and May 2005. Of these, four were men with an age range of 19–46 years (mean age, 30 years) and six were women with an age range of 20–45 years (mean age, 30 years). In order to exclude unknown liver and renal dysfunction, total serum bilirubin and creatinine were evaluated prior to MRI. All subjects completed both studies.

4.2. Contrast Media

One ml of contrast was administered as a test bolus followed by saline to determine the optimal timing of the imaging sequences. The contrast bolus was injected by power injector at 2 ml/s and immediately followed by an equal amount of physiologic saline.

The amounts of contrast media used in this study were 0.025 mmol/kg for Gd-EOB-DTPA (Primovist® 0.25 mmol/ml, Schering, Berlin, Germany), and 0.1 mmol/kg for Gd-BOPTA (MultiHance® 0.5 mmol/ml; Bracco Imaging, Milan, Italy). The contrast bolus was injected by power injector at 2 ml/s and immediately followed by an equal amount of physiologic saline. One ml of contrast was delivered as a test bolus followed by saline and the time delay for the arterial phase was determined by the time from the start of injection until contrast enhancement occurred in the proximal abdominal aorta. Total acquisition time was 20 seconds, and the center of k-space was reached 8 seconds from the start.

4.3. MRI Technique

All examinations were performed on a 1.5-T magnetic resonance system (Magnetom Vision, Siemens, Erlangen, Germany) combining the spine coil and the flexible phased-array body coil. Examinations were performed in the early morning after more than seven hours of fasting. After one hour of scanning, a light meal containing less than 2 g of fat was allowed. Each examination lasted about six hours, and the two examinations for each subject were performed at least six days apart.
The study protocol was designed by extending a standard protocol for contrast-enhanced examination of the liver by adding several late phases, resulting in a total of nine post-contrast axial breath-hold gradient-echo T1-weighted VIBE (64) sequence acquisitions (TE 1.9 ms, TR 4.5 ms, FOV 40 cm, 120 slices of 1.7 mm thickness) at arterial and portal venous phases (48 seconds after the arterial phase) and 10, 20, 30, 40, 130, 240 and 300 minutes after injection.

4.4. Image and Signal Intensity Analysis, Statistical Analysis

4.4.1. Paper I

Three radiologists performed all measurements independently, using diagnostic workstations (PACS IDS5 v10.1, Sectra Imtec AB, Linköping, Sweden). Signal intensity (SI) measurements of the biliary duct were made by placing a single measuring point in a central voxel in the common hepatic duct (CHD). The reviewers measured the mean SI of liver parenchyma by drawing circular regions of interest (ROI) of 0.7 cm² in the same slice, at the same anteroposterior level as the measurement in the CHD, avoiding large vessels (Figure 3).

The bile duct-to-liver image contrast, \( C_{\text{duct-liver}} \), at the time-points from 10 minutes until 300 minutes post-injection was calculated as

\[
C_{\text{duct-liver}} = \frac{SI_{\text{duct}} - SI_{\text{liver}}}{SI_{\text{liver}}} \quad \text{(Eq. 2)}
\]

Statistical analysis was performed in JMP 6.0 (SAS Institute Inc, Cary, NC, USA) using a mixed Analysis of Variance (ANOVA) model with the subject and the reviewer defined as random effects, testing for each time-point the null hypothesis of no difference in \( C_{\text{duct-liver}} \) between Gd-BOPTA and Gd-EOB-DTPA within subjects. To evaluate the possible difference in late enhancement behavior, a similar linear model was applied on the \( C_{\text{duct-liver}} \) values between 40 and 240 minutes post injection, using time, subject (random effect) and reviewer (random effect) as model effects.

4.4.2. Paper II

Three radiologists performed all measurements independently, using diagnostic workstations (PACS IDS5 v10.1, Sectra Imtec AB, Linköping, Sweden). Signal intensity measurements were made by placing ROIs in the common hepatic artery, the middle hepatic vein, a segmental branch of the right portal vein, and the liver
parenchyma, all in a single representative slice (Figure 4). The arterial and portal venous phases and the time-points from 10 minutes until 130 minutes post-injection were analyzed. The image contrast between the vessel and the liver parenchyma was calculated analogously to the biliary duct image contrast (Eq. 2).

Statistical analysis was performed for each time-point with a mixed ANOVA model with the subject and the reviewer defined as random effects. The signal intensity of liver parenchyma for Gd-BOPTA at 130 minutes versus Gd-EOB-DTPA at 10 minutes, representing the optimum for each contrast medium, was also compared with a similar model. These calculations were carried out in JMP 7.0 (SAS Institute, Cary, NC, USA).

Figure 3. Biliary enhancement measurements – Paper I. Axial T1-weighted 3D VIBE sequence through the liver, TR 4.5 ms and TE 1.9 ms. The arrow shows the contrast-enhanced common hepatic duct (CHD) and parenchymal enhancement at 130 minutes post injection of Gd-BOPTA. A circular ROI is placed in liver parenchyma and a point of measurement placed centrally in the CHD.

Figure 4. Vessel-to-liver contrast measurements – Paper II. Axial VIBE slice using Gd-BOPTA during the portal venous phase. MV = middle hepatic vein, PV = segmental branch of the portal vein, A = common hepatic artery, * = liver parenchyma, two regions.
5. RESULTS

The complete set of twenty MRI examinations was completed in a time span of 49 days without adverse reactions or subjective symptoms. Due to technical problems, one of the examinations did not include the acquisition at 20 min post-injection. Thus, at that time-point, 27 instead of 30 measurements were analyzed.

The time delay between the administration of the test bolus and the start of the arterial phase acquisition was derived from the data documentation, to provide a means of estimating a possible effect of the test bolus on liver signal intensity before the main bolus. The mean delay ±SD amounted to 13 ± 2.6 minutes for the Gd-BOPTA experiments and 15 ± 3.7 minutes for Gd-EOB-DTPA. The difference between delays for each individual ranged from 0.8 to 5.4 minutes for 9 out of 10 subjects, and was 11 minutes for one subject. No significant differences in liver SI depending on the type of contrast medium were detected.

5.1. Paper I

In the pre-contrast image series, there was no significant difference in \( C_{\text{duct-liver}} \) between Gd-BOPTA and Gd-EOB-DTPA. At 10 min post-injection, biliary enhancement was evident for Gd-EOB-DTPA (\( p<0.0001 \)), whereas there was none for Gd-BOPTA. At 20 min delay, slight biliary enhancement was noted for Gd-BOPTA (Paper I: Figure 3), but \( C_{\text{duct-liver}} \) was significantly higher for Gd-EOB-DTPA (\( p<0.02 \); Table 2). During the 30 min and 40 min time-points, \( C_{\text{duct-liver}} \) increased for both contrast media, with no significant difference between them. From 130 to 300 min after injection, \( C_{\text{duct-liver}} \) was significantly higher for Gd-EOB-DTPA (\( P<0.002 \)). After 40 min post-injection \( C_{\text{duct-liver}} \) decreased (\( P<0.0001 \)) for Gd-BOPTA, whereas it increased for Gd-EOB-DTPA until 240 min post contrast injection (\( P<0.0001 \); Figure 5).
Table 2. Mean and standard deviation of $C_{\text{duct-liver}}$ for Gd-BOPTA and Gd-EOB-DTPA (all subjects, all reviewers). In the rightmost column p-values from the ANOVA analysis are given.

<table>
<thead>
<tr>
<th>Delay (min)</th>
<th>Gd-BOPTA</th>
<th>Gd-EOB-DTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean $C_{\text{Duct-Liver}}$</td>
<td>Std Dev $C_{\text{Duct-Liver}}$</td>
</tr>
<tr>
<td>0</td>
<td>-0.57</td>
<td>0.14</td>
</tr>
<tr>
<td>0.25</td>
<td>-0.46</td>
<td>0.24</td>
</tr>
<tr>
<td>0.8</td>
<td>-0.56</td>
<td>0.15</td>
</tr>
<tr>
<td>10</td>
<td>-0.30</td>
<td>0.18</td>
</tr>
<tr>
<td>20</td>
<td>0.19</td>
<td>0.27</td>
</tr>
<tr>
<td>30</td>
<td>0.42</td>
<td>0.26</td>
</tr>
<tr>
<td>40</td>
<td>0.50</td>
<td>0.34</td>
</tr>
<tr>
<td>130</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td>240</td>
<td>0.22</td>
<td>0.39</td>
</tr>
<tr>
<td>300</td>
<td>0.24</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Figure 5. (Paper I) Mean contrast ($C_{\text{duct-liver}}$) between the common hepatic duct and liver parenchyma at 0, 10, 20, 30, 40, 130, 240, and 300 min after injection of contrast medium. P-values from the ANOVA model at each time point. Non-significant differences at delay 30 and 40 minutes (p=0.34 and p=0.08, respectively). From 40 to 240 min post-injection, there is an increase of $C_{\text{duct-liver}}$ when using Gd-EOB-DTPA versus a decrease when using Gd-BOPTA (p<0.0001, both).
5.2. Paper II

The signal intensity of the studied vessels was greater when using Gd-BOPTA than when using Gd-EOB-DTPA (Paper II: Table 1). When using Gd-EOB-DTPA, the vascular signal had returned to a level close to the native state after 10 minutes, but when using Gd-BOPTA it remained almost three times higher than the native level for 40 minutes after administration.

The image contrast of the hepatic artery measured in the arterial phase was significantly greater for Gd-BOPTA (Figure 6) than for Gd-EOB-DTPA (p<0.0001, Figure 7, Paper II: Table 2). Similarly, the portal vein was hyperintense in the portal venous phase with Gd-BOPTA, while being isointense with Gd-EOB-DTPA. In later phases, the portal vein was almost isointense after Gd-BOPTA, but distinctly hypointense after Gd-EOB-DTPA (Figure 6, Figure 7). Also the middle hepatic vein was hyperintense with Gd-BOPTA, and isointense with Gd-EOB-DTPA, measured in the portal venous phase (p<0.0001). Later, the image contrast of the middle hepatic vein was very low with Gd-BOPTA, while it was distinctly negative with Gd-EOB-DTPA.

The liver parenchyma reached its highest signal intensity during the portal venous phase with Gd-BOPTA and at 10 minutes for Gd-EOB-DTPA. Until 130 minutes after Gd-BOPTA administration, there was no significant variation in signal intensity. For Gd-EOB-DTPA, a plateau of high signal remained until 40 minutes post-injection, followed by a decrease to the 130 minute time-point. During this plateau, there was no significant difference in liver SI between the two contrast agents. The SI of liver parenchyma at 10 minutes after Gd-EOB-DTPA administration did not differ significantly from the liver SI at 130 minutes using Gd-BOPTA.
Results

Figure 6. (Paper II) Image contrast of the portal vein, common hepatic artery and middle hepatic vein versus liver parenchyma after injection of Gd-BOPTA.

Figure 7. (Paper II) Image contrast of the portal vein, common hepatic artery and middle hepatic vein versus liver parenchyma after injection of Gd-EOB-DTPA.
6. DISCUSSION

Imaging modalities are under continuous development and in liver imaging, the many aspects of the MRI technique itself and the diverse biological properties of the hepatobiliary system allow for a multitude of improvement strategies. One aim for these development efforts is to achieve the “one-stop-shop” examination, providing all morphological and functional information the clinician needs, in a single and not too complicated study. In the studies performed here, two contrast media developed at least partly with this focus were compared to evaluate their enhancement dynamics, which will be discussed in different aspects of liver imaging.

6.1. Biliary Imaging

In biliary imaging, functional information can be obtained with both Gd-BOPTA and Gd-EOB-DTPA thanks to biliary enhancement when the contrast media are eliminated. This is best appreciated when sufficient morphological information is available, which is readily achieved with heavily T2-weighted Magnetic Resonance Cholangiopancreatography (MRCP) sequences on modern MRI equipment. Using T1-weighted sequences, it is possible to depict biliary ducts containing Gd-BOPTA or Gd-EOB-DTPA, but as has been reported by Bollow (5), Carlos (8) and Lim (48) the peripheral branches of the biliary ducts are not visualized as distinctly as in a T2-weighted MRCP image. This is due to the fact that, at the doses studied, the substances give a prolonged enhancement of functioning hepatocytes, i.e. in the immediate vicinity of the smaller ducts and ductules. In MRCP, the image is simply formed by the great native contrast between the water (bile) in biliary ducts and the much lower water signal of liver parenchyma. In another study by Lim (49), overall image quality scores were higher for Gd-BOPTA-enhanced 3D T1-weighted images than for 2D and 3D T2-weighted MRCP images. However, analogous to the previous studies mentioned, biliary duct visualization with T2-weighted MRCP was superior to Gd-enhanced 3D T1-weighted imaging except for the common bile duct.

In Paper I, biliary enhancement was measured in the common hepatic duct which according to previous studies is more consistently visualized than the branch ducts. In normal subjects, the biliary ducts are free from obstructions, so the biliary contrast concentration over time is likely to be similar in peripheral and central parts of the biliary system. Clinical experience of Gd-enhanced cholangiography shows that a patient with obstruction of a duct branch will typically have ordinary excretion in the unaffected branches. When several or all branches are affected the excretion will be delayed or non-existent. To better recognize and quantify such delays, the
results from Paper I can provide some insight into the two patterns of normal biliary enhancement when Gd-BOPTA or Gd-EOB-DTPA is used. Also, it indicates that by offering an early time window for evaluation of suspected delays in biliary contrast excretion, Gd-EOB-DTPA is the more practical contrast medium to use. When using Gd-EOB-DTPA the excretion to bile is faster and provides a stronger enhancement of the biliary tree than that of Gd-BOPTA. However, with flexible scheduling at the MRI unit, normal and pathological biliary excretion can be studied also with Gd-BOPTA if the patient is scanned a second time 1–2 hours after contrast media administration (67).

The high contrast between the common biliary duct and liver parenchyma had an earlier onset and longer duration for Gd-EOB-DTPA. There was also a significant difference in the contrast increase (Gd-EOB-DTPA) vs. decrease (Gd-BOPTA) from 40 minutes to 240 minutes post-injection. Clinical hepatobiliary imaging that includes evaluation of the biliary elimination phase can therefore be performed in a shorter time when using Gd-EOB-DTPA. The vascular and early parenchymal phases of contrast-enhanced liver MRI are, however, very important to obtain. Therefore, Paper II was planned to evaluate enhancement dynamics of the same contrast media primarily in the arterial and portovenous phases.

6.2. Vascular Imaging

Ideally, the timing of the image acquisition should be optimized for each vessel studied. Here, the most critical timing problem is the arterial phase. The test bolus technique was used, since it was the most robust technique available on this MRI unit and since it was part of the standard liver MRI protocol. A fixed delay would have led to low precision in acquiring an optimal arterial phase, due to subject-related variation.

The timing of the portal venous phase is straightforward once the arterial phase is obtained. An additional delay is used to start acquisition at a total time of around 60 seconds post-injection, which is commonly reported in the literature (10, 36, 37, 70).

The hepatic vein receives contrast almost as early as the portal vein, so that the optimal enhancement likely lies just 10–15 seconds later. With an acquisition time of 20 seconds, this means that the hepatic vein is not imaged at its optimal time. A distinction is sometimes made between an early portal venous “inflow” phase and a later portal venous phase, where the former is aimed at providing portal venous enhancement before any significant enhancement is seen in the hepatic veins, while the latter is a more conventional phase where both portal and hepatic veins are enhanced (19, 23). Thus, the setup used in these studies reflect the typical clinical situation, where the arterial phase is the most important to optimize, followed by the portal venous phase in which also the hepatic veins are enhanced.
Optimal bolus timing for the arterial phase acquisition is more difficult to accomplish with Gd-EOB-DTPA than with standard extracellular agents or with Gd-BOPTA, because of the lower dosage. In the case of a subject weighing 70 kg, the Gd-EOB-DTPA bolus is 7 ml and with a standard contrast agent 14 ml (80). A smaller bolus will give briefer enhancement of lower amplitude during the first passage and will therefore be more difficult to image at the ideal moment when the center of k-space is acquired.

Whether the recommended dose of 0.025 mmol/L can be increased in order to facilitate early dynamic imaging has been discussed in recent studies by Halavaara (27) and by Tamada (70). If a Gd concentration equal to that of Gd-BOPTA had been given, there would have been a risk of artifacts (28) caused by increasing T2-effects (dephasing) at high Gd concentration where the contrast is accumulating, i.e. in hepatocytes and in the biliary system.

Both the vascular enhancement (Paper II: Table 1, Figures 4A and 4B) of the hepatic artery, the portal vein and the middle hepatic vein and their contrast to the surrounding liver parenchyma (Figure 6, Figure 7) significantly higher at the obtained imaging time-points when using Gd-BOPTA compared to Gd-EOB-DTPA.

In these studies Gd-BOPTA was used at the dose recommended for vascular and neurological studies (0.1 mmol/kg), which is the standard liver MRI protocol used. This dose is twice the recommended dose for liver MRI but is commonly used and the most often reported in recent studies (10, 25, 41, 42). Since the relaxivity of Gd-BOPTA is about 50% higher than that of standard extracellular contrast agents (Table 1), vessel enhancement will also be higher. In these studies, no comparison with extracellular contrast agents was performed, but other studies have reported superior vessel enhancement properties of Gd-BOPTA (44, 61).

### 6.3. Hepatic Parenchymal Enhancement

Most metastases and low differentiated HCC’s have no functioning hepatocytes and will therefore be more easily detected when the surrounding liver parenchyma has the highest hepatocyte-specific enhancement. The peak enhancement for Gd-BOPTA occurred at the portal venous phase and no significant decrease occurred during the measurement time of 130 minutes after contrast media administration (Figure 6). For Gd-EOB-DTPA the peak enhancement was from 10 to 40 minutes after injection (Figure 7). This is in accordance with measurements made in a phase I study on healthy volunteers by Hamm et al (28), where a “plateaulike enhancement” was described, from 20 minutes until 90 minutes post-injection. Initially, however, the high enhancement is a combination of the extracellular enhancement and the hepatocyte enhancement, while the desired more specific hepatobiliary enhancement occurs later (11, 24, 59, 67). This hepatobiliary phase thus gives the potential of a high
contrast between the liver and lesions lacking normally functioning hepatocytes, the most common being metastases.

**6.4. Study Design and Limitations**

In the following section, certain areas of study design and limitations not covered in the previous paragraphs will be discussed.

**6.4.1. Volunteer Sampling**

Volunteers presumed to be healthy may have subclinical liver disease not reflected in pre-study laboratory tests. Also, significant changes in diet, alcohol intake and exercise affects the liver, e.g. resulting in varying degrees of fat accumulation and temporary abnormal laboratory liver test results (38). These factors might have an impact on the liver physiology and the imaging studies, but are also represented in the general population. One way to obtain subjects more directly representative of normal physiology is to apply stricter exclusion criteria in the recruitment procedure, e.g. to avoid subjects who are in the middle of or have just performed a major change in their diet or exercise level.

The external validity of these results applies mainly to how they can be generalized to the healthy population. A repeat study with new subjects performed on another type of MRI unit should give more insight into the measurement uncertainty. A more thorough examination of the healthy subjects in order to avoid abrupt changes in diet and exercise during the study is also warranted. Further studies in patients are required to compare the imaging advantages of Gd-EOB-DTPA and Gd-BOPTA in clinical MRI examinations.

**6.4.2. Image Review, Documentation and Analysis**

We expected the measuring points to be affected by subjective judgment despite clearly defined instructions to the reviewers. To average the individual variations, more than one reviewer is needed. In choosing an image slice showing the relevant anatomy for ROI placement, it is likely that reviewers sometimes choose different slices. Also, the placement of a measurement point in the central pixel of a small structure and the positioning of a ROI can be accomplished in more than one way.

For all measurements, each reviewer documented his choice of image slice (in the data table) and measurement points (in the image), but without this being visible for the other reviewers. All data were anonymized, but during the image analysis there was no blinding of the subject alias, in order to facilitate that SI values were
registered under the correct alias in the data sheet. It was not possible to blind the reviewers to the time-point of the image, since contrast enhancement features, in general, are obvious for a radiologist. Registration of all SI values, image slice number, time-point of image acquisition etc was done manually by reading digits from the image display and entering data in a structured spreadsheet template, one copy used by each reviewer. The three spreadsheets were then merged. Simultaneous registration of redundant data from the images, e.g. both the image time stamp and the time-point of acquisition, was used to detect mistakes in data entry. To decrease the systematic variation in the placement of measurement points or ROIs, the reviewers were allowed to cross-reference image slices when choosing the representative slice for each image sequence. This assured the closest possible anatomical matching of the slices.

Some variation in the native signal intensity of bile has been described, in both T1- and T2-weighted imaging. Håkansson et al (32) reported that five percent of a series of 319 patients had a high gallbladder signal relative to liver, i.e. the opposite to the expected hypointense appearance. In Study I, all subjects had hypointense gallbladders on T1-weighted imaging before main contrast bolus administration.

The statistical analysis takes into account the fact that the experiments are paired (each subject received both substances) and that observations pertaining to the same subject or reviewer are related.

### 6.4.3. Contrast Media Administration

When using the test bolus technique with Gd-BOPTA and Gd-EOB-DTPA, approximately 5% and 50%, respectively, of the test bolus will be taken up by hepatocytes and excreted with the bile. This means that the liver parenchyma will already have increased signal intensity – albeit to a small extent – when the main bolus is administered. The greater volume of the main bolus combined with well-timed acquisition still gives prominent first-pass enhancement of the arteries and of the portal veins, since the parenchymal enhancement is small. In experimental situations the effect of the test bolus should, however, be discussed more thoroughly since it represents a methodological complication when judging the contrast enhancement in the liver parenchyma. Even a small dose will have accumulated in the liver when the main acquisitions start. In Study I, no enhancement of the biliary ducts was seen at the pre-contrast scan. Vascular enhancement values are smaller and are potentially more easily affected by an offset in liver parenchymal enhancement – the denominator in the image contrast equation (Eq. 2) – caused by the test bolus. No significant effect of the test bolus on the “pre-contrast” liver signal intensity was detected, although this problem was evaluated ad hoc and would have been better addressed by performing additional measurements.
The pre-contrast scan was performed only once. This is a limitation since there is a random variation in each scan within and between subjects. Performing 1–2 extra pre-contrast scans would have given the opportunity to control the intraindividual variation. The effect of the test bolus adds to the measurement uncertainty and is another reason why we should have used more than one pre-contrast scan, before as well as after the test bolus.

The contrast agents were given in different doses. Gd-EOB-DTPA is not approved for use at any higher dose than the given dose, whereas both 0.05 and 0.1 mmol/kg are approved doses with Gd-BOPTA, the higher dose currently being used as the standard dose. Since the local effects of the contrast medium on the neighboring protons are reflected as differing brightness/SI in the MR image and since there is a linear increase in SI with increasing concentration, the experiment does not control the influence on differing dosage. In other words, the contrast medium dose is a confounder. Instead these studies compare contrast media effects with the clinically used doses. The confounding effect causes uncertainty whether only the choice of contrast agent is the cause of a significant difference in enhancement at a particular time-point; the effect seen is the combination of contrast agent and dose. The shape of the contrast enhancement curve, i.e. the pattern of change over time, however, should be characteristic for the contrast agent and not affected by the dose.

In view of the general caution against the use of Gd-based contrast agents in patients with renal function deficit (20, 72), it is advisable to use as low a dose as possible. In patients with no renal impairment, the dose of Gd-BOPTA used here, in several other studies and also employed in MRA and in MRI of the CNS, poses no known additional medical risk compared to other Gd-based compounds. For a more detailed evaluation of the benefits of the higher vs. the recommended dose in different patient groups, very large studies are likely to be needed, since good diagnostic performance has been reported for both doses.

Diseases of the liver and biliary system may affect the vasculature, parenchyma, biliary excretion or a combination of these. The distribution of the pathological processes can be focal or diffuse or both at the same time. The combination of the clinical information available to the radiologist and the capacity of the MRI unit and personnel should determine how the examination is designed. The choice of contrast media is therefore based on the relative importance of vascular, hepatic parenchymal and biliary processes for each patient and referral.
6.5. Future Studies

In the clinical situation, patients will present with varying degrees of liver function impairment, with or without biliary involvement. The hepatocyte-specific uptake of the herein studied contrast media is a quality that potentially can be employed for more functional evaluation of the hepatic excretory function, and thereby contribute to better diagnostic methods sensitive for changes in liver function.

A more quantitative analysis of liver parenchymal enhancement will be performed on image data from a second set of healthy volunteers, who were examined on a different MR unit but according to a protocol similar to the one used in Paper I and II.

As discussed in Paper II, so-called blood pool contrast agents are of interest in further studies of the hepatic vasculature, since they are retained for a long time to the vasculature and at the same time have high T1 relaxivity in blood (18, 55).

The two studies reported here studied contrast enhancement only in healthy volunteers. Studies in patients are underway, using dynamic examination of the liver and biliary system with Gd-EOB-DTPA combined with quantitative image analysis to explore the spectrum of hepatic uptake rates in different stages of hepatobiliary disease. To provide the best available image data for quantitative analysis of enhancement, there is room for improvement in the MRI sequence design. A three-dimensional GRE sequence with reconstruction algorithms recently developed at CMIV has shown promising results in technical evaluations and is more suitable for the process of quantitative calculations.
7. CONCLUSIONS

I. The high contrast between the common biliary duct and liver parenchyma had an earlier onset and longer duration for Gd-EOB-DTPA. Hepatobiliary imaging that includes evaluation of the biliary elimination phase can therefore be performed in a shorter time when using Gd-EOB-DTPA.

II. At the time-points studied and at the dosage used, Gd-BOPTA yields higher maximum enhancement of the hepatic artery, portal vein and middle hepatic vein than Gd-EOB-DTPA.
8. ACKNOWLEDGEMENTS

This work has been conducted within the Center for Medical Image Science and Visualization (CMIV) at Linköping University, Sweden. CMIV is acknowledged for provision of financial support and access to leading edge research infrastructure.

I would like to express my sincere gratitude to all colleagues and collaborators, who have given me guidance, support and assistance. It has been a rewarding process to take part in this research and to be able to complete this thesis. Special thanks are due:

My supervisor Örjan Smedby and co-supervisors Torkel Brismar and Anders Ynnerman for being inspiring, supporting and promoting during all phases of these studies.

My collaborators and co-authors Anders Persson, Nils Albiin and Nick Edsborg, for the analysis work with our extensive amounts of image data and for scientific feedback.

MR technologists at the Department of Radiology, Karolinska University Hospital Huddinge, for performing studies of consistently high quality.

Olof Dahlqvist Leinhard for many fruitful discussions and inspiring ideas.

Marcel Warntjes, Johan Kihlberg, Annika Hall, Anna Lindh, Petter Quick, Maria Engström, Maria Antonson, Claes Lundström and Ingela Allert for providing great support and a pleasant learning environment at CMIV.

My fellow PhD students of the CMIV Graduate School, Master of Science students and all others working at CMIV, providing the right environment for scientific study and for cross-disciplinary insights.

My residency supervisors Alf Johansson and Björn Relefors at the Department of Radiology, Hudiksvall, for being insightful, positive and empathic as mentors and role-models.

Colleagues and co-workers in Hälsingland for providing the best of radiology training and a friendly working environment.

Division Diagnostik and radiology IT services, Gävleborg County, for providing great support.

Gävleborg County Research Council, for financial support.

Bild- och funktionsmedicinskt centrum, Linköping, for actively promoting integration of research and clinical radiology.

Finally, I would like to thank Linda and Gustav, our parents and relatives, for everything.
9. REFERENCES


