Clinical Blood Pool MR Imaging
The Vasovist® Product Monograph

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Foreword

Magnetic resonance angiography has made great strides, with continuing improvements in hardware, pulse sequencing, and know-how allowing ever-increasing speed, resolution, and suppression of artifacts. However, an inherent physical barrier has always been limited SNR. Gadolinium contrast agents help to increase SNR by facilitating T1 relaxation, but they can be injected only at a finite rate and at a limited molar dose, and there is a rapid drop in concentration following the brief arterial phase due to redistribution into the extracellular fluid compartment. With its sixfold increase in T1 relaxivity, blood pool distribution, and longer serum half-life, Vasovist® represents a new breakthrough which promises to revolutionize MRA image quality once again.

This excellent treatise on Vasovist®, created by a team of exceptional faculty who are pioneers in MR angiography, covers the basic techniques, safety, efficacy, image processing, and pharmacoeconomic details, to successfully implement a new level of MRA image quality with this new contrast agent. In addition to improving all the usual arterial phase MRA applications, the blood pool distribution opens up new possibilities, including detecting internal bleeding and imaging stent graft endoleaks, which are reviewed in detail. In the complex, competitive field of cardiovascular imaging, this book articulates the cutting edge in imaging vascular disease.

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VII

Almost two decades ago, Martin Prince was able to demonstrate that the limitations of non-contrast MRA techniques could be overcome by injection of contrast agent. Subsequently, contrast-enhanced-MRA established itself in clinical practice as the standard for non-invasive depiction of almost all blood vessels. MR manufacturers have addressed the demands for faster acquisition speed to allow higher resolution imaging during the finite and relatively short imaging window of first pass MRA by a combination of faster gradients, parallel imaging techniques, and novel K-space sampling strategies. However, a perceived limit for improvement in spatial resolution, coupled with the negative impact of faster acquisition on contrast-to-noise ratios, has led to the development of »Vasovist«, the first contrast agent »tailored« to the vascular tree.

With its high relaxivity and unique pharmacokinetics, Vasovist® opens up new horizons in vascular diagnostics with a prolonged imaging window, enhanced topographic information, and unrivaled new visualization options. The editors and authors have made groundbreaking contributions towards establishing MR angiography in various investigative settings, rendering it more precise and applying it for diverse indications. The work presented here is founded upon the extensive experience of the editors, and it includes a broad range of experience from other scientific working groups.

This book presents the applications of Vasovist®-enhanced angiography; its potential advantages, such as the change in signal-to-noise ratio and intravascular distribution, are discussed systematically, thus giving a comprehensive overview of the basic principles and imaging techniques. Presentation of the various clinical fields is well-structured and is illustrated with excellent image material that addresses the essential questions concerning vascular diagnostics. This includes imaging of the intracranial and supra-aortic vessels and visualization of the coronary arteries, as well as of the renal and visceral vessels. Key chapters cover MR angiography of the aortoiliac and peripheral vessels. Whole-body MR angiography represents a special challenge for angiography. The new options offered by Vasovist®-enhanced MR angiography are also discussed. All in all, this monograph presents the ideal opportunity to gain relevant information, read either as a review or as a detailed account of the increasing scientific potential offered by this method of vascular MR diagnosis.

What can we predict for the future? Two decades following Dr. Prince's (then) heretical thesis that contrast-agent injection was required for dramatically improved MRA, we are now equipped with a tailored vascular contrast agent. This development parallels improvements in scanner performance, satisfies a demand for higher spatial resolution, and opens up a whole new perspective on the benefit of additional information available from the steady state images as a routine part of the study.

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Foreword
Introduction

The successful introduction of extracellular gadolinium-based contrast agents for contrast-enhanced MR angiography, and their wide acceptance today, raise the question of what part an intravascular contrast agent might play in diagnostic imaging. The answer lies in the capacity of an intravascular agent to give us high-level diagnostic information from first pass arterial imaging and, at the same time, to yield additional diagnostic value by allowing delayed imaging from the same contrast injection.

Clinical experience gathered since the introduction of Vasovist® (Gadofosveset) appears to provide the answer «yes»: not only is Vasovist® useful for first pass arterial imaging, but it also provides high intravascular enhancement that lasts much longer and is significantly greater than that afforded by conventional extracellular agents. Taking advantage of this effect, one can now acquire additional high-resolution images in the steady state which lead to much better delineation of vessel pathology. Steady state imaging offers the possibility of depicting the entire vascular system without relevant extravasation of the contrast medium from the intravascular space.

The extended diagnostic window of Vasovist® makes the examination more convenient because it is less dependent upon bolus dynamics. Imaging of a Gadofosveset bolus missed in the first pass examination does not require an additional injection of contrast agent. For these reasons, Vasovist® may enable physicians to detect systemic vascular disease earlier and to optimize the evaluation of therapeutic options, including percutaneous intervention and vascular surgery. In addition, imaging of the vascular system and surrounding tissues in the delayed phase appears to promise new contrast mechanisms that may improve the detection of inflammatory or malignant changes.

In summary, Vasovist® has the potential to open new horizons in diagnostic MR angiography by increasing the spatial resolution and the robustness of MRA examinations and facilitating the examination of multiple vascular beds. Vasovist® was first approved in 2005, and we are now looking at an expanded spectrum of clinical applications that has rapidly evolved and addresses the majority of clinical questions in vascular medicine and related fields. Therefore, this monograph is subdivided into chapters on technology, followed by a detailed review of the clinical fields for MR angiography with Vasovist®. With this steady increase of applications and clinical experience it is necessary to review not only the technical feasibility and reliability of the method, but also the potential additional benefit for the patient. Therefore, aspects of patient management are also analyzed, with the aim of deriving more effective and comprehensive imaging standards.

We would like to thank all of the authors for their valuable contributions and dedicated collaboration, which made this current compilation of essential aspects of Vasovist®-enhanced MR imaging possible. Also, we gratefully acknowledge the contributions of our publisher, Springer, and Mr. Eric Henquinet for his constructive, friendly and patient collaboration.

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List of Abbreviations

2D Two-dimensional
3D Three-dimensional
3D FFT 3D Fast Fourier Transform
SSFP Steady state free precession
ADC Apparent diffusion coefficient
ALARA As low as reasonably achievable
AngioSURF Angiographic System for Unlimited Rolling Field-of-views
APAOD Atherosclerotic peripheral arterial occlusive disease
ASSET Array Spatial Sensitivity Encoding Technique
AVF Arteriovenous fistulae
BBB Blood-brain barrier
BOLD Blood oxygenation level-dependent
BPCAs Blood-pool contrast agents
CA Contrast agents
CAD Coronary artery disease
CE Contrast-enhanced
CE-MRA Contrast-enhanced magnetic resonance angiography
CENTRA Contrast-enhanced timing robust angiography
CFA Common femoral artery
CIS Clinically isolated syndrome
CKD Chronic kidney disease
CLI Critical limb ischemia
CM Contrast medium
CMR Cardiovascular MR
CNR Contrast-to-noise ratio
CNS Central nervous system
CSF Cerebrospinal fluid
CT Computed tomography
CTA Computed tomography angiography
CTEPH Chronic thromboembolic pulmonary hypertension
CVC Central venous catheters
cVR Color volume rendering
d Diameter
Da Daltons
DCE-MRI Dynamic contrast-enhanced MRI
DEALE Declining Exponential Approximation of Life Expectancy
DKG-NT Deutsche Krankenhausgesellschaft Nebenkostentarif
DOR Diagnostic odds ratio
DSA Digital subtraction angiography
DVT Deep venous thrombosis
E/P Equilibrium phase
ECCM Extracellular contrast media
ECG Electrocardiogram
EMEA European Medicines Agency
EMF Electromagnetic field
ECS Extracellular space
EUS Endoluminal ultrasonography
EVAR Endovascular ultrasonography
F/P First pass
FDA US Food and Drug Administration
FDG 18Fluorodeoxyglucose
FFT Fast Fourier-transformation
FLAIR Fluid attenuated inversion recovery
FLASH Fast low-angle shot
FMD Fibromuscular Dysplasia
FNAC Fine-needle aspiration cytology
FOV Fields-of-view
GBCA Gd-based contrast agent
GCP Good clinical practice
Gd Gadolinium
GI Gastrointestinal
GRAPPA Generalized Autocalibrating Partially Parallel Acquisitions
GRE Gradient recalled echo
H&E Histological examination
HIFU High-intensity focused ultrasound
HNSCC Head and neck squamous cell carcinoma
HSA Human serum albumin
HTA Health technology assessment
IA-DSA Intra-arterial X-ray-based digital subtraction angiography
IC Intermittent claudication
ICH-GCP International Conference on Harmonisation on Good-Clinical-Practice
ICNRIP International Commission on Non-ionizing Radiation Protection
IEC International Electrotechnical Commission
iPAT Integrated Parallel Acquisition Techniques
IVC Inferior vena cava
IVUS Intravascular ultrasound
KTWS Klippel-Trenaunay-Weber syndrome
LAVA Liver acquisition with volume acquisition
LGBB Lower GI bleeding
LITT Laser-induced thermal therapy
LNT Linear non-threshold
MAPCAs Major aorto-pulmonary collateral arteries
MBF Myocardial blood flow
MDCT Multidetector computed tomography
MIP Maximum intensity projection
MPR Multiplanar reconstructions
MR Magnetic resonance
MRA Magnetic resonance angiography
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<th>Abbreviation</th>
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<tr>
<td>MRCA</td>
<td>Magnetic resonance coronary angiography</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MRV</td>
<td>Magnetic resonance venography</td>
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<td>MS</td>
<td>Multi-slice</td>
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<td>mSENSE</td>
<td>Modified SENSE</td>
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<td>MSI</td>
<td>Maximal-signal-intensity</td>
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<td>MTT</td>
<td>Mean-transit-time</td>
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<td>NSF</td>
<td>Nephrogenic systemic fibrosis</td>
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<td>PAD</td>
<td>Peripheral artery disease</td>
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<td>PAH</td>
<td>Pulmonary arterial hypertension</td>
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<td>PAOD</td>
<td>Peripheral arterial obstructive disease</td>
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<td>PAT-factor</td>
<td>Parallel acquisition technique factor</td>
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<td>PC</td>
<td>Phase-contrast</td>
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<td>PE</td>
<td>Pulmonary embolism</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>PR</td>
<td>Perfusion reserve</td>
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<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted-life-year</td>
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<td>RARE</td>
<td>Rapid acquisition with relaxation enhancement</td>
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<td>RAS</td>
<td>Renal artery stenosis</td>
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<td>RES</td>
<td>Reticuloendothelial system</td>
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<td>RF</td>
<td>Radiofrequency</td>
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<td>R-factor</td>
<td>Acceleration factor</td>
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<td>RIME</td>
<td>Receptor-induced magnetization enhancement</td>
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<td>RVT</td>
<td>Renal vein thrombosis</td>
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<td>SAE</td>
<td>Serious adverse events</td>
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<td>SAR</td>
<td>Severe adverse reactions</td>
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<td>SENSE</td>
<td>Sensitivity encoding</td>
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<td>SI</td>
<td>Signal intensity</td>
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<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<td>SLN</td>
<td>Sentinel lymph node</td>
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<tr>
<td>SMA</td>
<td>Superior mesenteric artery</td>
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<tr>
<td>SMASH</td>
<td>Simultaneous acquisition of spatial harmonics</td>
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<tr>
<td>SNR</td>
<td>Signal-to-noise ratio</td>
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<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>SPGR</td>
<td>Spoiled gradient recalled echo</td>
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<td>SPIO</td>
<td>Superparamagnetic iron oxide particles</td>
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<td>SR</td>
<td>Surface rendering</td>
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<td>SSD</td>
<td>Surface-shaded display</td>
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<td>SSFP</td>
<td>Steady state free precession</td>
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<td>STD</td>
<td>Standard deviation</td>
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<td>STIR</td>
<td>Short tau inversion recovery</td>
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<td>SWI</td>
<td>Susceptibility-weighted imaging</td>
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<td>T2-FSE</td>
<td>T2-fast spin echo</td>
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<td>TAO</td>
<td>Thromboangiitis obliterans</td>
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<tr>
<td>TE</td>
<td>Echo time</td>
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<tr>
<td>THRIVE</td>
<td>T1-weighted high-resolution isotropic volume imaging</td>
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<td>TIPS</td>
<td>Transjugular intrahepatic portosystemic shunts</td>
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<tr>
<td>TOF</td>
<td>Time-of-flight</td>
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<tr>
<td>TR</td>
<td>Repetition Time</td>
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<tr>
<td>TREAT</td>
<td>Time-resolved echoshared angiography technique</td>
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<tr>
<td>TTP</td>
<td>Time-to-peak</td>
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<tr>
<td>UGIB</td>
<td>Upper GI bleeding</td>
</tr>
<tr>
<td>USg-FNAC</td>
<td>Ultrasound-guided fine-needle aspiration cytology</td>
</tr>
<tr>
<td>USPIO</td>
<td>Ultrasmall super paramagnetic iron oxide</td>
</tr>
<tr>
<td>VESPA</td>
<td>Venous-enhanced subtracted peak arterial</td>
</tr>
<tr>
<td>VIBE</td>
<td>Volumetric interpolated breath-hold examination</td>
</tr>
<tr>
<td>VQ scan</td>
<td>Ventilation-perfusion scintigraphy</td>
</tr>
<tr>
<td>VRT</td>
<td>Volume rendering technique</td>
</tr>
<tr>
<td>VSOP</td>
<td>Very small superparamagnetic iron oxide</td>
</tr>
<tr>
<td>XRA</td>
<td>X-ray angiography</td>
</tr>
<tr>
<td>τm</td>
<td>Average time</td>
</tr>
</tbody>
</table>
Part I  Contrast Agent Properties and Technical Aspects

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    Martin Rohrer

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MRI Contrast Media – Introduction and Basic Properties of the Blood Pool Agent Gadofosveset (Vasovist®)

Martin Rohrer

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Chapter 1 · MRI Contrast Media – Introduction and Basic Properties of the Blood Pool Agent Gadofosveset (Vasovist®)

1.1 Introduction

Twenty years ago, the first MRI contrast medium (MRI-CM) was introduced to the market: in 1988, Gd-DTPA (Magnevist®, Bayer Schering Pharma AG, Berlin, Germany) received market approval for clinical use in the United States, Europe and Japan. In the years to follow, application of MRI-CM became a widely established, powerful tool in MRI for improved diagnosis in approximately 30% of all MRI examinations worldwide [1,2,3,4,5].

During these two decades, only a few novel contrast media concepts have successfully stepped out of research laboratories to undergo clinical development and eventually to receive market approval. These include:

- Coated iron oxide nanoparticles, often referred to as SPIO (superparamagnetic iron oxide particles) with an average core particle size in the nanometer range. The SPIO-based MRI-CM Ferumoxide (Feridex®, Bayer HealthCare Pharmaceuticals, Wayne, NJ, USA) and Ferucarbotran Resovist® (Ferucarbotran, Bayer Schering Pharma AG, Berlin, Germany) are taken up predominantly by the reticuloendothelial system (RES) in the liver.

- Tissue-specific Gd- or Mn-based approaches. Marketed products are the liver-specific MRI-CM Gd-EOB-DTPA (Primovist®, Bayer Schering Pharma AG, Berlin, Germany), Gd-BOPTA (MultiHance®, Bracco, Milan, Italy) and Mn-DPDP (Teslascan®, GE Healthcare, Chalfont St. Giles, U.K.).

- Highly concentrated contrast media solutions, such as the 1.0 molar Gd-concentrated Gadobutrol (Gadovist 1.0®, Bayer Schering Pharma AG, Berlin, Germany).

Most recently, another class of MRI contrast agents has been introduced to the market, mainly to overcome current limitations of MR angiography (MRA): highly intravascular, slow-clearing blood pool contrast agents for MRI. Vasovist® (Gadofosveset, Bayer Schering Pharma AG, Berlin, Germany) – the first intravascular contrast agent approved for use in MRI in the European Union – is based on non-covalent transient protein binding, which leads to both an extended imaging window and strongly decreased Gd-dosage requirements.

1.1.1 Basic Mode of Action of MRI Contrast Media

Contrast media for MRI are well-known to strongly influence proton spin relaxation times, represented in vivo mainly by the vastly available hydrogen nuclei from water molecules in organic liquids and tissues.

The tissue-specific longitudinal ($T_1$) and transverse ($T_2$) relaxation times are – besides the less important local proton density – the most important physical parameters in MRI to obtain spatially resolved differences in signal intensity (SI) and hence the prerequisites for any soft-tissue and other contrasts in MRI. Taking effect at this most basic level, the option to additionally enhance contrast in MRI by introducing $T_1$- and $T_2$-shortening contrast media has made contrast-enhanced MRI such an important and often indispensable diagnostic tool.

Furthermore, not only does the use of MRI-CM provide an exclusive opportunity to directly modulate contrasts at the most basic biophysical level of MRI; because MRI-CM significantly shortens relaxation times, e.g. in $T_1$-weighted MRA, there is another important and basic advantage of contrast media use compared with unenhanced MRI procedures: contrast-enhanced MRI allows not only for additional contrasting with a minimum of artifacts, but also for substantially accelerated data acquisition due to much shorter repetition times (TR) and ultimately shorter scan times at a given spatial resolution. This is particularly the case for MRA, where the $T_1$ shortening achieved by contrast media reduces the native longitudinal relaxation time ($T_{1n}$) of blood from over 1 sec down to the millisecond range, as will be discussed below in more detail.

For all classes of MRI-CM, shortening of proton spin relaxation times is achieved by the paramagnetic properties of the contrast media. Paramagnetism is based on unpaired electrons, resulting in strong and fluctuating local magnetic field distortions in the vicinity of the contrast medium molecules. These local magnetic field distortions are capable of destroying the much weaker proton spin order in the external, static magnetic field. Consequently, shortening of spin-lattice ($T_1$) and spin-spin ($T_2$) relaxation times is obtained in the tissue or liquid containing a sufficiently high concentration of contrast medium molecules. A more detailed and quantitative explanation of these effects is provided in Sect. 4.2.

1.1.2 Metal Complexes (Gd-Chelates)

As a result of their high number of unpaired electron spins, ions of transition metals and of lanthanides have been found to be well-suited as paramagnetic atoms in MRI-CM. The Gd$^{3+}$ cation with seven unpaired electron spins ($S = 7/2$) and its large magnetic moment became the most important atom for use in MRI-CM. To assure the stability and biodistribution required for safety, Gd$^{3+}$ ions are chelated in different chemical complexes, which also modulate their magnetic and pharmacokinetic properties to some extent. (Please also refer to the chapters in this book related to safety.) The interaction between the unpaired electron spins of the metal ion and the nuclear spins of protons from the surrounding water molecules is dominated by the short-distance, anisotropic dipol-dipol...
hyperfine interaction, as well as by contributions from the isotropic Fermi-contact interaction. Longitudinal and transverse relaxation times are comparably affected, leading to ratios \( r_2/r_1 \) between 1 and 2 [6].

### 1.1.3 Iron Oxide Nanoparticles

As mentioned above, so-called superparamagnetic particles have also been shown to be suitable as MRI-CM. They are often referred to as superparamagnetic iron oxide particles (SPIO) and have been investigated with different coatings (e.g. carboxydextran or dextran), different core particle diameters, and hydrodynamic size distributions. Their basic magnetic properties are determined not only by the interactions of nuclear spins with single paramagnetic ions in a chelate, but also by the bulk effects of the much larger spin ensembles of the unpaired electrons from the \( \text{Fe}_2\text{O}_3 \) and \( \text{Fe}_3\text{O}_4 \) molecules in the iron oxide nanoparticles. For the larger SPIO particles and for SPIO clusters in particular, these effects add up to almost macromolecular conditions and local ferromagnetic properties (»superparamagnetism«). Consequently, depending on SPIO core diameters or SPIO clustering effects, their influence on proton spin relaxation times applies over larger distances and is characterized by strong susceptibility effects and larger-scale magnetic field inhomogeneities. Naturally, the transverse relaxation processes dominate, which makes the SPIOs often better suited for T2 and T2*-weighted MRI sequences. Resulting \( r_2/r_1 \) ratios can be up to the order of one hundred.

### 1.2 Blood Pool Contrast Media for MRI

Several classes of MRI contrast media have been briefly introduced in the previous section. This section takes a closer look at the characteristic properties of blood pool contrast media for MRI.

Intravascular contrast agents show less extravasation into the interstitium than conventional extracellular contrast agents. Depending on their mode of action, they also have a longer retention time in the vascular system due to slower blood clearance. Both characteristics can be realized only with special physicochemical and biochemical properties. For this reason, these properties, as well as the resulting typical pharmacokinetics, will be examined first in general, and then specifically for Vasovist®.

If we take a closer look, additional subgroups within the class of intravascular MR contrast agents can be distinguished, and it becomes clear that the terms »intravascular« and »blood pool« do not have to be synonyms in the strictly literal sense. According to the dominant effect – reduced extravasation, decelerated resorption, or glomerular excretion – and the resulting pharmacokinetics, the terms »intravascular« and »blood pool« will be used differently.

According to a proposal by Bogdanov and Weissleder [7,8], the components circulating in the blood vessel system may be divided into the following three groups:
1. Cellular components (predominantly erythrocytes)
2. Water
3. Proteins (mainly albumin as the most common plasma protein)

### 1.1.4 Overview of Currently Marketed MRI Contrast Media

<table>
<thead>
<tr>
<th>Short name or internal development code</th>
<th>Generic name (INN) (^1)</th>
<th>Trade name(s)</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gd-DTPA</td>
<td>Gadopentetate dimeglumine</td>
<td>MAGNEVIST*</td>
<td>Bayer Schering Pharma AG</td>
</tr>
<tr>
<td>Gd-DO3A-butrol</td>
<td>Gadobutrol</td>
<td>GADOVIST*</td>
<td>Bayer Schering Pharma AG</td>
</tr>
<tr>
<td>MS-325</td>
<td>Gadofossvet trisodium</td>
<td>VASOVIST*</td>
<td>Bayer Schering Pharma AG</td>
</tr>
<tr>
<td>Gd-EOB-DTPA</td>
<td>Gadoxetic acid, disodium</td>
<td>PRIMOVIST*</td>
<td>Bayer Schering Pharma AG</td>
</tr>
<tr>
<td>SH U 555 A</td>
<td>Ferucarbotran</td>
<td>RESOVIST*</td>
<td>Bayer Schering Pharma AG</td>
</tr>
<tr>
<td>AMI-25</td>
<td>Ferumoxide</td>
<td>FERIDEX* / ENDOREM*</td>
<td>Bayer Healthcare / Guerbet</td>
</tr>
<tr>
<td>Gd-HP-DO3A</td>
<td>Gadoteridol</td>
<td>PROHANCE*</td>
<td>Bracco</td>
</tr>
<tr>
<td>Gd-BOPTA</td>
<td>Gadobenate dimeglumine</td>
<td>MULTIHANCE*</td>
<td>Bracco</td>
</tr>
<tr>
<td>Gd-DTPA-BMA</td>
<td>Gadodiamide</td>
<td>OMNISCAN*</td>
<td>General Electric Healthcare</td>
</tr>
<tr>
<td>Mn-DPDP</td>
<td>Mangafodipir trisodium</td>
<td>TESLASCAN*</td>
<td>General Electric Healthcare</td>
</tr>
<tr>
<td>Gd-DOTA</td>
<td>Gadoterate meglumine</td>
<td>DOTAREM*</td>
<td>Guerbet</td>
</tr>
<tr>
<td>Gd-DTPA-BMEA</td>
<td>Gadoversetamide</td>
<td>OPTIMARK*</td>
<td>Tyco Healthcare</td>
</tr>
</tbody>
</table>

\(^1\) International Nonproprietary Name
Quite analogously, the optional modes for intravascular contrast agents may be presented according to these target components.

### 1.2.1 Cellular Target Component: Erythrocyte-bound or Liposomal Systems

So far it has not been possible to advance research strategies on intravascular MR contrast agents based on direct coupling or on cytoplasmatic «loading» of erythrocytes through to clinical development, owing to the excessive quantities of contrast agent that were required [9]. However, a vascular circulation pattern similar to that in natural cells has been observed in liposomal, cell-like systems, whereby liposomes could be formed with compartments separated by a double lipid layer similar to a cell membrane. Iron, manganese, or gadolinium complexes could be trapped in their aqueous inner space and thus transported into the circulatory system. However, the compounds investigated so far were not stable over a long period and became rapidly metabolized by the reticuloendothelial system (RES) [10].

### 1.2.2 Aqueous Target Component: Macromolecules – Polymers, Iron-oxide Particles and Covalently Bound Metal Complexes

The systems within this subcategory are characterized by their inherent or, in the case of covalently bound systems, their effective macromolecular size, which is why they are subject to extravasation to only a small degree, if at all. Only large Gd-based systems and coated iron-oxide particles are discussed here, as some of these compounds are currently undergoing preclinical or clinical development, respectively. An example of the first group is Gadomer [11], a dendritic macromolecule, in which 24 Gd$^{3+}$ ions are bound. Its molecular weight is approximately 17 kDa. This was the origin of the previous name, Gadomer-17, for this dendrimeric concept developed by Bayer Schering Pharma AG. The investigational drug successfully underwent preclinical evaluation for various indications, such as coronary angiography [12] and lymphography [13]. Another example is gadomeritol (Vistarem*, P792, Guerbet) [14], whose intravascular properties are also based on molecular size. Gadomeritol also shows rapid clearance through glomerular filtration [15]. Gadomer and gadomeritol are highly intravascular contrast agents in the strict sense with limited blood pool characteristics (fast-clearing intravascular contrast agents).

In terms of very small superparamagnetic iron oxide particles (ultrasmall superparamagnetic iron oxide (USPIO), very small superparamagnetic iron oxide (VSOP)), reference is made to VSOP-C184 (Ferropharm GmbH) [16], ferumoxtran-10 (Sinerem*, Guerbet, Combiexec®, Advanced Magnetics) [17,18], and Ferucarbotran (Supravist*, SH U 555 C, Bayer Schering Pharma AG) [19,20]. These compounds are partially also being investigated for other than MRA indications, such as lymphography.

### 1.2.3 Proteins as Target Component: Non-covalently Bound Metal Complexes

This group of innovative MR contrast agents includes Gadofosveset (Vasovist®) as the only blood pool contrast agent currently (January 2008) approved in the 27 member states of the European Union and several other countries, including Switzerland, Norway, Turkey, Canada and Australia. An increase in retention time in the vascular system is achieved by reversible binding of the magnetically active metal complex specifically to the most prevalent albumin (human serum albumin (HSA)) in the plasma. An essential feature is the non-covalent type of binding between the contrast agent molecule and the plasma protein, which distinguishes this type of intravascular contrast agent from those molecules which bind permanently to large proteins or cells. Nevertheless, a high fraction of binding can be achieved with this concept, and both a significantly longer retention time and greatly reduced extravasation combined with generally good tolerance are therefore ensured [21].

For the bound fraction in blood, the concentration of the contrast agent molecule is observed to be largely independent of the relative concentrations of proteins in the dynamic equilibrium, which is quickly attained after venous injection. This and other characteristics will be examined in detail below, based on the example of Gadofosveset.

### 1.3 Molecular Structure and Physicochemical Properties

The molecular structure of Gadofosveset is shown in Fig. 1.1 and in a 3-D model in Fig. 1.2. The molecule can be divided into two functional entities. The first, MR-active, part is formed by the stable chelate structure of the gadolinium acid, gadolinium diethylenetriaminepentacetic acid, Gd-DTPA [22]. The cation Gd$^{3+}$ bound within this structure and the dipole-dipole interactions of its unpaired electron spin (S = 7/2) lead to strong decreases in
nuclear spin relaxation times, especially of proton spins \( I = \frac{1}{2} \) of the \( \text{H}_2\text{O} \) in the immediate molecular vicinity.

The innovative, additional properties of Vasovist\(^*_\), on the other hand, are achieved by the second functional entity, a diphenylcyclohexyl group covalently bound with the Gd complex via a phosphate diester bridge. This enhances the hydrophilic character of the molecule and allows reversible, non-covalent binding of the molecule with albumin.

Further properties are provided in \( \square \) Table 1.2 [6,23].

The active substance consists of the metal complex as described (stable up to 282\(^\circ\)C), which, as a white powder, has a low solubility for organic solvents but a very high water solubility.

The administered formula of Vasovist\(\text{\textsuperscript{\textregistered}}\) consists of a 250-mM (244 mg/ml) aqueous solution of the active substance with a 0.1% excess (by mass) of the ligand.

### Table 1.2. Physicochemical properties of Vasovist\(\text{\textsuperscript{\textregistered}}\)

<table>
<thead>
<tr>
<th>Property</th>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity</td>
<td>at 20(^\circ)C</td>
<td>3.0 mPa (\text{s})</td>
</tr>
<tr>
<td>Density</td>
<td>at 25(^\circ)C</td>
<td>1.12 g/ml</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>at 37(^\circ)C</td>
<td>825 mOsm/kg</td>
</tr>
<tr>
<td>pH</td>
<td>Ready-to-use solution</td>
<td>6.5–8.0</td>
</tr>
<tr>
<td>Relaxivity ( r_1 ) in ( \text{H}_2\text{O} )</td>
<td>at 37(^\circ)C, 1.5 T, 0.5 mM</td>
<td>((5.2 \pm 0.3) \text{ l mmol}^{-1} \text{ s}^{-1})</td>
</tr>
<tr>
<td>Relaxivity ( r_1 ) in bovine plasma</td>
<td>at 37(^\circ)C, 1.5 T, 0.5 mM</td>
<td>((19 \pm 1) \text{ l mmol}^{-1} \text{ s}^{-1})</td>
</tr>
</tbody>
</table>
1.4 Biophysical Properties – Reversible Protein Binding

As described in the previous section, the diphenylcyclohexyl group (linked to the Gd complex via a phosphate diester bridge) leads to the specific, reversible binding of the molecule to albumin [22,23]. A spatial depiction of the molecule reversibly bound to a protein binding site is shown in Fig. 1.3. It is not a chemical process in the strict sense; rather the temporary link is based on structural molecular properties and on the formation of weak hydrogen bridges between the protein and the diphenylcyclohexyl group from the contrast agent molecule.

The key effects of these unique binding properties on the contrast agent effects are well-known phenomenologically: they are first to be found in modified pharmacokinetics compared with conventional extracellular contrast agents, which result in a significantly longer retention time for the active substance in blood circulation. In the bound state, the contrast agent is not subject to glomerular filtration in the kidneys, i.e. only a small part – according to the non-bound fraction at the time – is filtered out of circulation in the kidneys. Extravasation is also largely reduced, as this is limited to the non-bound fraction of the active substance in the blood.

The second key effect lies in the influence on pharmacodynamics and consists essentially of a considerably increased relaxivity compared with conventional extracellular contrast agents. This principle of increasing relaxivity through reversible protein binding was first described under the title Receptor-induced magnetization enhancement (RIME) [24].

The special characteristics of the pharmacokinetics and pharmacodynamics are interdependent owing to their common origins via protein binding, which is described in the following section.

1.4.1 Pharmacokinetics – Prolonged Retention Time

Different retention times are shown schematically in Fig. 1.4 for both a conventional extracellular and a slow-clearing intravascular contrast agent with extended retention time in the vascular system. The representation qualitatively illustrates that an initial bolus phase exists in both cases; in the case of an intravascular contrast agent with extended retention time, this is followed by an »equilibrium phase« or »steady state«.

Let us take a closer look at the special pharmacokinetics of Gadofosveset: Following injection, there is initially a high local concentration of Gadofosveset in blood. Due to its specific binding affinity to albumin, the fraction of the bound Gadofosveset molecules depends both on the local albumin concentration and on the local Gadofosveset concentration. At very high Gadofosveset concentrations (»excess Gadofosveset«), the binding fraction is, of course, lower than at low Gadofosveset concentrations (»excess albumin«). This is shown in Fig. 1.5 for plasma solutions under different example conditions [25]: Accordingly, below the respective minimum concentrations there is a plateau range with an almost constant fraction of bound molecules.

For the pharmacokinetics in the initial phase after injection this means that the relative binding share has to rise from a small initial value (with very high local Ga-
dofosveset concentration) to an equilibrium state. This is shown in Fig. 1.6 with measurements from a preclinical investigation in primates [26], especially well-suited for illustration purposes due to the relatively high dose used of 0.1 mmol/kg. The initial rise in the albumin-bound percentage fraction and the arrival at the plateau at approximately 80–85% for this species can be clearly seen.

Obviously, the time course of the protein-bound fraction has a direct influence on the pharmacokinetics: Because only the unbound fraction is subject to renal filtration, elimination from the vascular system is faster at first until an approximately homogeneous distribution is attained in the total blood volume. Furthermore, the unbound fraction is subject to extravasation, into the interstitial space or by passage of a defect blood-brain barrier.

The two half-lives $t_{\text{-half}}$ and $t_{\text{half}}$ must be taken into consideration for an accurate, quantitative description of the pharmacokinetics of Gadofosveset; these characterize the typical initial ($t_{\text{half}} = 0.48 \pm 0.11$ h) and the subsequent time course ($t_{\text{half}} = 16.3 \pm 2.6$ h) of the Gadofosveset concentration in blood. In Fig. 1.7 this is depicted on the basis of the results of a clinical licensing study over a period of 48 h after injection [27]. From the logarithmic scale of the parameter axes (plasma concentration in mmol/l) the typical, averaged half-lives $t_{\text{half}}$ and $t_{\text{half}}$ may be recognized in the early and the later time points, respectively.
The half-life labeled here with disposition phase and characterized by \( t_{1/2\alpha} \) is also known as the (terminal) plasma elimination time. It has to be distinguished from the terminal elimination time \( t_{\text{term}} \), with which the active substance is eliminated not only from the vascular system, but also from the organism. For Vasovist® this is \( t_{\text{term}} = 18.5 \pm 3 \) h [27].

### 1.4.2 Pharmacodynamics – Relaxivity

The reduction in the longitudinal \( (T_1) \) and transversal \( (T_2) \) relaxation times of the proton spin detected by magnetic resonance imaging with an MR contrast agent is quantitatively described by relaxivity values \( (r_i) \). The definition of \( r_i \) (with \( i = 1, 2 \)) is given by the difference in the relaxation rates (inverse relaxation times \( 1/T_i \)) of a solution with and without contrast agent \( (1/T_{i(0)}) \). In the definition, there is also division by the contrast agent concentration, which yields independence of the relaxivity values from the concentration in the first approximation [28]:

\[
r_i = \left( \frac{1}{T_i} - \frac{1}{T_{i(0)}} \right) \cdot \frac{1}{[\text{CM}]} \quad i = 1, 2
\]

**Eq. (1)**

The contrast medium concentration (in mmol/l) is termed [CM].

Equation (1) is obviously a very expedient definition for the relaxivities, especially for conventional contrast agents, which have little or no interaction with plasma proteins. The difference in the relaxation rates \( (1/T_i - 1/T_{i(0)}) \) is often abbreviated as \( \Delta 1/T_i \). \( \Delta 1/T_i \) represents the actual observed reduction in relaxation times under the given conditions quantitatively and is therefore one of the most important parameters to describe contrast agent effects in MRI. The \( \Delta 1/T_i \) measurement values are often entered in a graph as a function of concentration [CM]. For non-protein-binding contrast agents a good approximation to a linear fit is obtained, whose constant slope \( (\Delta 1/T_i) / [\text{CM}] \) corresponds to the respective relaxivity \( r_i \).

However, for MR contrast media which interact appreciably with proteins and whose relaxivity is influenced by protein binding – which is the case for Vasovist® and some other MR contrast agents – there is also a clear dependence of the reduction in relaxation time on the relative concentration of the respective plasma proteins as well as on the concentration of the contrast agent. The relaxivity can therefore no longer be described by a straight line over a large concentration range in this case [29,30]. This is shown in Fig. 1.8 for Vasovist® on the basis of results from a clinical study [27].

As is apparent in Fig. 1.8, the slope \( (\Delta 1/T_i) / [\text{CM}] \) of the curve falls with higher concentrations as anticipated, because the relative fraction of bound molecules – as described above – is lower at higher Gadofosveset concentrations. At the same time, Fig. 1.8 also shows that the deviation from linearity in the concentration range shown is moderate overall and especially at low concentrations below 0.1 mmol/l is negligible. This means that relaxation values measured at concentrations up to 0.1 mmol/l cannot necessarily be extrapolated to very high concentrations. According to international recommendations for the nomenclature of MR contrast agent parameters [28], the concentration should also be specified when specifying the relaxivity in such cases. The good agreement with a linear relationship of \( \Delta 1/T_i \) versus concentration [CM] in the concentration range up to 0.5 mmol/l within the statistical measurement accuracy allows good comparability in this range, also with relaxivity values of non-protein-binding contrast agents. It is important in comparative analyses that the measured concentration ranges, as well as other measurement conditions, are always identical.

Moreover, relaxation values are generally dependent on additional conditions: Both the magnetic field strength and the temperature have an influence on the measurement values. Hence, these conditions should also be specified for the respective solution environment of the contrast agent (e.g. blood, plasma, albumin concentration, water). Table 1.3 compares several values for Gadofosveset and a weak protein-binding contrast agent (Gd-BOPTA, MultiHance®, Bracco, Milan, Italy).
1.4 Biophysical Properties – Reversible Protein Binding

1.4.3 Causes for Increased Relaxivity Due to Protein Binding

Within the theoretical framework given here, a simplified, illustrative description of the biophysical relationships is provided to make the increased relaxivity due to protein binding comprehensible. Mathematical presentations will not be offered; instead reference is made to some reviews on relaxation theory [31,32,33,34].

As with other gadolinium-based MR contrast agents, magnetic interactions take place between unpaired electron spins (= paramagnetic center) of the Gd$^{3+}$ cation bound to the complex (S = 7/2) and unpaired nuclear spins from the solution environment of the molecule. The nuclear spins are essentially attributable to protons (hydrogen nuclei) from neighboring H$_2$O molecules. The known reduction in nuclear spin relaxation times arises from the much larger magnetic moment of electron spins compared with proton spins. The magnetic moment of the unpaired electrons can be viewed as a local disturbance or an additional, fluctuating, and highly inhomogeneous magnetic field for the nuclear spins.

The precise mechanisms on a molecular level are divided into contributions based on interactions with protons in direct coordination with the metal ion of the complex – inner-sphere effects – and those based on more distant protons above the second coordination level and also diffusing protons – outer-sphere effects (see Fig. 1.9) [31,32].

For paramagnetic metal complexes, the contributions can largely be described mathematically with the Solomon-Bloembergen-Morgan equation [35]. The magnetic interactions between electron and nuclear spins are described here with anisotropic dipole-dipole interactions and scalar Fermi-contact interactions. The contributions to longitudinal relaxation of the first coordination level (inner sphere), which usually dominate, depend on the number of transiently bound water molecules (hydration number) and their relaxation time ($T_{1m}$), as well as on

| Table 1.3. Relaxivity values$^1$ for Gadofosveset and a weak protein-binding MR contrast agent measured in bovine plasma at concentrations up to 0.5 mmol/L. Temperature at 1.5–4.7 T: 37°C [6] |

<table>
<thead>
<tr>
<th></th>
<th>0.47 T$^2$</th>
<th>1.5 T</th>
<th>3 T</th>
<th>4.7 T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r_1$</td>
<td>$r_2$</td>
<td>$r_1$</td>
<td>$r_2$</td>
</tr>
<tr>
<td>Vasovist*</td>
<td>28 (27-29)</td>
<td>40 (38-42)</td>
<td>19 (18-20)</td>
<td>34 (32-36)</td>
</tr>
<tr>
<td></td>
<td>9.9 (9.4-10.4)</td>
<td>60 (56-64)</td>
<td>6.9 (6.6-7.2)</td>
<td>60 (57-63)</td>
</tr>
<tr>
<td>MultiHance</td>
<td>9.2 (8.7-9.7)</td>
<td>12.9 (12.2-13.6)</td>
<td>6.3 (6.0-6.6)</td>
<td>8.7 (7.8-9.6)</td>
</tr>
<tr>
<td></td>
<td>5.5 (5.2-5.8)</td>
<td>11.0 (10.0-12.0)</td>
<td>5.2 (4.9-5.5)</td>
<td>10.8 (10.1-11.5)</td>
</tr>
</tbody>
</table>

$^1$ values in l mmol$^{-1}$ s$^{-1}$; $^2$ measured at 40 °C

Fig. 1.8. Dependence of observed relaxation rates ($1/T_1$) on the Gadofosveset concentration. Note the high linearity at low concentration as depicted separately
the average time ($\tau_m$) for the coordination of these water molecules with the metal ion.

The latter factor, the average time ($\tau_m$) for the coordination of individual water molecules on the metal complex (which corresponds to the inverse exchange rate $k_e$) is worthy of closer examination. Intuitively, a longer average period of presence of the directly influenced water molecule in the immediate vicinity of the Gd complex can also contribute to a more pronounced reduction in overall relaxation times. It is similarly intuitive that $\tau_m$ is influenced by the respective characteristic times of molecular movements, such as rotation, vibration and diffusion: If there are slower molecular movements (e.g., caused by Brownian motion due to lower temperature, by higher viscosity of the solution environment, and in larger molecules) the respective values for $\tau_m$ are correspondingly larger and the relaxation time reduction achieved increases.

The molecular movements are characterized by correlation times; the rotation correlation time is abbreviated by $\tau_r$ for example. The molecular dimensions of proteins, such as serum albumin, are several orders of magnitude above those of low-molecular-weight Gd complexes. Hence, the contrast agent molecule experiences a strong increase in its effective rotational correlation time of around two orders of magnitude (factor 100) as a result of protein binding. Correspondingly, the much slower motions in the protein-bound state are expressed by a decreased rotation rate [31]. The average period of presence $\tau_m$ of the water molecules coordinated with the Gd complex is thereby significantly increased as a consequence, accompanied by the strong increase in the relaxivity of Gadofosveset through protein binding.

### 1.5 Implications for Clinical Application

The product properties of Vasovist® as described above reveal important aspects about how the product should be used to optimally exploit its extraordinary diagnostic potential in clinical applications. It must be stressed, however, that although the basic properties certainly lead to essential, trend-setting information for optimizing sequence parameters and injection protocols, successive identification and exploitation of the new imaging methods with Gadofosveset finally depend on radiological experience and expertise.

Some summaries of initial application recommendations were published early [36,37,38] and are based both on the experiences of early-stage clinical studies and on theoretical considerations. Special attention should be drawn to the chapters of this book describing clinical applications as well as to the previous publications on selected studies [39,40,41], which also examine technical application aspects. However, some fundamental aspects of first pass and steady state applications are described in the following sections.

#### 1.5.1 Relevant Implications for Application in the First Pass

As a result of its considerably higher relaxivity, a significantly lower gadolinium dosage of 0.03 mmol/kg body weight compared with conventional contrast agents could be found for MRA with Gadofosveset. This results in around one third of the standard dose of conventional contrast agents of 0.1 mmol/kg body weight. Bearing in mind the concentration of 0.25 mol/l of the ready-to-use solution (compared with 0.5 mol/l for most other contrast agents), the volume-related dose is 0.12 ml/kg body weight.

As with any other conventional contrast agent, Vasovist® can be intravenously administered manually or with an automatic injection system for first pass MRA. All the well-established techniques regarding bolus dynamics and correct timing are the same as with first pass MRA using conventional contrast agents. The situation in a patient to be examined can be determined with a test bolus of 1 ml volume prior to the measurement itself. The parameters covered here are: the individual synchronization of bolus injection, arrival time of the bolus in the target region, and the start of measurement. Alternatively, the respective manufacturer’s «fluoroscopic» methods of bolus detection with fast 2D imaging of suitable target regions can be carried out in real-time (for example BolusTrack, CareBolus or SMARTprep). A saline flush following the injection is obligatory.

To obtain a comparable length of the contrast agent bolus and, at the same time, to use the tested relation-
ship between the period of injection, scan delay, and data acquisition as established with 0.5-molar contrast agents, the Vasovist\textsuperscript{*} injection rate can be adapted as follows:

**Example case:** A protocol using the standard dose of 0.1 mmol/kg of a 0.5-molar contrast agent has become established for a specific MRA application. For a patient with 75 kg body weight, a typical volume of 15 ml was injected at a rate of 3 ml/s over a period of 5 s. According to the standard dosage for a 75-kg patient, the Vasovist\textsuperscript{*} contrast agent volume is 9 ml. To reproduce the same injection period with the lower volume, Vasovist\textsuperscript{*} requires a roughly 1/3 reduced injection rate in this case. Consequently, the volume of 9 ml should be applied at 2 ml/s in 4.5 s in this case.

Comparison with the common application of a double or triple dose of conventional MR contrast agent yields even more pronounced variations. For instance, comparing the «double dose» of 0.2 mmol/kg body weight of a conventional MR contrast agent with Vasovist\textsuperscript{*}, the Gd standard dose is reduced by 85% and the injection volume by 70% (9 ml instead of 30 ml).

In principle, the specific pharmacodynamics caused by protein binding (including higher relaxivity and concentration dependence) described in the last section could also be taken into account for the initial bolus phase to optimize the sequence parameters. However, the lower binding fraction in the initial bolus is offset by the very high initial concentration of Vasovist\textsuperscript{*}, so that, all in all, it can be safely assumed that this relative effect is over-compensated by the effect of the absolute very high local concentration of Vasovist\textsuperscript{*} to produce the actual reduction in T\textsubscript{1} relaxation time.

Hence, this aspect appears rather insignificant for most clinical applications and therefore adaptation of sequence parameters (e.g. flip angle) to improve image quality would not appear worthwhile in most practical cases. This is supported by quantitative estimates as well as by current experience, which shows the use of established sequence parameters with the common, fast 3D gradient echo sequences to produce excellent results in first pass MRA using Vasovist\textsuperscript{*}.

### 1.5.2 Relevant Implications for Application in the Steady State

The situation in the later acquisition phases, i.e., advanced distribution throughout the entire vascular system, differs from the well-known first pass, as described previously. The situation in the steady state can certainly be viewed as generally far simpler and easier to calculate, as both the spatial and temporal dynamics have changed from the contrast agent bolus rapidly propagating in the vascular system with inhomogeneous concentration distribution into a now homogeneous distribution and approximate temporal equilibrium. This applies particularly to the period of time following the actual distribution phase, whose start is very much dependent on the individual circulatory parameters of the respective patient. For patients with normal cardiovascular function, an approximately homogeneous distribution may be assumed after just a few circulation cycles within the first 3–5 min after injection, whereas in patients with cardiac insufficiency or other relevant diseases of the circulatory system, complete distribution can take up to 10 min, according to current knowledge. These precursory comments are in no way intended to imply that acquisition prior to the attainment of a homogeneous distribution should be generally avoided. Rather, it should be pointed out that, dependent on the individual circulatory parameters, relative fluctuation in arterial and venous contrast enhancement is still to be expected during the later distribution phase.

Assuming a homogeneous distribution of the protein-binding contrast agent in the entire vascular system in the steady state, the blood pool agent is generally further diluted compared with the initially higher concentration of a bolus in the first pass. This dilution effect also leads to somewhat longer relaxation times compared with the first pass, even for the very high relaxivity of Gadofosveset. The anticipated order of magnitude of T\textsubscript{1} is therefore estimated in the following simple example calculation [36].

**Estimation of T\textsubscript{1} in the steady state on the basis of an example calculation:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>75 kg</td>
</tr>
<tr>
<td>Total blood volume</td>
<td>5.5 l</td>
</tr>
<tr>
<td>Vasovist\textsuperscript{*} standard dose</td>
<td>0.03 mmol/kg</td>
</tr>
<tr>
<td>Individual Gd dose</td>
<td>2.25 mmol</td>
</tr>
<tr>
<td>Vasovist\textsuperscript{*} injected concentration</td>
<td>0.25 mmol/l</td>
</tr>
<tr>
<td>Vasovist\textsuperscript{*} injected volume</td>
<td>9 ml</td>
</tr>
<tr>
<td>Calculated maximum concentration</td>
<td>0.45 mmol/l</td>
</tr>
<tr>
<td>Estimated concentration following initial distribution phase 80% of [CM]\textsubscript{max}; [CM]:</td>
<td>0.36 mmol/l</td>
</tr>
</tbody>
</table>

Entering typical values for the non-enhanced longitudinal relaxation time in blood T\textsubscript{100} and for the relaxivity r\textsubscript{i} of Vasovist\textsuperscript{*} under the given standard conditions:

\[ T_{100}^{-1} = 0.8 \text{ s}^{-1} \text{ (equivalent to 1.25 s = T}_{100} \text{ of blood)} \]

\[ r_{i} = 19 \text{ l mmol}^{-1} \text{ s}^{-1} \text{ (measured in whole blood at 37 °C, 1.5 T, 0.5 mM concentration)} \] [6],

and using the general relationship between relaxivity, concentration and relaxation times (Eq. 1)

\[ T_{i}^{-1} = T_{100}^{-1} + r_{i}[CM] \]
The estimated relaxation rate $T_1$ in blood is derived as:

$$9.35 \text{ s}^{-1} = 0.8 \text{ s}^{-1} + 19 \text{ l mmol}^{-1} \text{ s}^{-1} \cdot 0.36 \text{ mmol l}^{-1}$$

and the corresponding reciprocal value for the estimated relaxation time $T_1$ of approx. 130 ms. Dependent on the exact time of observation and on widely varying individual physiological conditions, $T_1$ can be used to calculate relaxation times of approx. 100–200 ms.

In comparison, $T_1$ relaxation times of 20 ms and below can exist in the bolus for first pass MRA due to the higher contrast agent concentrations here. It is quite obvious that the common protocols for fast 3D gradient echo sequences established for contrast-enhanced MRA, for example, allow leeway for optimization in the steady state with Vasovist®: The sequence protocols implemented for MRI scanners are generally optimized for shorter first pass relaxation times, especially in regard to the signal intensity as a function of the parameters flip angle, echo time (TE), repetition time (TR), and relaxation times.

Accordingly, the parameter changes in the steady state tend towards smaller flip angles and longer repetition times, whereby optimization of the flip angle is calculated with the Ernst angle $\alpha$:

$$\alpha = \arccos(\exp(-\frac{\text{TR}}{T_1})) \quad \text{Eq. (2)}$$

The option also arises of acquiring images with Vasovist® in the steady state over an extended period of time with a considerable increase in spatial resolution. There are different ways for 3D gradient echo sequences to achieve this without sacrificing signal-to-noise ratio. One of these is to increase the repetition time (for example in the 8–15-ms range), to select the flip angles smaller (approximately 15°–25°), to keep TE at the minimum, and to reduce the detection bandwidth, as appropriate. A complementary strategy would be to improve the signal-to-noise ratio by increasing the number of acquisitions, while maintaining TR short in the usual range (for example 4–7 ms), but to lower the flip angle by around 10° to account for the longer $T_1$. The latter method can be considered, for example, for body regions that are subject to respiratory motions, and may be applied in conjunction with respiratory triggering and advanced navigator techniques.

Specific descriptions and sequence parameters found for various regions of examination are described in the following chapters.

References


Take home messages

- Based on unpaired electrons and their paramagnetic properties, MRI contrast media shorten proton spin relaxation times in vivo. Thereby enhancing the most important contrast mechanism in MRI, they provide a valuable option for obtaining additional diagnostic information.
- The most frequently applied class of MRI-CM consists of 0.5-molar, Gd-based metal complexes with extracellular biodistribution and fast glomerular filtration via the kidneys. Other concepts include a highly concentrated 1.0-molar contrast medium, coated superparamagnetic iron oxide (SPIO) particles, and liver-specific Gd-based MRI-CM with weak protein binding.
- Blood pool MRI-CM have been developed, but so far only gadofosveset, based on non-covalent and reversible binding to serum albumin, has successfully undergone clinical development and received market authorization.
- The mode of action of Gadofosveset is characterized basically by the two effects of the reversible protein binding: 1. significantly increased relaxivity in the protein-bound state; 2. vastly prolonged retention time in the vascular system, providing much longer imaging windows of up to 1 h (slow clearing, intravascular).
- In addition to the well-known first pass imaging, the blood pool properties and the much longer period of $T_1$ shortening (steady state) of Gadofosveset overcome the limitations of conventional extracellular MRI-CM, for example poor resolution in peripheral MRA.
- Application of Gadofosveset for both first pass and steady state MRA is easily achieved, and is optimized in the steady state by minor protocol adaptations.
References


27 Clinical Study Report MS-325-06, Clinical Summary 2.7.2. Schering AG


