Contrast Agents in Magnetic Resonance Imaging

An Offprint from

Peter A. Rinck

Magnetic Resonance in Medicine
A Critical Introduction

The Basic Textbook of the European Magnetic Resonance Forum

13th edition • 2021
335 figures, 36 tables
Foreword

"Why, sometimes I've believed as many as six impossible things before breakfast."
The White Queen in Lewis Caroll’s 'Alice Through the Looking Glass'.

We like books – printed on paper, if possible with a beautiful hard-cover binding. Thus, putting this standard textbook on the internet some years ago was a challenge. Now we return with a printed version of the magnetic resonance textbook. The reasons I have described elsewhere.¹

Celebrating the 50th anniversary of MR imaging in 2021 was a good occasion to publish a new edition. The textbook-child has grown up, become an adult or, in our case – a rather successful standard textbook. The reviews and public reaction to the book were extremely positive.

The first version of this primer – a little booklet – was written at Paul C. Lauterbur's laboratories in the early 1980s. Lauterbur was the father of MR imaging and received the Nobel Prize twenty years later. The text was intended to be used as the Basic Textbook for EMRF, the European Magnetic Resonance Forum. After Lauterbur saw the first edition, he commented: "It looks like a fine book, especially for residents, nurses, and technicians."

Initially we thought this statement was not very encouraging, but in hindsight this was exactly what we had intended to write. We worked on it for another twenty years – and finally Lauterbur found the last edition he read before his death "gratifying". How-

ever, the target audience today includes scientists and university professors. They should be able to acquire a basic knowledge which enables them to pursue studies of their own and to cope with some of the most common problems, among them tissue relaxation, image contrast and artifacts or questions concerning possible hazards to patients – and to become aware of how to perform reliable research, and to ask and be critical.

The main author and the contributors have not attempted to cover the field completely nor to be exhaustive in the topics discussed, as the field of magnetic resonance still is in a permanent stage of development and therefore changing year by year. Clinical MR machines and even equipment sold for scientific purposes have been increasingly altered into push-button black boxes with pre-fab, given and unchangeable protocols. We are not interested in certain gadgets or "apps" of commercial machines, and won't mention or describe them. We try to explain the fundamentals any user should know and understand.

As with everything in life, MR imaging does not only require knowledge of facts but also of background information and of the historical development of the field for critical decision making. Therefore we have interspersed some subjective, critical, and opinion-oriented sections – interludes – intended to offset the technical nature of the teaching sections and provide some insights into more practical questions faced by MR users.

Most of them were taken from Rinck-side (www.rinckside.org), a collection of columns published since 1990.

Many of the recent developments concerning MR equipment and its medical and biological applications have turned away from magnetic resonance itself to novel engineering and software approaches in image processing including artificial intelligence. Techniques, ideas and algorithms were imported from fields outside medicine and adopted by software engineers with little or no background in MR and medicine nor insight into medical needs. We mention some of the prime approaches without going into details of signal or image processing – they are of no importance for the understanding of fundamental facts of magnetic resonance imaging.

There has been a long list of contributors to this and earlier versions (see page 418). Their support, ideas, dedication, and feedback have added much to the quality of this work. This book was peer-reviewed by a number of competent reviewers in different fields whom I thank for their efforts.

If you want to learn something about magnetic resonance imaging or its applications choose your topic of interest. If you want to learn it from scratch start with Chapter 1; and if you want to air your brain, read the interludes that are scattered in between.

If you find any mistakes in this book, rest assured that they were left intentionally so as not to provoke the gods with something which is perfect. Still, we would be happy about your feedback. We hope that this textbook will be useful for you and that you will enjoy it. If you have comments or suggestions, please write to us.

Peter A. Rinck, July 2021
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# Magnetic Resonance in Medicine

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*Claustraphobia, MRI, and the human factor*

*Officially supervised magnetism*

*Commercial forces and MR safety*

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More Magnetism

Magnetic resonance contrast agents aim at changing signal intensity and thus image contrast. The main contrast parameters in MR imaging are proton density, the relaxation times, and magnetic susceptibility.

It is rather difficult to alter the water content of tissues. Therefore, the magnetic properties have been the major target for the development of contrast changing agents.

Magnetic susceptibility describes the ability of a material or substance to become magnetized by an external magnetic field.

So, let’s change – for instance – the field lines (Figure 12-01).

All substances are diamagnetic. A strong external magnetic field speeds up or slows down the electrons orbiting in atoms in such a way as to oppose the action of the external field. These materials partly expel from their interior the magnet field in which they are placed.

Certain materials have ferromagnetic properties, among them iron, nickel, cobalt, and their alloys. Ferromagnetic materials are strongly attracted by magnets. In ferromagnetic materials, there is a strong coupling of the individual magnets, resulting in their lining up parallel to one another (Figure 12-02a).

They lose their magnetic properties when heated above a temperature known as...
Then they begin to show a kind of magnetic behavior which is called paramagnetic. Many other elements and compounds are paramagnetic at all temperatures, among them oxygen, gadolinium, and manganese (see also Chapter 4).

Paramagnetism is due to the presence of little colonies of atomic magnets, in which the individual magnets are weakly, if at all, bound to one another and therefore capable only of random orientation in the absence of an external field (Figure 12-02b).

Paramagnetic substances are feeble in their response to an external magnetic field. Superparamagnetic substances have a substantially higher susceptibility.

Ferrimagnetic materials, such as ferrites, are also coupled in an antiparallel fashion, but the overall effect of the individual magnets pointing in one direction exceeds. Thus, the net effect is that of weak overall magnetism (Figure 12-02c).
Antiferromagnetic materials consist of elementary magnets coupled together in opposite directions, resulting in zero net magnetization (Figure 12-02d).

For diamagnetic material, the value of susceptibility is always negative; for paramagnetic, superparamagnetic, and ferromagnetic substances positive.

Figure 12-03 shows the response of diamagnetic, paramagnetic, and ferromagnetic substances to an outside magnetic field.

**Magnetic Resonance Contrast Agent Terms**

To be able to develop and compare contrast agents, there has to be agreement of how their properties should be measured.

Table 12-01 summarizes the latest version (published in 1997) of the *Standard Nomenclature of Magnetic Resonance Contrast Agent Terms* for relaxation times, relaxation rates, and relaxivities.

### Nomenclature of Magnetic Resonance Contrast Agent Terms

<table>
<thead>
<tr>
<th>Relaxation times</th>
<th>T1, T2 (T₁, T₂)</th>
<th>(s; also: ms)</th>
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<tr>
<td>Relaxation rates</td>
<td>R₁, R₂ (R₁, R₂)</td>
<td>(s⁻¹)</td>
</tr>
<tr>
<td>Relaxivities</td>
<td>r₁, r₂ (r₁, r₂)</td>
<td>(s⁻¹ × mM⁻¹ × L) [pH = ...]</td>
</tr>
</tbody>
</table>

Relaxivities *r₁*, *r₂* should be

(a) expressed per paramagnetic center (at least), and

(b) measured under standard conditions (i.e., 37°C ± 2°C at physiological pH in water or saline).

When working under standard conditions, the following term is sufficient:

frequency *r₁*, *r₂* (s⁻¹ × mM⁻¹ × L)

**Note:**

1. one digit (decimal) is sufficient;
2. R1 and R2 measurements should be performed in solutions with relaxation rates of 3 s⁻¹ minimum (approximately 10 times the R1 and R2 of the solvent);
3. *r* must be concentration independent;
4. the spellings of T1/T2 (versus T₁ / T₂), R1/R2 (versus R₁ / R₂), and *r*₁/*r*₂ (versus *r*₁ / *r*₂) are acceptable.

This standard was set in 1990 and revised in 1992 and 1996.

**Citation rule:** EMRF. Recommendations for the Nomenclature of Magnetic Resonance Contrast Agent Terms. Acta Radiol 1997; 38,S1: 5.

**Table 12-01:**

Recommendations for the Nomenclature of Magnetic Resonance Contrast Agent Terms.
Introduction

Despite the fact that inherent contrast in MR imaging can be manipulated to a much greater extent than in other imaging techniques, certain diagnostic questions cannot be answered easily and require the application of contrast agents (Figure 13-01).

In general, contrast manipulation in MR imaging by application of contrast agents is most useful when inherent contrast cannot be attained successfully.

Since it is nearly impossible to alter the water content of tissues, contrast agents on the market or in clinical or pre-clinical trials focus on relaxation time and susceptibility changes.

As early as 1946, in one of the first papers describing NMR, paramagnetic catalysts were mentioned to accelerate the T1 relaxation process.\(^{210}\)

This concept was recognized by Paul C. Lauterbur shortly after his invention of MR imaging and tested and proved in imaging studies in animals: the first pathologies enhanced by a contrast agent.\(^{211}\)

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Figure 13-01:
Nature likes mimicry; radiologists like to highlight lesions. With plain photography (or MR imaging), the object of the examination might be visible but nor clearly delineated. Changing contrast with an extrinsic agent may help ... for instance, painting the wall in the background or injecting a contrast agent.
The most efficient elements are listed in Table 13-01. Particulate agents form a different class. Important goals and requirements for the development and use of MR contrast agents are listed in Table 13-02.

In many instances, the pattern of enhancement of paramagnetic contrast agents in MR imaging is very similar to that of contrast-enhanced x-ray CT. However, it should be taken into account that in reality MR contrast agents behave differently from CT agents and do not in any case follow the CT enhancement patterns: In x-ray CT one sees the agent, in MR imaging one sees the effect of the agent.

Many efforts in contrast agent development were channeled in certain directions more by the relative ease of chemical synthesis than by the goal of specific medical applications or product safety. Thus, when applied properly, contrast agents available for clinical routine examinations today are safe and good enhancers. However, they are unspecific. This means that they do not highlight specific pathologies but rather unspecific pathological tissue changes.

At present, paramagnetic contrast agents are the most frequently used. Yet, despite the fact that approximately one thousand compounds were developed during the last thirty years, only a few agents are on the market – and today’s ‘newcomers’ are some of those that were withdrawn years ago and are now coming back. Table 13-03 gives an overview of some of the MR contrast agents currently in use, already withdrawn from the market, or being developed.

A detailed and exhaustive description of the state of R&D in the field can be found in a review from 2019.²¹²

---

<table>
<thead>
<tr>
<th>Code Name (or short chemical name)</th>
<th>Generic Name (or short description)</th>
<th>Brand / Trade Name *</th>
<th>Enhancement / Physico-Chemical Properties</th>
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<td>Gd-DOTA</td>
<td>gadoterate (+ numerous generics)</td>
<td>Dotarem</td>
<td>• macrocyclic</td>
</tr>
<tr>
<td>Gd-HP-DO3A</td>
<td>gadoteridol</td>
<td>ProHance</td>
<td>• macrocyclic</td>
</tr>
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<td>gadobutrol</td>
<td>Gadovist</td>
<td>• macrocyclic</td>
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<tr>
<td>Gd-BOPTA</td>
<td>gadobenate</td>
<td>MultiHance</td>
<td>• linear</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>gadopentetate (+ numerous generics)</td>
<td>Magnevist</td>
<td>• linear</td>
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<tr>
<td>Gd-DTPA-BMA</td>
<td>gadodiamide</td>
<td>Omniscan</td>
<td>• linear</td>
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<tr>
<td>Gd-DTPA-BMEA</td>
<td>gadoversetamide</td>
<td>Optimark</td>
<td>• linear</td>
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<tr>
<td>Mn-DPDP</td>
<td>mangafodipir for R&amp;D only</td>
<td>formerly Teslascan</td>
<td>→ liver, pancreas; myocardium, brain</td>
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<tr>
<td>Gd-BOPTA</td>
<td>gadobenate</td>
<td>MultiHance</td>
<td>• linear</td>
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<td>gadoxetate</td>
<td>Primovist</td>
<td>• linear</td>
</tr>
<tr>
<td>AMI-227</td>
<td>ferumoxtran-10 (USPIO)</td>
<td>for R&amp;D only</td>
<td>formerly Sinerem</td>
</tr>
<tr>
<td>**Blood Pool Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS-325</td>
<td>gadofosveset</td>
<td>Vasovist (et al.)</td>
<td>• linear</td>
</tr>
<tr>
<td>**Enteral Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMP</td>
<td>ferristene (MPIO)</td>
<td>Abdoscan</td>
<td></td>
</tr>
</tbody>
</table>

= agent available for clinical and/or research application;  = agent withdrawn from the market;  = agent available for clinical and/or research application with limited indications ("medium risk");  = agent suspended by the European Medicines Agency (10 July 2017).
  = positively enhancing agent;  = negatively enhancing agent;
  = globally charged agent;  = globally neutral agent.
* = trademark or registered trademark; ** = with high concentrations, negative contrast can be achieved (e.g., first-track bolus); *** = all ECF agents are also kidney-specific agents.

Table 13-03: Classification of some magnetic resonance contrast agents being marketed or withdrawn.
Positive and Negative Contrast Agents

The magnetic field produced by an electron is much stronger than that produced by a proton. However, in most substances the electrons are paired, resulting in a weak net magnetic field. As seen in Table 13-01, with its seven unpaired electrons gadolinium is best suited for this purpose, followed by manganese. Paramagnetic contrast agents, with the exception of dysprosium-based compounds, are called positive agents. Their effect on T1 and T2 is similar, but since T1 of tissues is much higher than T2, the predominant effect at low doses is that of T1 shortening. The principle was shown in Figure 04-05.

Thus, tissues taking up such agents will become bright in a T1-weighted sequence.

Negative contrast agents influence signal intensity usually by shortening T2* and T2. This darkens the region of interest (Figure 13-02 and Figure 13-04). Superparamagnetic and ferromagnetic agents belong to the group of negative agents.

Figure 13-02:
Influence of positive (T1) and negative (T2, T2*) MR contrast agents upon signal intensity. Paramagnetic agents are mainly used to shorten T1 relaxation and thus brighten the region of interest, whereas ferro- and superparamagnetic agents shorten T2 and T2* and thus darken the image (red arrows).

Figure 13-03:
Patient with breast cancer and recent neurological symptoms. T1-weighted images. The plain MR images (precontrast: a and c) do not reliably reveal brain lesions. However, the contrast-enhanced MR images (postcontrast: b and d) show a large number of metastases.
Ferromagnetic agents consist of particles which show permanent magnetism. If one reduces their size, they lose their permanent magnetic characteristics and are then called superparamagnetic particles. Depending on their particle size and coating, these compounds can also become T1 agents.

Magnetite, Fe₃O₄, is such a superparamagnetic particle. Coated with an inert resin, magnetites can be used for oral or intravenous applications (cf. iron oxides further below).

Ferro- and superparamagnetic contrast agents produce local magnetic field gradients which disrupt the homogeneity of the local magnetic field. T2 is reduced due to the diffusion of water through these field gradients. However, their principal effect is a reduction in T2*. For this reason, the effects of such contrast agents are best observed using GRE sequences where T2* effects are retained. This kind of effect is referred to as susceptibility effect. It is field strength-dependent, with the effect increasing as the square of the field strength.

![Figure 13-04: Influence of a positive (T1) and negative (T2, T2*) contrast agent upon signal intensity (SI). T1 relaxation is accelerated by positive agents, and the spins recover faster. Therefore, at a given TR, signal intensity (yellow curve) is higher than in the same tissue without contrast agent (red curve). Only a T1-weighted sequence (in this case a spin echo sequence) with short TE highlights this contrast enhancement. With negative contrast agents, T2 relaxation is accelerated; signal intensity is lower (light blue curve; in the "TR" part of the graph this curve overlaps with the red curve and is not visible).](image-url)
Extracellular Fluid Space
Gadolinium-Based Agents

Low molecular weight paramagnetic agents distribute into the intravascular and extracellular fluid (ECF) space of the body. Thus, they are also known as ECF space agents. Among the positive contrast agents, they are the most commonly and, basically, the only ones sold and used (Table 13-03).

They are water-soluble and not tissue-specific. Their majority does not bind to protein. Their effect is caused by the metal ion in their center which contains unpaired electrons, and their relaxation depends on dose and the magnetic field strength. With its seven unpaired electrons and relatively long electron-spin relaxation time, gadolinium possesses the highest ability to alter the relaxation times of adjacent protons.

Figure 13-05:
Some Gd-based contrast agents (GBCA) on the market or withdrawn. Upper row: Most common macrocyclic compounds. Middle and bottom row: Some linear compounds.
Chelates

Because the metals suitable as relaxation agents and their salts are rather toxic, they have to be bound in stable complexes in which they are safely kept until the contrast agent is excreted. Such complexing organic molecules are called chelators, after the Greek word for claw. The bond should be as tight as possible to counteract the lability of the compound and to prevent the release of “free” gadolinium into the human body.\(^\text{213}\)

Bound to such chelators, gadolinium forms low-molecular-weight water-soluble complexes (the final contrast agents) which are commonly excreted through the kidneys. Chelates come as linear (stretched), or cyclic (macrocyclic) molecules (Figure 13-05).


Gd-DTPA and Gd-DOTA are called ionic agents, whereas Gd-DTPA-BMA, Gd-
DTPA-BMEA, Gd-DO3A-butrol, and Gd-HP-DO3A are called nonionic. In this context, the respective terms globally charged and globally neutral are better. The relaxivities of all these agents are similar in water, but can slightly differ in serum and plasma.

Further compounds include gadolinium bound to the chelators BOPTA, EOB-DTPA, and similar ligands that are slightly more lipophilic and excreted both via the kidneys and via the liver. The relaxivities of such agents can be significantly higher because they may bind to protein. They are, however, extremely dependent upon field strength with a high peak around 0.7 T and, in the case of EOB-DTPA, a sharp drop afterwards, losing 30% of its relaxivity at 1.5 T and 60% at 3.0 T.

Figure 13-06 depicts the relaxivity behavior of the ECF-space agents versus field strength.

### Dose

With one exception, the regular clinical formulation of all Gd-based ECF-space agents contains gadolinium at a concentration of 500 mM.

Increasing the dose of the agents above the recommended normal dose (i.e., higher than 0.1 mmol/kg body weight = 0.2 mL/kg body weight) may have both beneficial and unwanted effects (Figures 13-07 and 13-08). Depending on the field strength, it may facilitate the detection of small CNS lesions that have minimal blood-brain barrier breakdown.

The curves in Figure 13-07 correspond to the contrast between glioblastoma and white matter after enhancement. Before enhancement the contrast between glioblastoma and white matter is negative (the tumor is dark; its contrast behavior curve is below ½ dose but is not depicted in Figure 13-07).214 Only the regular (yellow) and double (light blue) doses give rise to sufficient contrast at all fields. Increasing them is counterproductive (8×). Figure 13-08 shows the behavior in a meningioma where the dose increase beyond the recommended dose leads to a complete loss of contrast.

This is because a T2 shortening remains and can take over primary influence upon image contrast. The same holds for cutting the contrast dose, which in most cases is

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counterproductive. Increasing dose, for instance in MR angiography, beyond the recommended dose or repeating contrast-enhanced examinations within a short time period may lead to severe late side effects (nephrogenic systemic fibrosis, NSF; see page 243).

As an exception, gadobutrol (Gadovist, Gadavist) is sold at twice the regular concentration (1M) and applied at half the volume of the other ECF-space agents (0.1 mL/kg body weight for 0.1 mmol/kg body weight) which can lead to confusion.  

**Timing and Imaging Parameters**

**Timing.** The uptake of these agents is relatively fast. Conventional imaging exploits the uptake after 4-5 minutes; often image acquisition already starts after two minutes. Depending on the tissue, the local enhancement peak in the extracellular space is reached 5-30 minutes after injection.

Chapter 16 describes the organ and tissue transit of contrast agents after slow and after bolus injection in more detail.

**Imaging parameters.** Because paramagnetic contrast agents are T1-agents, their effect is most pronounced on T1-weighted MR images, for instance on spin-echo images with short repetition and echo times.

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and gradient-echo images with short repetition times and high flip angle (50°-90°). Intermediately (ρ) weighted images will still show enhancement. The agents lose most of their efficiency on T2-weighted pictures; in many cases, even an isointense behavior can be observed (Figure 13-09).

Imaging protocols should include pre-contrast T1-weighted images to exclude or differentiate high signal intensity pathologies such as hematoma, and T2-weighted images to exclude pathologies such as small edematous white-matter lesions. The acquisition of only pre- and postcontrast T1-weighted images cannot be recommended in brain studies trying to rule out unknown pathology.

The patient of the figure above has a huge meningioma in the left frontal lobe, which is easily visible on the non-enhanced images, mostly because of its mass effect and the bright surrounding edema on T2-weighted images. Yet, this case is a good example of the enhancement pattern of gadolinium contrast agents.

This kind of tumor enhances brightly on T1-weighted images; there is still enhancement on ρ-weighted images. T2-weighted images, however, show the same contrast pattern before and after injection of the agent. If the meningioma or similar enhancing lesions are very small and no indirect signs of lesions can be found, only contrast enhancement will reveal the pathology (see also Figure 13-04 and Figure 13-08).
Tissue Uptake and Indications

The diagnostic development of low molecular weight paramagnetic contrast agents was primarily focused on their use in lesions of the central nervous system (CNS), an indication where plain MR imaging had found its first major field of application.

Stable ECF-space agents do not cross the intact blood-brain barrier (BBB). Thus, in the healthy CNS, clear enhancement is only seen in regions without this barrier, such as the choroid plexus. Normal enhancement in the brain is also seen in the pituitary gland and infundibulum, the cavernous sinus, dura mater, and nasal mucosa. Vessels may also enhance, particularly during the first pass of the contrast agent (Figure 13-10).

Pathological breakdown of the BBB allows paramagnetic contrast agents to cross straight into the extracellular space and to alter T1 relaxation locally. This occurs in a variety of pathologies such as tumors, infections, acute demyelination, etc. The contrast enhancing effect of the contrast agent combined with the ease of demonstrating a lesion in different planes (sagittal, coronal, and transversal) with MR imaging, has proven to be of use in preoperative and preirradiation planning, as well as in follow-up during and after treatment.

Among other applications, Gd compounds have been found to be especially useful for increasing the detection rate of metastases and small tumors, and for improving tumor classification, the latter by allowing the differentiation of vital tumor tissue (well perfused versus impaired or absent blood-brain barrier) from central necrosis and from surrounding edema or macroscopically uninvolved tissue.

Isointense benign tumors like meningiomas and hamartomas are among the major indications for paramagnetic contrast agents.

Acoustic neurinomas, in particular small ones within the internal auditory canal, are clearly enhanced. In malignant tumors, contrast agents can help in delineating tumor
and edema. Absence of enhancement is sometimes of as great a value as its presence, e.g., when distinguishing a low-grade astrocytoma at the cortical surface from a meningioma or small vascular white-matter lesions from metastases. Enhancement might also be seen in infections (e.g., toxoplasmosis and tuberculoma).

A comprehensive coverage of clinical aspects can be found in relevant textbooks.

Figure 13-11 is an example of the ability of an intravenous Gd contrast agent to enhance brain tumors. The application of a contrast agent allows the delineation and definition of tumor extent – with certain limitations, as explained in the figure.

Applications outside the CNS include the musculo-skeletal system, ear-nose-throat diseases, the heart, kidneys and adrenals, gynecological diseases, lym-
phomas, joints, and the breast. For MR breast examinations application of a gadolinium based agent is mandatory.\textsuperscript{216}

One of the approaches to increase specificity was the exploitation of faster imaging techniques. These techniques reduced examination times from several hundred seconds per image to below 100 seconds, later to under 10 seconds (\textit{dynamic imaging}). Details are described in Chapter 16.

\section*{Adverse Events}

\textbf{Acute adverse events and precautions.} Gd-compounds are considered safe with acute adverse events happening in less than 1\% of all patients; the number of side effects is at least one order of magnitude lower than adverse events with x-ray contrast media; this includes nephrogenic systemic fibrosis (see below).

The most common side effects are headache, nausea and vomiting, as well as injection site reactions. In patients with a history of allergies and asthma the application of contrast agents should be carefully considered.

Severe anaphylactoid reactions are rare. Still, proper supervision of the patient after injection and access to an intensive care unit must be guaranteed.\textsuperscript{217}

A precautionary 12-hour suspension of breast-feeding was recommended following the administration of gadolinium-containing contrast agents.\textsuperscript{218}

Both x-ray and MR contrast agents can interfere with a number of blood tests. Such tests should not be performed for 48 hours after a contrast-enhanced x-ray or MR examination.

\textbf{Late adverse events.} In the early days of research and development of these contrast agents, their feared toxicity was associated with the possible competition with endogenous ions such as zinc and calcium. Such an exchange, called transmetalation, frees gadolinium from the chelate into the body. When dissolved in water, all commercially available complexes are very stable; only one molecule over several millions or billions releases its gadolinium.

When in the human body, however, challenged by other ions that want to replace gadolinium, these molecules behave differently. Macroyclic compounds minimize this \textit{in vivo} dissociation process. This was already pointed out in 1988.\textsuperscript{219,220}

\begin{itemize}
  \item \textsuperscript{217} ACR American College of Radiology. ACR Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. Version 10.2. Reston, VA, USA. 2016.
  \item \textsuperscript{218} Hylton NM. Suspension of breast-feeding following gadopentetate dimeglumine administration. Radiology 2000; 216: 325-326.
  \item \textsuperscript{220} Tweedle MF. Work in progress toward nonionic macrocyclic gadolinium (III) complexes. in: as above. 65-73.
\end{itemize}
Macrocyclic compounds are the most stable regardless whether they are charged (Dotarem) or neutral (ProHance and Gadovist; cf. Figure 13-04). For the other contrast agents, the so called open-chain or linear chelates (Omniscan, Magnevist, MultiHance, Vasovist, and Optimark), the situation is different: analytical tests show that their ability to retain their gadolinium ion is weaker.\textsuperscript{221, 222, 223, 224} Among these compounds, the negatively charged Magnevist, MultiHance, Vasovist, and Optimark are more stable than the neutral Omniscan.

Thus, from a chemical point of view, certain agents minimize the risk of late side effects and are to be preferred over others. In general, one must not exceed the recommended dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

High-dose and/or repetitive examinations have led to severe (deadly or mutilating) late side effects (nephrogenic systemic fibrosis, NSF) in patients with severe renal failure and acute kidney injury. This was first described in 1997; the connection to gadolinium contrast agents was made by Grobner in 2006.\textsuperscript{225} An "epidemic outbreak" happened in Denmark shortly later.\textsuperscript{226, 227}

In general, where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan), followed by gadopentetate (Magnevist), and gadoversetamide (Optimark).\textsuperscript{228}

Gadolinium deposits were also found in brain tissue after serial MR examinations in patients without kidney disease.

A major study provided evidence from a large animal model that linear gadolinium-based contrast agents leave traces of gadolinium within the deep cerebellar nuclei, while there was no significant difference of


\textsuperscript{228} Krefting I, US Food and Drug Administration. Gadolinium-based contrast agents (GBCAs) and the NSF risk: update. 21 January 2011.
Magnetic Resonance in Medicine

The Gadolinium Debacle

If physicians apply a drug outside the recommended and approved protocol, they bear the responsibility for the outcome ... or don't they? A comment – on page 257.

Gadolinium concentrations between three marketed macrocyclic agents and the control group.\textsuperscript{229} In general, for contrast-enhanced MRI preference should be given to macrocyclic agents, as well as agents excreted by both the liver and kidneys.\textsuperscript{230, 231, 232}

Risk Categories according to the European Medicines Agency (EMA):

- **High risk:** gadoversetamide (OptiMark), gadodiamide (Omniscan) and gadopentetic acid (for instance, Magnevist, Magnegita, and Gado-MRT-ratiopharm);
- **Medium risk:** gadofosveset (Vasovist), gadoxetic acid (Primovist), and gadobenic acid (MultiHance);
- **Low risk:** gadoteric acid (Dotarem), gadoteridol (ProHance), and gadobutrol (Gadovist).

In July 2017, EMA recommended the suspension of the marketing authorisations of gadodiamide (Omniscan), gadoversetamide (OptiMark), and gadopentetic acid (Magnevist and similar brands), except for a few “emergency” indications.\textsuperscript{233}

The US Food and Drug Administration did not restrict any Gd-containing agents: "To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure ... A review to date has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents."\textsuperscript{234}

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\textsuperscript{233} European Medicines Agency. EMA’s final opinion confirms restrictions on use of linear gadolinium agents in body scans. Recommendations conclude EMA’s scientific review of gadolinium deposition in brain and other tissues. 20 July 2017.

\textsuperscript{234} FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. 19 December 2017.
Targeted and Organ-Specific Contrast Agents

One of the ultimate goals of contrast agent research in MR imaging is the development of agents that actively identify specific tissues or pathologies. In order to target organs and obtain higher disease specificity, iron oxides and liposomes have attracted special interest. To optimize such agents, one has to evaluate three parameters:

- **Improvement of tolerance**, although tolerance of existing compounds is already very good; this includes chemical and biological inertness, as well as complete elimination from the body;
- **improvement of the enhancing effect**; high and ultrahigh fields require a different contrast agents than low and medium/high fields;
- **selective distribution in the body** to reach high local concentrations (organ or pathology specific tracers).

**Liposomes.** Liposomes are one group of particulate agents. Paramagnetic ions can either be encapsulated in the aqueous compartment of the liposomes or be linked to their lipid bilayers. Both manganese and gadolinium chelates attached to liposomes have been studied preclinically. None of these compounds are clinically used.

**Iron-based Contrast Agents**

**Iron chelates.** In the 1980s and 1990s, many avenues were explored in contrast agent research, among them iron chelates analogous to the gadolinium chelates, e.g., Fe-DTPA and Fe-tCDTA. These compounds are positive enhancers that were thought to be usable for indications similar to the gadolinium-based ECF-space agents.

However, the relaxivities of the Fe-chelates were substantially weaker; sufficient enhancement required a major dose increase.

Moreover, toxicological aspects added to the abortion of the development of iron chelates; severe acute side effects were observed, and long-term effects were predicted.\(^\text{235, 236, 237, 238}\)

**Iron oxides.** Iron-oxide particles are incorporated into cells of the reticulo-endothelial system (RES), mainly through phagocytosis. This opens a selective access route to liver, spleen, lymph nodes, and bone marrow. These particles can also be applied for receptor and antibody imaging, as well as perfusion imaging of the heart and brain.

These agents can either be positive (T1) or negative (T2/T2*) enhancers, depending on particle size, composition and concen-

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\(^{235}\) Wesbey GE, Engelstad BL, Brasch RC. Paramagnetic pharmaceuticals for magnetic resonance imaging. Physiological Chemistry and Physics and Medical NMR 1984; 16: 145-155.


\(^{238}\) Tweedle MF. Science to practice: Will gadolinium chelates be replaced by iron chelates in MR imaging? Radiology. 2018; 286: 409-411 [short review].
tration, saturation magnetization of the material, as well as equipment hardware and pulse sequences used.

Their biodistribution is determined by size, shape, charge, hydrophilicity, chemical composition, and surface coating (cf. negative contrast agents | susceptibility effects).²³⁹,²⁴⁰

Three classes of superparamagnetic nanoparticles exist; they depend on their particle size:

- **superparamagnetic iron oxides (SPIO)**, with a size > 50 nm,
- **ultrasmall superparamagnetic iron oxides (USPIO)**, with a size < 50 nm, and
- **micron-size particles of iron oxide (MPIO)**, with a size ~ 1000 nm.

The majority of compounds are polydisperse (more than one size population of iron oxide crystals) and polycrystalline (particle aggregates).

Actively targeted iron oxides preferably contain smaller superparamagnetic labels;²⁴¹ they are monodisperse (only one

Because of severe side effects, among them serious and life-threatening anaphylactic reactions and immune responses, some iron oxide nanoparticles were withdrawn from most markets. Iron can also be deposited in the choroid plexus.

Used intravenously, such particles should possess a (postulated) particle size smaller than 50 nm in diameter so that they are not entrapped during their passage through the lungs.

For some time, ferumoxtran-10 is being clinically re-evaluated. It is claimed to detect early-stage cancer metastases in lymph nodes in patients with progressive prostate cancer.²⁴²,²⁴³

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²³⁹ Corot C, Warlin D. Superparamagnetic iron oxide nanoparticles for MRI: contrast media pharmaceutical company R&D perspective. WIREs Nanomed Nanobiotechnol 2013; 5: 411-422. [review].


Liver Agents

The liver was selected as the primary organ for developing passive targeting compounds: vascular, hepatobiliary, and reticuloendothelial.

Different possible enhancement patterns are depicted in Figure 13-12.\textsuperscript{244}

Aside from the vascular structures, either the hepatocytes or the RES can be targeted. Vascular structures and highly vascularized lesions are commonly highlighted by dynamic examinations with the conventional low molecular weight contrast agents (Figure 13-13). Dynamic imaging is discussed in detail in Chapter 16, manganese liver agents in the section on manganese.

Gd-EOB-DTPA and Gd-BOPTA (Figure 13-14) are two positive gadolinium based agents with lipophilic side groups.

Gd-EOB-DTPA is a targeted liver agent, whereas Gd-BOPTA is a multipurpose contrast agent, well suited for liver imaging.\textsuperscript{245}

Although the chemical composition of Gd-BOPTA appears similar to that of the extracellular gadolinium agents, it combines both extracellular and liver-targeted properties, because some 5% of it is excreted through the liver, as is shown in this case of multiple metastases.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure13_12.png}
\caption{Enhancement patterns of different liver contrast agents (modified from Leander).}
\end{figure}

Ferumoxides, or super-paramagnetic iron oxides, are negative enhancers taken up by the normal liver, which contains reticuloendothelial cells, but not by lesions that lack reticuloendothelial cells (Figure 13-15).\textsuperscript{246}

\textsuperscript{244} Leander P. Liver-specific contrast media for MRI and CT. Experimental studies. Acta Radiol Supplementum 1995; 36: S 396.


Figure 13-13 (top):
Focal nodular hyperplasia (FNH) of the liver. Dynamic enhancement with Gd-DOTA; first highlighting of the arterial vessels, then strong enhancement of the tumor during the early phase of arterial enhancement; followed by the depiction of the veins. Time scale approximately 90 seconds.

Figure 13-14 (center):
Gadolinium-BOPTA in liver metastases of a pancreatic tumor.
(a) plain T1-weighted GRE sequence; (b) plain T2-weighted GRE sequence;
(c) enhanced T1-weighted GRE sequence 40 minutes after injection; (d) T1-weighted GRE sequence 90 minutes after injection.

Figure 13-15 (bottom):
Example of a negative liver contrast agent (ferumoxide). This particulate agent is taken up by endothelial and Kupffer's cells. They darken the liver tissue due to their effective shortening of the T2 relaxation time. T2-weighted GRE: (a) precontrast; (b) postcontrast. The liver metastases are well delineated on the postcontrast image; with this agent, the normal liver tissue becomes black.
Manganese

The odds are that there will be drastic changes in contrast agent use in the near or medium future. It seems as if manganese-based agents could replace gadolinium agents for selected indications.

Manganese was the first element applied to enhance pathologies in MR imaging; its use was described by Lauterbur, Mendonça-Dias and Rudin in 1978. They imaged five dogs with myocardial infarctions after injecting a manganese salt solution and were able to highlight the lesions. Manganese was chosen because it is only moderately toxic and its distribution and elimination had been investigated earlier.

Yet, gadolinium became the element of choice for MR contrast agents because of its high relaxivity and patent issues. However, it is an element foreign to the human body whereas manganese is an endogenous metal and essential trace element.

During the recent years, there is increasing activity in the preclinical research of Mn-based agents. However, the only compound available on the market is Mn-DPDP (mangafodipir), a positive multipurpose agent releasing a limited amount of Mn ions. Oral or intravenous MnCl₂ can have a similar effect, but dosing is difficult.


Figure 13-16:
The uptake of Mn-DPDP (mangafodipir) in the liver relies on the ability of hepatocytes to excrete metal ions. Manganese separates from the DPDP-complex and is taken up by the hepatocytes. T1-weighted GRE images. (a) The metastases are well delineated 15 minutes after the injection, and (b) even 24 hours after administration some of the contrast agent remains. (Images courtesy of Dr. Martí-Bonmatí; Valencia.)
The enhancement is long lasting and can be achieved with such low doses as 5-10 µmol/kg body weight (Figure 13-16). Magnafodipir is considered the preferred agent in patients with kidney problems.

Manganese also has an affinity for the myocardium and can act as biomarker in heart disease. Manganese ions compete with calcium for entry into cardiac cells. There the ions bind to macromolecules and influence the relaxation of cell and tissue water. Heart diseases gradually inactivate calcium transport mechanisms due to lower metabolic activity. Thus, manganese uptake is reduced accordingly; manganese-induced changes of tissue relaxation reflect tissue calcium homeostasis and thus myocardial viability (Figures 13-17a and b).249, 250

In addition to imaging of the liver and the heart, manganese-enhanced MRI with mangafodipir has a wide range of potential applications. Research is focused upon both depiction of brain damage and functional mapping of neural pathways to map brain activation independently and with higher contrast than measurements of hemodynamics in fMRI.251

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251 Koretsky AP, Silva AC. Manganese enhanced magnetic resonance imaging (MEMRI). NMR Biomed 2004; 17: 527–531 [review].
During the development of mangafodipir it was discovered that it and its metabolite manganese pyridoxyl ethyldiamine (Mn-PLED) possess therapeutic properties. Mn-DPDP’s contrast enhancement in MR imaging relies on the release of manganese from the chelate, the therapeutic activity depends on manganese that remains bound to the chelate.\(^{252}\)

**Dysprosium**

Dysprosium possesses a large magnetic moment and a poor T1 relaxivity, despite its relationship with gadolinium and manganese. It can be used as an intravenous negative contrast agent, as was shown with Dy-DTPA-BMA, a paramagnetic bulk susceptibility perfusion agent.\(^{253, 254}\) Dysprosium compounds are not used clinically.

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Further Applications

The bone marrow, lymph nodes, adrenals, muscles, in particular the heart, as well as inflammations and specific tumors have been proposed as additional target regions for some contrast agents. None of these, nor a number of other agents not mentioned here, are available for clinical imaging.

Agents for contrast-enhanced MR angiography (i.e., ECF space and blood pool agents) are discussed in Chapter 14 on pages 279-283.

Enteral Contrast Agents

Abdominal MR imaging suffers from the motion created by respiration, heart beat, peristalsis, and blood flow, as well as a general lack of contrast between feces and fluid filled or collapsed bowel loops, adjacent organs or pathological structures.

Cardiac and respiratory gating, special software, faster imaging sequences, and the use of intravenous contrast agents have solved some of these problems.

Still, a number of substances applied enterically were proposed and studied during the last years in phantom, animal, and clinical trials.

Among them were positive and negative contrast agents.\(^{255, 256}\) Gadolinium-containing compounds belonged to the first group,

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while fluorine-containing compounds and magnetic particles are found in the second group (Figure 13-18).

For studies of the upper abdomen blueberry or pineapple juices are also useable. The application of enteral contrast agents has been limited, and with today’s imaging techniques, in particular custom-tailored pulse sequences, most clinical questions can be answered without the application of oral or rectal agents.

### Ventilation Imaging

Not all exogenous contrast enhancement is performed with proton magnetic resonance imaging. One can also exploit magnetic properties of nuclei different from hydrogen, for instance fluorine. The feasibility of in vivo application of perfluorinated compounds has been demonstrated for lung ventilation and perfusion studies (Figures in Chapter 20).

Gadolinium-based aerosols, hyperpolarized gases, and oxygen were also proposed to be used as possible ventilation agents.

In the case of hyperpolarized gases helium seems better suited than xenon. However, special hardware is necessary: devices for production, storage, and installation of the hyperpolarized gases, as well as special coils and receivers for imaging. This makes ventilation imaging with these gases more difficult than comparable methods. The methods are only applied in a few clinical imaging facilities. An in-depth explanation of the technique is given by Roos et al.

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Molecular Imaging

Definition. Molecular imaging is a catchword and misnomer used as an umbrella term for all biological and medical imaging technologies and methods that aim at picturing anatomy, histology as well as features and processes at the cellular and molecular level.\textsuperscript{260, 261} It is basically an extension of radioisotope tracer scanning and imaging into other fields of medical imaging.

Commonly, molecular imaging is just a synonym of contrast-enhanced imaging. Molecular imaging media are contrast agents of one kind or another (plain contrast enhancers, static tracers, or responsive agents).

Given the increasing understanding of molecular mechanisms of disease and the development of innovative therapies at the genetic level, molecular imaging is aimed at the exploitation of specific molecules as the source of image contrast (Figure 13-19).

However, although MR imaging does not possess sufficient sensitivity to image single molecules, responsive MR agents can dynamically change one or more of their physico-chemical properties when interacting with their intended molecular biomarker.

\textsuperscript{260} James ML, Gambhir SS. A molecular imaging primer: Modalities, imaging agents, and applications. Physiol Rev 2012; 92: 897–965 [review].
\textsuperscript{261} Weissleder R, Nahrendorf M. Advancing biomedical imaging. PNAS 2015; 112, 47: 14424-14428 [review].
For the time being, clinical molecular imaging will stay in the realm of radioisotope scanning and contrast-agent enhanced imaging, sometimes related to hybrid systems such as PET-MRI or PET-CT. A good review of responsive MR agents has been published by Hingorani et coll.  

At the organ level, diagnostic imaging today is able to visualize gross parameters of disease and to describe, e.g., tumor burden. In the future, it will be possible to mark tumors and to target drugs as well as contrast agents. At the genetic level researchers hope to highlight genetic mutations and thus perform gene targeting and therapy.

Researchers will try to leave some of the existing pathways: instead of looking for relatively gross parameters of disease, they will try to explore beyond the tissue level on the cell or even the molecular level. They will try to connect diagnosis with therapy; one of the main goals being the imaging assessment of therapeutic effectiveness at the molecular level, long before phenotypic changes occur.

MRI and Molecular Imaging. Whereas the spatial resolution of MR imaging is very good, its sensitivity is low and thus limiting. Present software and hardware improvements, such as more sophisticated coil design, seem not to be able to bridge the existing gap.

Any increase of field strength beyond today's ultrahigh fields (3 Tesla) to gain crucial signal strength is restricted by the specific absorption rate (SAR) and by side effects of the magnetic fields.

A detour would possibly be the use of hyperpolarization; however, hyperpolarized clinical ventilation imaging was not promising and mostly abandoned for commercial reasons.

MEMRI of the heart is a good example of one of the few promising molecular imaging methods, because the same manganese-based compound can be used for diagnostics and treatment of, e.g., myocardial infarctions, cancer, and drug intoxication (theragnostic properties). It is inexpensive and addresses a mass market.

Intelligent and/or responsive agents might be feasible in magnetic resonance imaging. They could alter their relaxivity according to local temperature, pH, or chemical activity.

Yet, there are a lot of uncertainties in this kind of research, and with the advent of in vitro screening techniques such as easy-to-use blood tests for Alzheimer's disease, molecular imaging will be increasingly challenged.

It will, however, remain one of the major R&D topics in diagnostic and therapeutic imaging and contrast agent research of the coming decades.


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