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# Diagnostic Imaging

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# MR Angiography of the Body

## Technique and Clinical Applications

With Contributions by

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# Foreword

Indirect angiography following intravenous bolus injection of iodinated contrast media entered clinical practice as an alternative less-invasive method to direct (arterial) angiography when digital substraction X-ray techniques became available.

Because of its technical shortcomings, IVDSA was later replaced by CT angiography as another less-invasive modality for vascular imaging. The introduction of multislice CT scanners and rapid progress in electronic image reconstruction allowed CT angiography to become the actually well-known, highly performing, and reliable radiological modality.

MR angiography offers better patient safety than CT angiography because of the absence of ionizing irradiation. As compared with ultrasound vascular imaging, it offers and superior accuracy as well as better contrast resolution.

This book offers a comprehensive overview of the latest technological advances in MR angiography, including up to date image acquisition techniques as well as optimal sequences. Special attention is given to flow-based angiography, optimal and safe use of MR contrast media, rapid and reliable image procession, as well as to the correct interpretation of common artifacts.

The main section of this book is devoted to the current clinical applications of MR angiography in the different body organs and anatomic regions as well as to the important role of this method in the managing of transplant patients. The book is exquisitely illustrated with multiple high-quality demonstrative cases and as always presented in technically impeccable printing and lay out

The editors are internationally well known for their superior and longstanding knowledge in MR angiography and image procession. They are supported by a group of distinguished collaborating authors, who are also experts in the field.

I am very much indebted to the editors and especially to E. Neri for preparing this outstanding volume in a record short time period, which enabled them to include the latest technical advances in this rapidly evolving important radiological method.

It is highly recommended to general and organ specialized radiologists as a most welcome update of their knowledge and as a practical guide in their daily practice. I am convinced that this volume, which nicely completes the list of topics dealt with in our series, will meet appropriate interest and success with our readers.

Leuven, Belgium

Albert L. Baert

# Preface

Magnetic resonance angiography, in short MRA, is a fast growing imaging procedure that fills many sessions of our busy MR suites.

However, at early introduction, when only unenhanced sequences could be acquired by using phase contrast and time-of-flight, MRA was considered just an optional tool that could be used to complement a standard MRI examination.

Nowadays, the technique is a well-established noninvasive angiographic examination, substitutive of conventional diagnostic angiography and of paramount importance in many clinical situations.

The use of contrast-enhanced sequences has improved both contrast and spatial resolution, making MRA a key imaging tool in the study of abdominal aorta and peripheral vessels, where it plays a significant role in the planning of interventional procedures.

Moreover, MRA is increasingly moving toward the study of more complex clinical situations, as in the case of transplantation surgery.

This book was made possible because of the valuable contributions of many outstanding experts in this field, and it covers all the relevant clinical applications of MRA in the study of the whole body. Starting from the basic imaging techniques, it moves to a detailed description of the vascular anatomy and deals with the most appropriate strategies for the diagnosis of vascular pathology.

We hope that this book may help practicing radiologists in making the best use of this exciting methodology, and encourage referring physicians to include MRA in the diagnostic work-up of their patients.

Pisa, Italy

Emanuele Neri
Mirco Cosottini
Davide Caramella

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# Image Acquisition Technique and Sequences

# Flow-Based MRA

1

Angelo Vanzulli

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**ABSTRACT**

MR imaging is particularly suited to depict vessels and this can be obtained using sequences that highlight flow. In the era of nephrogenic sistemic fibrosis these unenhanced sequences are used more frequently than in the past.

These sequences are based on three principles: time of flight, phase contrast, and fresh blood acquisitions. The physical principles of these acquisitions are explained in order to understand the basis of MR angiography.

In the evaluation of vessel lumen, MR sequences can be applied in order to detect flow. These sequences are based mainly on three principles: (a) using the inflow into the slab of fresh spins, which are not subjected to all the radiofrequency pulses, unlike the stationary tissue: time-of-flight phenomenon; (b) detecting the phase changes of moving spins subjected to a gradient: phase contrast; (c) optimizing an ultrafast spin echo or gradient echo sequence, in order to obtain bright signal from blood due to its T2 properties.

In all three techniques, the signal and resulting image are produced by physiological flow, and these methods will be degraded by artifacts in case of complex or turbulent flows [1].

In general, the MR angiography techniques use sequences derived from T1-weighted gradient echo sequences. In fact vessels generally appear as hyposignals in spin echo sequences because of the outflow effect. The spins in the blood are excited during the slice selection pulse. At time TE/2, the flowing spins move out of the slice and are not subjected to the 180° pulse: therefore they do not give any signal in the original voxel (signal void). When the flow is turbulent and not laminar, some spins are back in the

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original voxel at the time of the echo refocusing and give some signal (artifact) [2].

## 1.1 Time of Flight (TOF) MR Angiography

In time-of-flight MR angiography [3], gradient-echo sequences are optimized to favor the vascular signal over that of the surrounding tissues by saturating the stationary tissue signal with very short TR (TR largely inferior to the tissues T1). The longitudinal magnetization of these tissues does not have time to regrow after some 90° pulses and after their signal weakens. The flowing spins coming into the slice volume have not been saturated yet, giving high signal intensity. The strength of the vascular signal is proportional to the flow velocity (faster flow gives higher signal intensity) and depends on the length and orientation of the vessel (the vascular signal will be higher if the slice is perpendicular to the axis of the vessel) due to shorter travel of the spins into the slice volume. In the case of a long vessel tract traveling into the slice, flowing spins will receive many saturating pulses, lowering the signal they can return from them. The shorter the TR and the higher the flip angle, the stronger is the stationary tissues suppression, but slow flowing spins can also be suppressed. A longer TE causes dephasing of the flowing spins, lowering vessel signal intensity. An increased slice thickness also causes a longer travel of the flowing spins into the imaging plane with some degree of vessel signal loss due to the progressive saturation of the spins.

The main limitations of time-of-flight MRA are signal loss linked to spin dephasing when the flow is complex or turbulent (stenosis), when the flow is too slow or oriented parallel to the slice plane and poor signal suppression of the stationary tissues when substances with very short T1 relaxation time are present (fat, blood degradation products) [4]. Vascular contrast can be improved by suppressing the signal coming from static tissues, by means of a magnetization transfer preparation pulse or by selective excitation of water, or by fat saturation [5].

To selectively visualize arterial or venous flow, presaturation bands can be applied upstream to the selected slice (arterial suppression to detect venous flow only) or downstream to the selected slice (venous suppression).

Time of Flight MR angiography can be obtained in 2D or 3D mode.

In 2D acquisition, single thin slices are obtained in sequential order while in 3D acquisition, a thicker slice is excited and many single partitions are reconstructed from this thick slab by different phase encoding steps. The main advantage of the 2D technique is better sensitivity to slow flows (shorter travel of the moving spins into the slice), with the possibility of using higher flip angles (giving better stationary tissue saturation). The main drawback of 2D acquisition is poor through plane spatial resolution due to the thickness of the slices.

Contrary to the 2D TOF and 3D TOF, volumetric imaging gives good spatial resolution in all spatial directions, with a better signal-to-noise ratio, but the flowing spins travel through a thick volume, with progressive signal loss due to in-plane saturation. The slowest flows are more sensitive to this artifact. Flow saturation can be reduced by (a) dividing 3D acquisition into thinner slabs (MOTSA: multiple overlapping thin slab acquisition), (b) by using a variable excitation angle that is lower as the flow enters the volume and higher as it leaves the volume (TONE: tilted optimized nonsaturating excitation), thus compensating relaxation of short T1 tissues.

## 1.2 Phase Contrast (PC) MR Angiography

Phase contrast angiography relies on dephasing the moving spins submitted to a bipolar gradient in gradient echo acquisitions. In the presence of a bipolar gradient of a given intensity and time, the moving spins will dephase in proportion to their velocity while stationary spins will be dephased and rephased by the opposite gradients, returning to their original status. So the flow velocity is proportional to the phase shift and the stationary tissues phase shift is null.

Similar to spatial encoding in the phase direction, the possible phase values range from $-\pi$ to $+\pi$. Beyond this range of values, aliasing occurs, causing wrong velocity encoding [6].

The encoding gradient characteristics are thus defined in order to encode flows within a certain velocity range from −venc to +venc; this range has to be determined by the user before acquiring the data. Any velocity outside this range will be poorly encoded

(similar to what happens in pulsed and color Doppler with pulse repetition frequency-PRF). The bipolar gradients are applied in a particular axis (*x*, *y*, or *z*) and the dephasing of the spins moving along the gradient axis is proportionate to their velocity, gradient intensity and the application time of a gradient lobe. Magnetic field heterogeneities can cause stationary spin dephasing. To compensate for these dephasings, a second acquisition is obtained, reversing the order of the encoding gradient lobes, and subtracting the two acquisitions: the moving spins will cumulate dephasings in the opposite direction, while dephasing of stationary spins due to field heterogeneities will be identical for both acquisitions, disappearing in subtraction.

To depict the movements in all the directions of space, the acquisitions are repeated with flow-encoding gradients in each of the three spatial directions. An additional acquisition with no flow-encoding gradient will serve as a reference.

The images acquired with flow-encoding gradient are summed to depict flow in all directions and subtracted from the reference image without encoding gradient. With this subtraction only vessels are depicted, as well as those that run parallel to the imaging plane.

Phase data allow the measurement of flow velocity and direction [7].

The limitations of this technique relate to intravoxel dephasing in case of complex or turbulent flow with loss of flow signal in the presence of vascular loops, bifurcations, or stenoses.

Phase contrast MRA can be obtained from a thick slab 2D acquisition, allowing synchronization with ECG pulse (cine MR phase contrast angiography) or allowing to test different flow velocities for further 3D longer acquisitions.

To obtain a quantitative evaluation of flows, the slice plane has to be perpendicular to flow direction. Thus a flow velocity curve can be obtained as a function of time, which, when coupled with the area of the vessel section, will permit one to calculate flow rate.

In phase contrast 3D MR angiography, each partition is encoded in three directions, resulting in long acquisition time.

The 3D acquisition gives thinner partitions with better image quality than in 2D single-slice technique.

Because Phase Contrast MR Angiography is more sensitive than time-of-flight to slow flow, its main application is cerebral venous imaging. The scan time of these sequences can be greatly reduced by parallel imaging [8].

## 1.3 T2-Based MR Angiography

These MR angiography techniques are based on two different sequences: a very short TR-TE gradient echo acquisition called balanced fast gradient echo (or truFISP) and a 3D half-fourier fast spin echo sequence prospectively synchronized with ECG pulse.

The first technique (balanced fast gradient echo) relies on an ultrafast gradient echo sequence in which the TR value is exactly equal to 2TE. This causes the production of a stimulated spin echo signal every three gradient echo read-out which gives a particular high signal for fluids and blood (proportional to T2/T1).

This sequence allows the detection of the vessel, but fluids also have the same high signal intensity, preventing one from obtaining MIP images.

The other MRA technique based on T2 relaxation of blood is based on a 3D ultrafast half Fourier spin echo acquisition with prospective ECG synchronization and fat suppression with an inversion pulse (STIR) [9].

The half Fourier spin echo sequence is fast (less than 1 s per slice) and its movements are insensitive. The center of k-space is filled by precocious echo (short effective TE) in which the flow-induced dephasing has not reduced the vascular signal yet. The acquisition plane is parallel to the axes of the vessels. The phase encoding direction is chosen parallel to the axes of the vessels in order to prevent the read-out gradient from weakening the vascular signal.

Prospective ECG synchronization triggers acquisitions at the same moment in the cardiac cycle. The optimal interval between R wave of the ECG and acquisition is determined by a prior calibration sequence and optimized for the vessel of interest. This interval is chosen with different 2D images obtained with different time delays.

A 3D acquisition with a time delay adjusted to obtain signals from slow flowing venous vessels can be used as a reference and be subtracted from the arterial acquisition to depict only arteries.

STIR preparation reduces the signal from the surrounding fat tissues.

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# MR Angiography Contrast Agents

2

Ilaria Pesaresi and Mirco Cosottini

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## ABSTRACT

Gadolinium-based agents are the most widely employed agents for CE-MR angiography. They act as positive paramagnetic substances, thus they increase the vascular signal by strongly reducing the *T1* relaxation time of blood. Several Gd-based agents have been approved for clinical application to date. On the basis of their distribution, Gd-agents are subdivided into extra-cellular fluid (ECF) and blood-pool agents.

Conventional ECF agents have been employed for long time in vascular imaging. Given their brief plasma half-life, they require a careful timing of the MRA acquisition in order to properly sample the contrast bolus first pass.

Blood-pool agent have been recently introduced. They are characterized by high relaxivity constants. Since they persist in the vascular compartment for a quite long time, blood-pool agents allow the steady state acquisition of angiograms with higher spatial resolution.

Contrast agents for magnetic resonance imaging reached clinical validation in 1988 and were initially employed for the visualization of diseased tissues. MR angiography imaging was related to flow-based phenomenon until the introduction of MRA with contrast agents in early 1990s (Creasy et al. 1990).

## 2.1 Magnetic Properties

MR contrast agents are represented by molecules endowed with not-null magnetic properties, which act by affecting the relaxation times of the surrounding water protons.

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The magnetic property of a substance derives from the existence of unpaired electrons within the externals orbitals, a typical characteristic of transitional metal (e.g., iron, manganese) and lanthanide ions (e.g., gadolinium). The number of unpaired electrons influences the magnetic moment of a substance, which reflects the efficiency of that substance to modify the environmental magnetic field (magnetic susceptibility).

Substances with not-null magnetic properties are divided into paramagnetic, ferromagnetic, and superparamagnetic. Paramagnetic substances acquire a net magnetism only when exposed to an external magnetic field. They are made of multiple ions which act as isolated magnetic dipoles without reciprocal magnetic interaction, so that the overall net magnetization is given by the sum of single ion magnetizations.

Ferromagnetic and superparamagnetic materials are characterized by a cooperative interaction among the constituting magnetic elements so that the resulting magnetic field is much higher than the sum of the single dipoles. While superparamagnetic materials acquire a net magnetic field only when submitted to an external magnetic drift, ferromagnetic ones maintain a net magnetism even under neutral external conditions. Iron oxides may exhibit either superparamagnetism (when arranged in small particles) or ferromagnetism (when organized in large crystals).

## 2.2 Relaxivity

All contrast agents shorten both T1 and T2 relaxation times of surrounding protons. This effect on proton relaxation is ruled by the relaxivity constant, which indicates the contrast agent's ability to decrease the T1 (longitudinal relaxivity, r1) and T2 (transversal relaxivity, r2) relaxation times of the water protons per unit (mM) concentration of metal ion.

The relaxation effect differs for paramagnetic, superparamagnetic, and ferromagnetic contrast agents.

### 2.2.1 Paramagnetic Contrast Agents

The relaxation effect of paramagnetic substances in solution is mainly realized through dipolar interactions between the paramagnetic ions and the hydrogen molecules of water belonging to the so-called inner sphere. Indeed, paramagnetic contrasts can be modelled as isolated ions surrounded by an inner and an outer sphere of interacting water molecules. While the energetic transfer between the metal ion and inner sphere water molecules is explained by dipolar interactions, the relaxation effect on outer-sphere molecules is explained by the Curie-spin relaxation theory (Gueron 1975; Muller et al. 2001; Caravan and Randall 2006).

The relaxation efficiency (i.e., relaxivity) of paramagnetic materials is governed by many factors such as the magnetic moment of the ion, the number of water molecules within the inner-sphere and the rate of exchange among the inner sphere and the bulk solvent. Moreover, the local magnetic field generated by the ion must fluctuate at a rate ($\omega_i$) close to the hydrogen Larmor frequence ($\omega_H$) in order to stimulate hydrogen relaxation.

As free metal and lanthanide ions are embedded into chelates to avoid in vivo toxicity, contrast agent relaxivity is influenced by both paramagnetic ion and molecular ligands properties.

In particular, ligands influence the number of water molecules within the inner sphere and the fluctuation rate of the ionic magnetic field $\omega_i$.

Paramagnetic agents modify proton relaxation according to the following equations:

$$1/T1 = 1/T1_0 + r1 \times C \quad (2.1)$$

$$1/T2 = 1/T2_0 + r2 \times C \quad (2.2)$$

where T1 and T2 identify the final relaxation times in the presence of the contrast agent, $T1_0$ e $T2_0$ the initial relaxation times, *C* the molar concentration of the contrast agent, r1 and r2 the longitudinal and transversal relaxivity respectively of the contrast agent.

For all medically used paramagnetic contrast agents r2 is higher than r1. However, as $1/T1_0$ is lower than $1/T2_0$, a dominant effect on T1 relaxation is observed.

### 2.2.2 Superparamagnetic and Ferromagnetic Contrast Agents

The relaxation effect of superparamagnetic and ferromagnetic agents is not based on direct dipolar interactions. These agents are constituted by particles of variable dimension which form a stable suspension. As no water molecules are admitted within the particles, direct interactions between ions and water molecules are prevented. The relaxation effect is exerted on water molecules diffusing near the particles (the outer

sphere) through the Curie-spin relaxation (Muller et al. 2001; Gueron 1975).

Most superparamagnetic and ferromagnetic agents are made of iron oxide crystals enveloped by a dextran or siloxan coating which prevents agglomeration. Each crystal is made of several thousands of magnetic ions which interact cooperatively so that the magnetic moment of the entire crystal tends to align with the external magnetic field.

Ultrasmall particles of iron oxides (USPIOs) contain a single iron oxides crystal within the particle core and show a superparamagnetic behavior. Small particles of iron oxide (SPIOs) contain multiple iron oxide crystals within the particle core and behave as ferromagnetic agents.

Relaxivity constants are strictly influenced by the particles core dimension. In particular, r2/r1 ratio increases with increasing particle size; thus smaller particles are much better T1-shortening agents than larger ones (Roch et al. 1999).

USPIOs show high r1 and r2 values, so they can be employed to either increase signal intensity on T1-weighted images or decrease signal on T2-weighted images.

SPIOs are characterized by the highest r2 constant, and then they cause a dramatic signal drop on T2-weighted images.

To sum up, paramagnetic substances are classified as *T1 agents* or *positive agents* because they relevantly increase signal intensity on T1-weighted images. Ferromagnetic agents (SPIOs) are classified as *T2 agents* or *negative agents* as they cause a signal drop on T2-weighted images. Superparamagnetic agents (USPIOs) can be classified as T1 or T2 agents as they can either increase signal intensity on T1-weighted images or decrease signal on T2-weighted images.

## 2.3 Susceptibility Effect

Even if contrast agents are generally exploited for their effect on proton relaxation, they can also exert a relevant susceptibility effect (*T2* agents*).

All contrast agents locally increase the static magnetic field (effective magnetic field). If field inhomogeneities reach a sufficient strength, they can significantly affect signal intensity by broadening the Larmor frequency and fastening the protons dephasing within a voxel. This effect is most evident with long TE (on T2-weighetd images) as intravoxel dephasing and diffusion of water molecules through regions of variable magnetic field become more evident (Caravan and Randall 2006).

The existence of strong field inhomogeneities subsequent to contrast agent administration can be due to crystals aggregation, as observed with SPIOs, or due to compartmentalization.

Ferromagnetic, superparamagnetic, and paramagnetic agents can all undergo compartmentalization in tissues or vessels and manifest a medically relevant susceptibility effect.

## 2.4 Contrast Agents for Vascular Imaging

Vascular MR contrast agents for clinical application are mainly represented by positive paramagnetic agents. Few studies have dealt with superparamagnetic iron oxides for vascular imaging, however, to date these agents have generally been restricted to the investigation of the reticulo-endothelial-system (RES).

### 2.4.1 Paramagnetic Gadolinium Agents

Most contrast agents approved for human applications are gadolinium-based. Gadolinium is a lanthanide ion endowed with a high magnetic moment and a proper magnetic field fluctuation rate which result in a high relaxivity constant. Given its high toxicity, gadolinium needs to be embedded into chelates to be administered in vivo. Different gadolinium chelates show different relaxation properties and different biodistribution and must be subdivided into extracellular fluid (ECF) and blood-pool agents.

#### 2.4.1.1 Extracellular Fluid Agents

ECF agents represent the first generation of clinically approved gadolinium contrast-agents and their role in contrast-enhanced magnetic resonance imaging is well established. They are characterized by a brief vascular phase, then they rapidly equilibrate in the extracellular space (distribution half-life of about 5 min) reaching roughly the same concentration in the vascular and interstitial compartments.

Given their brief vascular phase, the adoption of ECF agents for MR angiography implies a careful

timing and a fast imaging in order to capture the contrast bolus first pass in the arterial district.

The clearance of ECF agents is mainly mediated by the renal system, with an elimination half-life of about 80 min.

All gadolinium ECF agents are characterized by an eight-coordinate ligand binding to gadolinium (III) to prevent the release of ions in solution. Gadolinium ligands are represented by small molecules (polyaminocarboxylate/phosphonate derivatives) which differ in their electrical charge, either neutral or negative, and in their chemical structure, either cyclic or linear (Table 2.1 and Fig. 2.1).

Neutral chelates allow lower osmolarity in solution with respect to the ionic ones and can be formulated at high-concentration.

Linear chelates have been reported to present a slightly lower thermodynamic stability with respect to cyclic complexes and they might theoretically facilitate the release of gadolinium ions because of biochemical competitions for the binding site (Wiginton et al. 2008). However, no evidence of relevant effects in vivo has been reported.

Despite different chemical structures, ECF agents are characterized by almost the same relaxation properties, biodistribution, and plasma half-life.

ECF agents are employed in contrast-enhanced MRA for bright blood imaging. Their effect on T1 relaxation is ruled by (2.1) and thereafter, it linearly depends on the concentration of contrast agents. While performing CEMRA examination, the concentration of contrast media within the vessel depends

**Table 2.1.** Gadolinium-based extracellular fluid contrast agents approved for marketing

| Type | Generic name | Trade name | Chemical abbreviation | Chemical structure | R1 (0.5 T, 37°C) (1/mM/s) | R2 (0.5 T, 37°C) (1/mM/s) | Osmolarity[a] (Osm/Kg) |
|---|---|---|---|---|---|---|---|
| Ionic | Gadopentate dimeglumine | Magnevist (Bayer Schering) | Gd-DTPA | Linear | 3.8 | 3.8[b] | 1.96 |
| | Gadoterate meglumine | Dotarem (Guerbet) | Gd-DOTA | Cyclic | 3.6 | 4.8 | 1.35 |
| Neutral | Gadodiamide | Omniscan (GE Healthcare) | Gd-DTPA-BMA | Linear | 3.9 | 4.3[b] | 0.79 – (1.90) |
| | Gadoteridol | Prohance (Bracco) | Gd-HP-DO3A | Cyclic | 3.7 | 4.8[b] | 0.63 – (1.91) |
| | Gadobutrol | Gadovist (Bayer Schering) | Gd-BT-DO3A | Cyclic | 3.6 | | 0.57 – (1.39) |
| | Gadoversetamide | OptiMARK (Mallinckrodt) | Gd-DTPA-BMEA | Linear | 4.7 | | 1.11 |

[a]Osmolarity values at 0.5 M concentration, except those in parentheses (1 M concentration)
[b]Relaxivity at 0.5 T

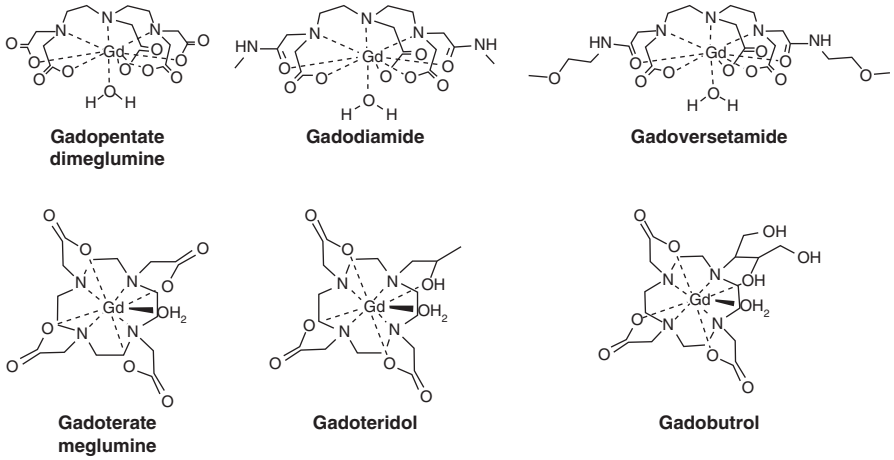


**Fig. 2.1.** Chemical structure of gadolinium-based extracellular fluid (ECF) agents

not only on contrast media formulation but also on physiological parameters as well as the injection rate and the contrast amount, as detailed in Chap. 7.

Contrast agents formulated at high concentration potentially allow higher relaxation effects. However, they modify the bolus geometry by reducing the bolus length and are thus particularly suited for fast angiographic imaging.

### 2.4.1.2 Blood-Pool Agents

While ECF agents rapidly leak out from the vascular compartment, the blood-pool agents (BPAs) are confined within vessels for a quite long time.

In order to keep gadolinium contrast complexes within the vascular compartment, two main approaches have been adopted. The first approach consists in increasing the size of gadolinium ligands (large-size BPAs) and the second one in utilizing small gadolinium ligands reversibly bound to plasma proteins (small-size BPAs).

Large-size BPAs were initially obtained through covalent binding of gadolinium to macromolecules such as polylysine, dextran, or modified bovine serum albumin. These compounds showed a negligible leakage in the extravascular compartment and provided optimal vascular imaging. Moreover, they were associated with very high gadolinium relaxivity because large-size ligands lessen the gadolinium magnetic field fluctuation rate and favor energetic exchange between the protons and gadolinium. Despite such promising features, large-size BPAs did not achieve clinical approval as they were limited by a very-slow blood clearance and by potentially dangerous immunologic effects.

To overcome these problems, a second generation of large-size BPAs has been developed. This new class of BPAs agents (Table 2.2 and Fig. 2.2) is made of gadolinium complexes large enough to persist within vessels for long time but small enough to be excreted

**Table 2.2** Gadolinium-based blood pool agents approved for marketing or under clinical investigation

| Type | Generic name | Trade name | Chemical abbreviation | Affinity for albumin | Bound-fraction (%) | R1 (0.5 T/37°C) (1/mM/s) | R2 (0.5 T/37°C) (1/mM/s) |
|---|---|---|---|---|---|---|---|
| Large-size BPAs | Gadomer 17,24 | Gadomer-17 (Bayer Schering) | Gd-DTPA-17 cascade polymer | – | – | 11.9[a] | 16.5[a] |
| | Gadomelitol | Vistarem (Guerbet) | P792 | – | – | 45 | 50 |
| Small-size BPAs | Gadobenate | Multihance (Bracco) | Gd-BOPTA | Weak | 10 | Buffer: 4.4 Plasma: 9.7 | 5.6 |
| | Gadofosveset trisodium | Vasovist[b] (Bayer Schering) | MS-325 | Strong | 91 | Buffer: 6.6 Plasma: 50 | |
| | Gadocoletic acid | B22956 (Bracco) | B22956 | Strong | 95 | Buffer: 39 Plasma: 44.5 | |

[a]Relaxivity at 1 T
[b]Approved for marketing in Europe and USA

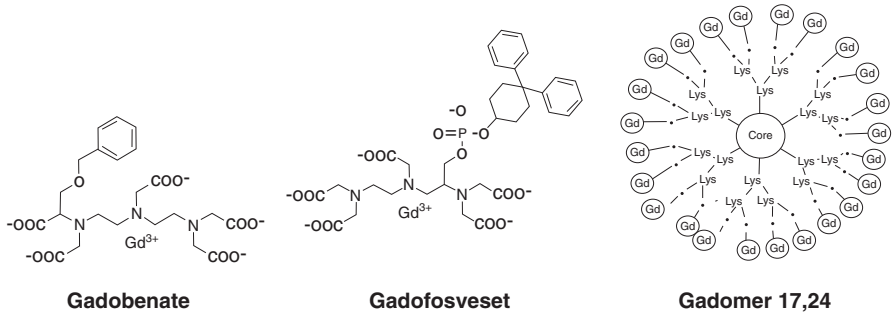


**Fig. 2.2.** Chemical structure of some gadolinium-based blood-pool agents

through glomerular filtration. They are still characterized by high relaxivity. An example is represented by Gd-DTPA-17 cascade polymer (*Gadomer-17*, Bayer Schering), a macromolecular complex with a dentritic architecture which includes multiple gadolinium ions. *Gadomer-17* does not show significant affinity for plasma proteins and undergoes renal clearance.

Biodegradable macromolecular complexes which decompose through disulfide-thiol exchange, facilitating the excretion of gadolinium chelates, are currently under development (Lu et al. 2004).

Small-size BPAs (Table 2.2) are designed to reversibly bind to plasma proteins, in particular to albumin which represents the protein with the highest concentration in plasma (about 0.67 mM). The not-covalent binding to albumin is mediated by hydrophobic moieties attached to the chelating agents.

This class of contrast agents can be further subdivided on the basis of the level of affinity for plasma proteins. Low-affinity BPAs (e.g., Gd-BOPTA, *Multihance*) are characterized by bound-fractions of about 10% while high-affinity BPAs (e.g., Gadofosveset trisodium, *Vasovist* or B22956) reach bound-fractions of 90–95%.

Similar to large-size BPAs, small-size BPAs have r1 relaxivity that is much higher than ECF agents, because of the lower fluctuation rate of gadolinium magnetic field secondary to the albumin binding.

It should be noted that neither large nor small-size BPAs can be considered pure blood-pool compounds, as they show a minimal diffusion into the interstitial space (Bremerich et al. 2007).

Contrast enhanced MR angiography may take advantage from BPAs. Given the extended imaging window (concentration of BPAs in plasma remains stable for over 1 h), BPAs minimize the problem of sequence temporization and temporal resolution. Furthermore, they potentially allow higher spatial resolution with acquisitions at the steady-state (Fig. 2.3)

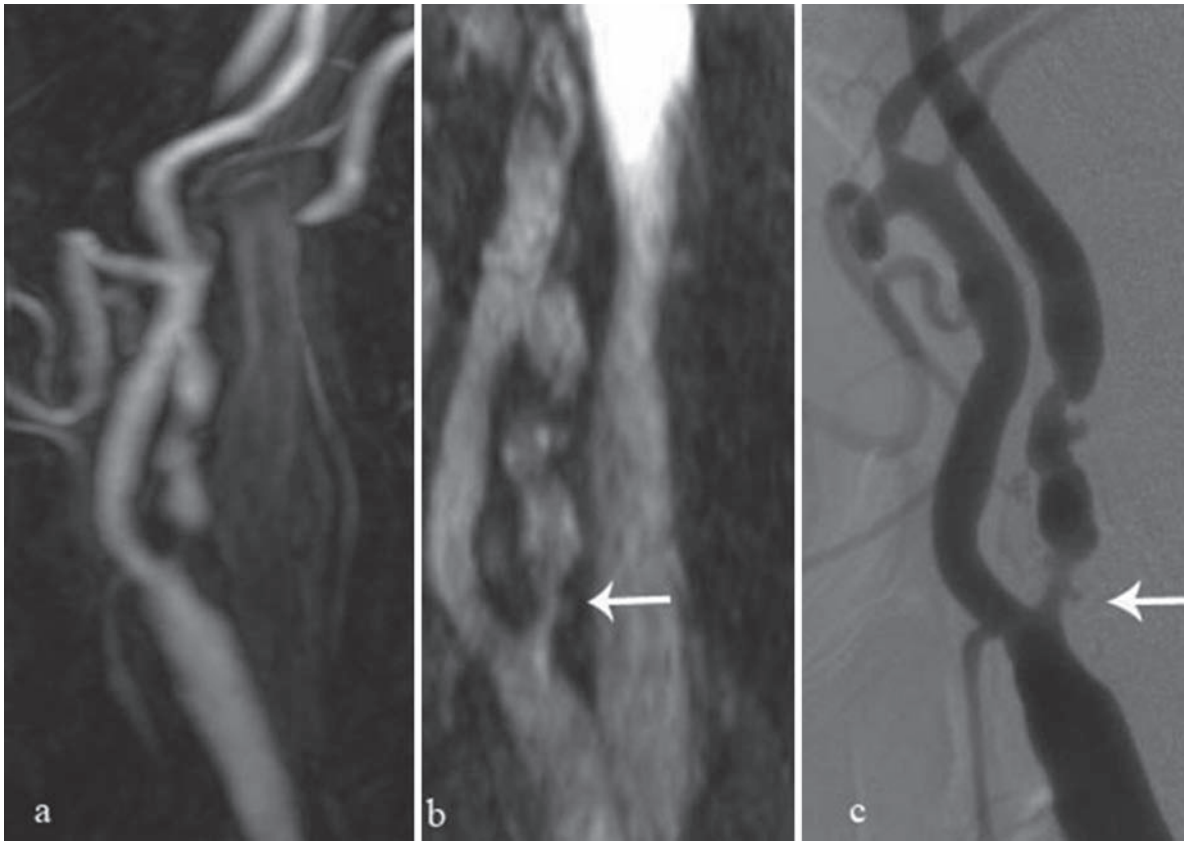


**Fig. 2.3.** Contrast-enhanced MR angiography with a gadolinium blood-pool agent (Gadofosveset trisodium, Vasovist, Bayer Schering). First pass contrast-enhanced angiograms (**a**) correctly classify the patient as having severe stenosis (>70%). Nevertheless, the stenosis is overestimated with respect to the gold standard DSA (**c**) and the residual patent lumen is poorly defined. The high spatial resolution MRA at steady state (**b**) increases the vessels' sharpness and allows a more clear depiction of the stenosis morphology (ulcerated plaque)