Diagnostic Imaging

MR Angiography of the Body

Technique and Clinical Applications

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Emanuele Neri, Mirco Cosottini, Davide Caramella

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MR Angiography Contrast Agents

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Ilaria Pesaresi and Mirco Cosottini

CONTENTS

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.

Ilaria Pesaresi, MD
Diagnostic and Interventional Radiology, Department of Oncology, Transplants, and Advanced Technologies in Medicine, University of Pisa, Via Roma 67, 56100 Pisa, Italy
Mirco Cosottini, MD
Unit of Neuroradiology, Department of Neurosciences, University of Pisa, Via Roma 67, 56100 Pisa, Italy

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 (ω_i) close to the hydrogen Larmor frequence (ω_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 ω_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

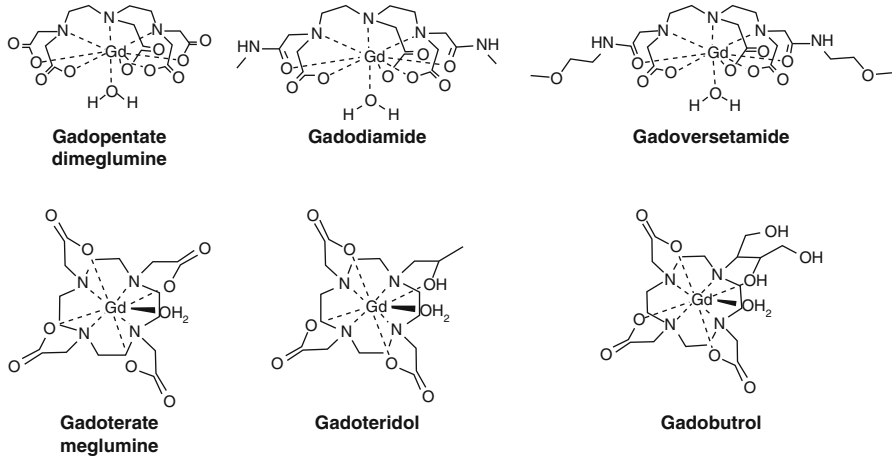

Fig. 2.1. Chemical structure of gadolinium-based extracellular fluid (ECF) agents

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

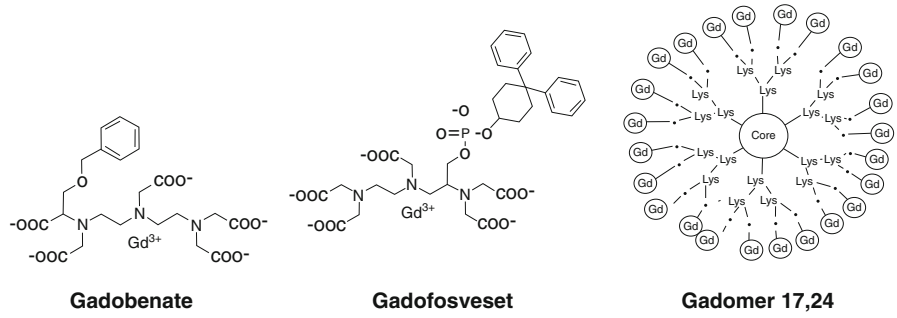

Fig. 2.2. Chemical structure of some gadolinium-based blood-pool agents

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)

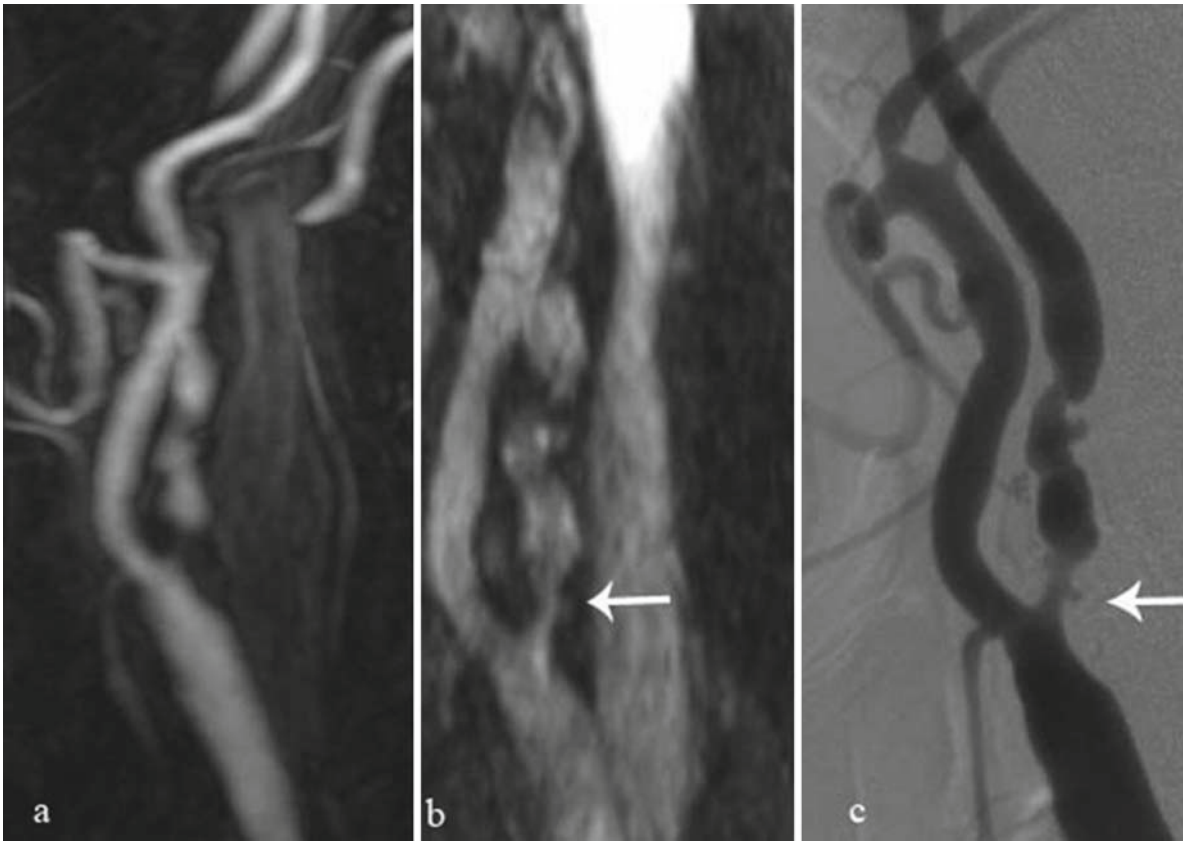

Fig. 2.3. Contrast-enhanced MR angiography with a gadolinium blood-pool agent (Gadofosveset trisodium, Vasovist, Bayer Schering). First pass contrast-enhanced angiograms (**a**) correctly classify the patient as having severe stenosis (>70%). Nevertheless, the stenosis is overestimated with respect to 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)

and extend the investigation from the arterial to the venous district. All gadolinium-based BPAs, due to their high r1 relaxivities, provide potentially higher vessel-to-background signal ratio than ECF agents allowing the utilization of lower concentrations and doses. Nevertheless, the effective signal gain on first pass magnetic resonance angiograms with BPAs, with respect to ECF agents, is controversial. Indeed, according to both literature (Klessen et al. 2007) and personal data (Fig. 2.4), BPAs may show a reduced vessels-to-background relative contrast. This finding could be explained by the nonlinear relationship between the T1 relaxation effect and the concentration of small-size BPAs. Indeed, the relaxivity of small-size BPAs is strongly influenced by the albumin-bound fraction. The reversible reaction between contrast complexes and albumin reaches equilibrium after a time interval, which depends on the reciprocal affinity constant. During the contrast agent's first pass in the arterial district, the equilibrium between bound and unbound fractions may not be achieved yet. Therefore, the first pass contrast relaxivity may be lower with respect to the steady-state one (Caravan and Randall 2006).

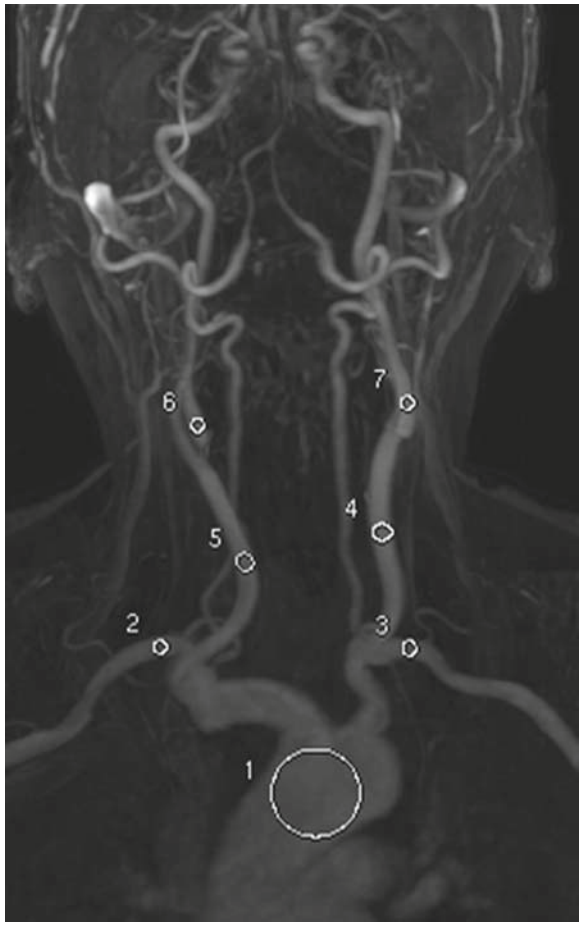

Fig. 2.4. Vessels-to-background relative contrast on first pass CEMRA with gadolinium blood-pool and ECF agents. The signal enhancement of a blood-pool agent (Gadofosveset trisodium, Vasovist, Bayer Schering) is compared with that of ECF agents on first-pass MRA. Vessels' signal is measured by placing regions of interest in the aortic arch, in the subclavian and in the carotid arteries. The relative vessels-to-background contrast (RC) is calculated by the ratio (SV − SF)/(SV + SF), where SV is the signal into the vessels and SF the signal of the background. Gadofosveset shows a significantly lower signal enhancement in two regions

To date the only gadolinium blood-pool agent approved for marketing is Gadofosveset trisodium (*Vasovist,* Schering).

2.4.2 Superparamagnetic Ultrasmall Iron Oxide Particles

USPIOs (Table 2.3) represent true BPAs, as they are too large to leak out from vessels. While SPIOs (Table 2.3) are rapidly removed from the blood stream by endocytosis in liver, spleen, or lymp nodes through the reticulo-endothelial system (vascular half-life of about 10 min), USPIOs persist within vessels for quite a long time so that they can be exploited to obtain high-resolution steady-state angiograms. Subsequent to RES clearance, iron oxide agents are incorporated in the body iron pool.

To date, SH U555 C (*Supravist*, Bayer Schering) is the only USPIO agent which has completed the clinical trials, even though it has not achieved FDA approval. It is a derivative of ferucarbutran with smaller dimensions with respect to *Resovist,* Bayer Schering (particle diameter of about 20 nm vs. 50 nm).

While SPIO agents and some USPIOs (e.g., Sinerem, Guerbet) can be administered only by slow intravenous infusion, SH U555 C admits bolus injection, so it can be employed for both first pass and high-resolution steady state angiography (up to 42 min postinjection) (Bremerich et al. 2007).

Given their superparamagnetic properties, USPIOs can be adopted as T1 agents to perform bright blood contrast-enhanced angiography. To avoid signal loss due to rapid intravoxel dephasing (high r2 values and susceptibility effect), angiographic sequences with very low echo times are required (Bremerich et al. 2007).

Table 2.3. Iron oxides-based contrast agents approved for marketing or under clinical investigation

Particle type	Generic name	Trade name	Chemical abbreviation	Crystals diameter (nm)	Particle diameter (nm)	R1 (0.5 T, 37°C) (1/mM/s)	R2 (0.5 T, 37°C) (1/mM/s)
USPIOs	Ferumoxtran	Sinerem[a] (Guerbet) Combidex (AMAG Pharmaceuticals)	AMI-227	4.3–4.9	50	22.7	53.1
	Feruglose	Clariscan (GE Healthcare)	NC 100150	4–7	20	21.8	35.3
	Ferucarbotran	Supravist (Bayer Schering)	SH U555 C	3–5	20	22	45
SPIOs	Ferumoxide	Endorem[b] (Guerbet) Feridex[b] (AMAG Pharmaceuticals)	AMI-25	4.3–4.8	200	24	107
	Ferucarbotran	Resovist[b] (Bayer Schering)	SH U555 A	4.2	62	20	190

[a]Withdrawn from market
[b]Approved for marketing in Europe and/or USA

2.5 Safety

ECF gadolinium agents have been widely employed in clinical setting and their safety profiles have been deeply investigated. For example, Gd-DTPA (*Magnevist*) has been used in more than 45 million magnetic resonance imaging procedures since 1988 and is currently used globally in more than 5 million applications annually. The broadest category of spontaneously reported adverse events, that is subjective symptoms, occurs in less than 0.01% of procedures. Within the total number of adverse events reported, the distribution of serious and non-serious reports was 9.3 and 90.7% respectively (Knopp et al. 2006).

With regard to blood-pool gadolinium agents, in particular Gadofosveset trisodium (Vasovist), phase II and phase III clinical trials report a safety profile comparable to that of conventional ECF gadolinium agents (Shamshi et al. 2006).

As gadolinium agents require very low doses to ensure adequate contrast enhancement compared to iodinate contrast agents, for many years they were considered safe compounds to be used in patients with renal function deficiency. In the last years, an increasing alert on gadolinium-related nephrogenic systemic fibrosis (NFS) has arisen.

NFS is a sclerosing disorder clinically characterized by indurated dermal plaques, mainly distributed in the lower extremities, and by fibrosis in other tissues such as striated muscles, myocardium, lungs, and dura mater (Wiginton et al. 2008).

The first case of NSF was reported by Cowper et al. in 2000. The association between NSF and gadolinium contrast agents relies on the identification of gadolinium deposits in skin biopsies (Wiginton et al. 2008). Up to now, the number of reported cases in the USA (about 130) is extremely small when compared with the millions of patients who have been exposed to gadolinium-based agents, which makes the overall risk of developing NSF very low (Geraldes and Laurent 2009). NFS has been exclusively identified in patients with severely impaired renal function. In these patients, the longer half-life of the contrast agents potentially increases the risk of trans-metallation with the release of free gadolinium ions in tissues (Bongartz 2007).

Although there is currently evidence of a strong association between gadolinium exposure and the development of NSF in patients with severe renal failure, the causative role of gadolinium in the pathogenesis of the disease can not be stated with absolute certainty (Kurtkoty et al. 2008).

On 23 May 2007 the U.S Food and Drug Administration has asked manufacturers to include a new boxed warning on all gadolinium-based contrast agents, stating that patients with severe kidney insufficiency are at risk of developing NSF. FDA has assessed that all gadolinium-based contrast agents marketed in the United States should be equally treated in this regard as it is not possible to know the extent of risk associated with each agent (Kanal et al. 2008).

Given the great concern on gadolinium-related NSF in patients with renal function impairment, an increasing interest has been addressed to iron oxide

agents. Indeed, USPIOs clearance is mediated by the reticulo-endothelial system and their safety profile is not altered in patients with kidney insufficiency (Neuwelt et al. 2009).

2.6 Future Perspectives

2.6.1 Contrast Agent Use at High Field

Even though most contrast-enhanced MR angiography studies are currently performed with clinical 1.5 T scanners, higher magnetic fields (from 3 up to 7 T) are getting more and more widespread. By increasing the external static magnetic field (B_0) both the relaxation properties of hydrogen protons and of contrast agents get modified.

Indeed, as B_0 increases, water protons lessen their longitudinal relaxation and fasten their transversal relaxation. The dependence of contrast agent relaxivity from B_0 strength varies on the basis of the magnetic and chemical properties of the compounds.

Gadolinium ECF compounds manifest a minimal relaxivity field-dependence, while blood-pool gadolinium agents show relevant r1 variations at different B_0. Such discrepancy between ECF and BPAs agents is mainly determined by the different fluctuation rates of gadolinium magnetic field (ω_g). Indeed, BPAs ligands (both large-size and small-size ligands) slow down molecule tumbling and reduce ω_g. This effect may strongly enhance r1 with a variable effectiveness depending on the external magnetic field B_0.

Iron oxide agents dramatically increase their transversal relaxivity (r2) together with their susceptibility effect at higher magnetic fields. As a consequence, a confounding $T2^*$ shortening may affect the signal intensity on bright-blood angiograms so that the signal-to-noise ratio from blood is similar at 1.5 and 3 T (Bremerich et al. 2007).

2.6.2 Other Contrast Agents

A huge variety of new contrast agents are currently under development. In some cases they represent a further evolution of traditional paramagnetic and superparamagnetic agents, while in other cases they exploit completely different principles.

2.6.2.1 Gadolinium-Based Particulate Agents

Gadolinium (III) can be employed in numerous particulate contrast agents in order to improve their relaxation efficiency (Geraldes and Laurent 2009). For example, Gd^{3+} ions can be bound to amphiphylic chelates in micelles or liposomes, or to porous materials like zeolites. Gadolinium oxide nanoparticles can also be formed. Although promising, none of these agents has passed the preclinical status to date.

2.6.2.2 Hyperpolarized Contrast Agents

The signal intensity on magnetic resonance imaging is related to the number of protons which align to the external magnetic field. At 1.5 T approximately 0.0006% of protons are polarized.

In order to increase signal intensity, contrast agents made of hyperpolarized nuclei have been designed. Hyperpolarization is obtained by using a high-power laser on noble gases (^{3}He, ^{129}Xe) or ^{13}C-enriched molecules. In order to be exploited as contrast agents, these compounds require T1 relaxation times long enough to allow imaging before the recovery of the equilibrium status. ^{13}C-labeled water-soluble compounds have been employed for contrast-enhanced magnetic resonance angiograms in rats (Caravan and Randall 2006).

2.6.2.3 Chemical Exchange Saturation Transfer (CEST)

Chemical exchange saturation transfer (CEST) agents contain exchangeable hydrogen atoms (-NH, -OH, etc) which resonate at a Larmor frequency different from that of the bulk water. CEST protons can be saturated by an off-set RF pulse and can transfer their magnetization to water molecules. This effect results in water signal loss and negative image contrast. By utilizing proper pulse sequences a positive-contrast effect can also be obtained (Caravan and Randall 2006; Geraldes and Laurent 2009). CEST agents currently require a very high dose to obtain a relevant effect on signal intensity, so further development is needed for in vivo applications.

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