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Introduction

While X-ray contrast agents lead to an attenuation of the transmitted x-rays; MR agents use a completely different biophysical effect by exhibiting their properties in locally changing the relaxivity. We classify today's available agents into paramagnetic (mostly gadolinium-based) and superparamagnetic (mostly iron oxide-based)[1]. We also experience a substantial variability in country specific availability of MR contrast agents for MR imaging as well as regulatory approvals which is especially evident for cardiovascular imaging. MR contrast agents are clinically developed similar to any therapeutic medication. After completion of preclinical evaluations and extensive toxicology, contrast agents undergo a typical Phase I (feasibility), Phase II (dose-ranging) and multiple Phase (III) (efficacy and safety) assessments prior to submission for regulatory approval to market and distribute a contrast agent. The regulatory approval by an agency such as the FDA in the U.S. defines the *indicated use* frequently also referred to as the *labeled use* as well as how to use it appropriately, any warnings and contraindications[3]. For healthcare providers, the package insert and the prescribing information is the locally appropriate and always updated contrast agent specific information source.

Safety of MR Contrast Agents

While any contrast agent that received marketing approval needed to previously prove safety and identify use and warnings labels, MR imaging had its share of specific issues in the recent past that are highlighted to raise proper awareness and understanding in managing patients.

The non-imaging community was warned in a 2003 letter to the editor (NEJM) that severe pseudohypocalcemia was observed after gadolinium-enhanced MRA[7]. The authors noted lower calcium values in blood samples obtained in patients immediately after they had an MRA performed with gadodiamide as MR contrast agent. The interaction of excess chelate in the gadodiamide with colorimetric calcium tests was recognized by experts but was neither included in the product label nor commonly known and caused multiple issues especially in patients receiving MRA[8,9]. A subsequent letter and editorial educated that these drug – laboratory test interactions are not specific to MRA, but to two contrast agent formulations, gadiodiamide and gadoversetamide that interact to lead to false lower calcium levels in colormetric but not in ionic calcium tests[10]. These observations and subsequent public discussion can be credited with increasing awareness about MR contrast agent safety which was perceived as entirely safe with considerable complacency evolving.

One of the most essential safety aspects of a contrast agent is that it needs to be completely eliminated after injection into the patient. Most MR imaging agents including gadolinium chelates are eliminated via renal clearance, iron oxides with the liver and RES. It is important to understand the specific characteristics and elimination pathway of an agent as well as what happens if elimination is impaired. Therefore, it should not be a surprise that a drug that depends on renal elimination has the potential to change its biologic behavior if the pathway is impaired, consequently making agents with multiple or other elimination pathways highly desirable for patient populations with renal impairment. Contrast agents should always be given at the lowest effective dose to enable diagnostic appropriate visualization of the target organ system. From a safety perspective, the rapid elimination from the body, no or limited drug-drug interactions and no or limited toxicity are the key desirable safety aspects of a contrast agent.

Pharmacovigilance of MR Contrast Agents

Pharmacovigilance is the analysis of observed adverse events of an available drug, here MR contrast agent, and is the methodology employed to monitor the safety once a drug is broadly available. Outside of post-marketing, Phase IV studies, the information source is solely based

on adverse event reporting. A healthcare provider is encouraged and sometimes mandated by country specific laws to report any adverse event observed during the clinical use of medications/drugs either directly to the vendor or to a regulatory body sponsored website such as MedWatch by the FDA[12]. While this spontaneous adverse event reporting has its shortcomings, it is the best and only broad-based mechanism currently available. The largest released reporting on pharmacovigilance data on an MR contrast agent is available on the use of Gd-DTPA (Magnevist) and has been voluntarily reported. These data indicate for specific event categories such as cardiovascular reactions rates of 4 to 8 events per 100,000 doses administered[13]. Renal impairment was identified in adverse event reports from 0.1 to 0.8 events per 100,000 doses and was with angioedema the only major category that showed an increasing trend in the recent years of adverse event reporting. Further analysis of those reports indicating renal impairment indicate that patients most commonly had preexisting renal conditions due to nephrotoxic medications and were receiving higher than labeled contrast agent doses. The current global utilization of MR contrast agents is estimated to be around 12 M patient doses. In order to further put adverse event reporting in perspective it has to be highlighted that those for the Gd-DTPA MR contrast agent is 2–3 times lower than those reported for non-ionic monomeric X-ray contrast agents and allergic reactions are reported about 8 times more frequently for non-ionic contrast media than for the Gd-DTPA MR contrast agent[14]. Anaphylactoid reactions have been seen in Gd-DTPA at a reporting rate of 3-4 per million, while Urticaria has been reported at a rate of 29 to 79 per million.

Necrotizing systemic fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF) initially also referred to as Nephrogenic Fibrosing Dermopathy (NFD) is a condition that, to date, has occurred only in people with kidney disease. NSF is a systemic disorder with its most prominent and visible effects in the skin, hence its original designation as a dermopathy[15]. Our current knowledge recognizes that kidney disease seems to be a prerequisite for developing NSF and therefore it has been accepted as the terminology most reflective of the reality of the disorder. Neither the duration of kidney disease nor its underlying cause appears to be related to the development of NSF. No specific form of dialysis has been linked to NSF, although most patients with NSF do undergo dialysis procedures which are coinciding with severe renal impairment. Some patients who have never been dialyzed have developed NSF. NSF affects males and females in approximately equal numbers. NSF has been confirmed in all age groups however trend to affect the middle-aged most commonly. It has been identified in patients from a variety of ethnic backgrounds from North and South America, Europe, Asia and Australia with the majority of reported cases occurring in the United States.

The current concepts on the underlying causative factors are the combination of two factors, severe renal impairment and exposure to Gadolinium. Gadolinium (Gd), an element of the lanthanide series (atomic number 64), is used in nearly all currently marketed MRI contrast agents. It is always used in a chelated form as it is toxic in its free form. All standard, non-protein interacting Gd-chleates are virtually entirely excreted via the kidneys and therefore any impairment leads to increase in vivo retention and circulation times. If there is no residual urine output, the only way such agents can exit the body is through dialysis. In patients with normal kidney function, the Gd-chelates are considered safe because the bond between the toxic Gd atom and its ligand molecule is very strong; however differences between agents are established. There is a small risk that Gd atoms can unbind from their carrier ligands and then Gd reacts like calcium ions most likely binding to readily-available phosphates and forming insoluble molecules. In patients who receive large doses of Gd-chelates and do not undergo rapid and effective dialysis, there is a risk that larger amounts of these gadolinium compounds could develop and remain in the body in a form that is not readily removable. Another relevant drug/drug interaction might be caused by the co-administration of erythropoietin (EPO) and

intravenous iron. Erythropoietin has the potential to affect the growth of other cells in the bone marrow, and as the cell responsible for producing much of the collagen deposition seen in NSF develops in the bone marrow.

As highlighted in the FDA warning, a GFR below 30 ml/min, which means patients with chronic kidney disease (CKD) of 4 or 5 or patients who have had or are waiting for a liver transplantation, have an elevated risk for this severe adverse event. Some see patients with CKD 3 or a GFR between 30 – 60 ml/min as a potential or lower risk group.

The issue of multiple imaging studies in short time periods is furthermore evolving as a safety concern seeing that potential cumulative effects are difficult to study and are frequently superimposed on other underlying medical ailments. Therefore, it is also highly advisable to have a current eGFR available in such patients.

How to most appropriately handle the medical indications to use Gd-chelates in patients with renal impairment requires a patient specific assessment and continues to rapidly evolve. As with all procedures that have elevated risks, a patient specific risk benefit analysis has to be done by the physician prescribing the MR contrast agent and current literature should be consulted. In addition to the already identified medical conditions, special considerations need to include a review of frequency of imaging studies and potential drug / drug interactions, patient compliance as well as appropriate follow up capabilities. There are alternate MR contrast agents on the horizon which are iron oxide-based and do not use the renal elimination pathway that appears to be a promising option in the patient population with severe renal impairment. While non-contrast enhanced MR angiography is frequently not as capable as contrast enhanced, it still might be the most appropriate alternative if ultrasound-based imaging cannot clarify the medical question to be resolved. In summary, the awareness of the potential for NSF has substantially changed our practice with the unambiguous need to be able to identify patients with renal impairment prior to dosing with Gd-chelates, the need to follow the labeled use and indications as well as being more aware of cumulative effects of multiple imaging studies and/or drug/drug interaction.

Classification of MR Contrast Agents

MR contrast agents currently fall into two broad categories; those based on gadolinium, which are predominately paramagnetic in nature, and those based on iron oxide particles of different coating and size that are superparamagnetic. The broadest utilization for cardiovascular imaging is based on gadolinium chelates which can be sub-classified into agents revealing no interaction with proteins, those that have weak temporary interaction with proteins leading to increased relaxivity and/or having an additional extrarenal elimination pathway and those that have strong protein binding. Table 1 summarizes the contrast agents that are currently available or have been in clinical trials at varying stages relevant for MR imaging[16].

Currently, nine gadolinium chelate contrast agents are approved in one or more countries. Seven of those have been developed as multi-purpose imaging contrast agents and all have at least neuroimaging as a labeled indication. Two gadolinium chelates are approved with targeted indications, Gadotexetate disodium (Eovist, Bayer) as a liver specific imaging “to detect and characterize lesions in adults with known or suspected focal liver disease and gadofosveset trisodium (Ablavar, Lantheus) as an MRA agent “to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected periperheral vascular disease.

Non-Protein Interacting Standard Gadolinium Chelates

This group of “conventional” gadolinium chelate agents was introduced more than 20 years ago with nearly simultaneous approval of gadopentetate dimeglumine (Gd-DTPA, Magnevist, Bayer Healthcare) in all three key markets, Europe, U.S. and Japan. Five of these agents are available as 0.5 Molar formulations and one, gadobutrol (Gd-BT-DO3A, Gadovist, Bayer Healthcare) is being marketed at a 1.0 Molar formulation. Although differences exist between these agents in

terms of the molecular structure and chemical and physical properties (Table 1, 2), all agents are non-specific and are eliminated unchanged via the renal pathway by glomerular filtration. The T1 relaxation rates of these agents are comparable and fall in the range between 4.3 and 5.6 L/mmol s^{-1}. These similarities therefore lead to equivalent imaging characteristics at the same dose and injection rate.

From the molecular structure, the agents can be sub-classified into ionic or non-ionic, linear or macrocyclic. The concept of the non-ionic agents was that those would have an even better safety profile with fewer adverse events comparable to the impact of reducing iconicity in iodinated contrast agents. This idea could not be realized with the agents and the stability of the binding of the Gadolinium central atom has become much more critical. From this perspective, the non-ionic linear molecules are the least stable and the ionic macrocyclic agents the most stable ones. Therefore, the binding strength of the gadolinium by its surrounding chelating complex has become a differentiating factor. The two agents, gadodiamide (Gd-DTPA-BMA, Ominscan, GE-Healthcare) and gadoversetamide (Gd-DTPA-BMEA, Optimark, Mallinckrodt) have substantially lower binding and therefore include excess chelate in the formulation in order to trap any dissociated gadolinium ion in the vial which has also been the causative factor for the interference with colormetric calcium tests and the spurious hypocalcaemia[10].

Gadobutrol is the only agent that is available at 1.0 Molar formulation which enables twice the concentration of gadolinium to be delivered.

Gadolinium Chelates with Weak Protein Interaction

This class represents a second generation of gadolinium chelates that possess a higher T1 relaxivity in blood such as for gadobenate (Gd-BOPTA, Multihance, Bracco) (9.7 L/mmol · s^{-1}) due to the weak transient interaction between the agent and serum proteins, particularly albumin and a T1 relaxivity of (8.2 L/mmol • s–1) in human plasma for gadotexetate disodium (Eovist, Bayer Healthcare). Both agents are ionic, linear chelates and have a dual elimination pathway with partially hepatobiliary elimination, gadobenate weaker than gadotexetate. The higher T1 relaxivity manifests as a significantly greater intravascular signal intensity enhancement compared to that achieved with conventional gadolinium chelates at equivalent doses with the benefits of a more pronounced effect in smaller vessels as well as in the margins of the tumors. In order to objectively assess if differences in the intravascular contrast exist between the first group of standard gadolinium chelates and the new group, an intraindividual crossover study was performed that revealed that gadobenate dimeglumine presented a significantly more intense contrast enhancement with a higher, longer peak duration and larger area under the vascular contrast enhancement curve[17]. This finding was confirmed in a subsequent larger MRA studies for the run-off vasculature[18], pelvic and carotid vasculature. The practical impact is that for the same dose and administration approach a more intense intravascular contrast was noted of longer duration. The clinical advantages of the increased relaxivity have been also demonstrated for all vascular territories from the carotid vasculature[16] to the distant run-off vessels[16]. Like the conventional non-protein interacting gadolinium chelates, gadobenate dimeglumine has an excellent safety profile with a very low incidence of adverse events noted for the clinical development program as a whole[16], however the potential risk to cause NSF cannot be excluded and the same level of diligence also applies to this group., The fact that more signal / enhancement can be obtained for the same dosing more readily enables full diagnostic quality at lower dose thereby reducing dose and accumulation dependent potential effects.

Gadotexetate disodium has only recently been developed, and is being marketed in many countries for liver imaging and is packaged in a 0.25 mol/l concentration, half that of the standard chelates. This agent is not currently being used nor has it been clinically evaluated for cardiovascular imaging however it can certainly be used for MR angiography associated with liver imaging.

Gadolinium chelates with strong protein interaction

The contrast agents in this category exhibit strong affinity for serum proteins which increase the relaxivity and also have extended intravascular half-life making them by design cardiovascular imaging agents. Gadofosveset trisodium, developed under the identifier MS-325, then under the proposed product name of Vasovist and now under the new product name of Ablavar has gone through full clinical development and is approved in several countries for specific MRA indications. This agent is available in a 0.25 mol/l concentration, has been reported to be 88-96% non-covalently bound to albumin in human plasma and to exhibit a relaxivity at 0.5T that is 6 to 10 times that of gadopentetate dimeglumine. The agent has a recommended dosing of 0.03 mmol/kg bodyweight[19] and therefore achieves its desired intravascular contrast at a substantially lower dose due to its higher relaxivity. The elimination pathway is primarily renal but also has some hepatobiliary elimination. This agent can be utilized both for first pass contrast enhanced MRA and for steady-state imaging in a number of vascular territories. While this agent has been investigated in trials in many vascular territories, its 2008 FDA approval and label states the indication as “MRA to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease”. The European Medicines Agency (EMA) already approved the agent in 2005 with the labeled indication “for contrast-enhanced magnetic resonance angiography for visualization of abdominal or limb vessels in patients with suspected or known vascular disease”, which is a much broader indication. The agent also exhibits an extravasation in the case of blood brain barrier breakdown and is currently the only approved agent that will allow both first pass and steady state imaging.

The second agent with strong affinity for serum proteins and increased relaxivity is gadocoletic acid (B22956, Bracco). This agent has undergone Phase II trials for enhanced coronary MRA and has been shown to have even stronger affinity for serum albumin than gadofosveset (approximately 94% bound non-covalently) with a similarly long intravascular residence time[20].

There are two principal types of paramagnetic “blood pool” contrast agents: those whose intravascular residence time is prolonged due to a capacity of the gadolinium chelate for strong interaction with serum proteins, and those that have a macro-molecular structure whose large size limits the extent of extravasation compared to the first pass gadolinium agents. Another important factor to characterize blood-pool agents is in their capability and efficacy to be used both in first pass as well as for steady state vascular imaging.

Gadolinium contrast agents with macro-molecular structures

Examples of gadolinium-based blood pool agents with macromolecular structures are P792 (Vistarem, Guebert) and Gadomer-17 (Bayer Healthcare)[16]. These agents differ from the currently available low molecular weight gadolinium agents in possessing large molecular structures that prevent extravasation of the molecules from the intravascular space following injection, but do have slow, reduced leakage in case of blood brain barrier breakdown. The molecular weights of P792 and gadomer-17 are 6.5 kDa and 35 kDa, respectively, which compare with weights of between approximately 0.56 kDa and 1.0 kDa for the purely first pass gadolinium agents. Whereas the structure of P792 is based on that of gadoterate substituted with four large hydrophilic spacer arms, gadomer-17 is a much larger polymer of 24 gadolinium cascades. In addition to differences in molecular weight and structure, these two agents appear to differ in terms of their rates of vascular clearance, with P792 considered a rapid clearance blood pool agent. Despite these differences, both agents have cardiovascular imaging capabilities and have been evaluated for these indications in clinical trials. Currently, it is not clear if and when any of these agents will receive regulatory approval or would be marketed.

Superparamagnetic Iron Oxide Agents

The second major category of contrast agents for MR imaging consists of the superparamagnetic group, which is based on particles of iron oxide (PIO) that are differentiated

by the size and by its coating and are frequently also referred to as nanoparticles. Those with a diameter larger than 50 nanometer are referred to as small (SPIO) and those smaller as ultrasmall (USPIO). Iron oxide particles have either a starch, dextran or carbohydrate coating and its biologic characteristics are predominately dependent on its coating, while its imaging characteristics as T1w or T2*w agent on its size.

The first approved and marketed iron oxide-based contrast agent was AMI 25 also known as ferumoxide and marketed as Endorem (Guebert) or Feridex (Bayer) with an indication for T2w liver imaging. This SPIO has also been used for cell-tracking and has a demonstrated potential for molecular-based cardiovascular imaging applications[21]. While there were no regulatory issues, the sole manufacturer of this agent, AMAG Pharmaceuticals, decided in November 2008 to cease manufacturing.

The second available iron oxide was developed under the code name of SHU555, also known as Ferrixan or Ferucarbotran, and subsequently marketed as a liver imaging agent under the brand name of Resovist (Bayer). These superparamagnetic iron oxide particles are coated with carboydextran and are accumulated by phagocytosis in cells of the reticuloendothelial system (RES) of the liver. The product formulation had a distribution of particle sizes that predominately led to the RES uptake. However a filtered subfraction of this agent SHU555 C consists only of USPIOs and has been developed as a cardiovascular imaging agent for both first pass and steady state MR Angiography. Another USPIO with starch coating was developed for MRA known as Feruglose, NC100150 or Clariscan, however development was discontinued after substantial longer term liver retention was observed. All iron oxides have been used as carrier molecules for targeted imaging and it remains a highly exciting research area with great potential for molecular targeted cardiovascular imaging. AMI 227 (Ferumoxtran), also known as Combidex or Sinerem, is another USPIO that has been specifically evaluated for lymphatic MR imaging[22,23] but has not yet received final regulatory approval. The fifth iron oxide agent that has been evaluated for MRA imaging is ferumoxytol, formerly known as Code 7228 and now as fereheme. While its initial development goal envisioned it to be an imaging agent, it was subsequently developed as an iron replacement therapeutic indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD), the very same population at higher risk for NSF from Gd chelate imaging agents. Overall, it can be speculated that iron oxides, especially the USPIOs, will have an important place in cardiovascular MRA in the future, not only for intravascular contrast but also as a molecular targeted MR contrast agent. The contrast agent field will continue to evolve and the efforts over the last decade are leading to exciting new, safe and robust imaging approaches further increasing the clinical importance of safe, effective and non invasive MR imaging.

While contrast agents for both CT and MR did not reveal distinctively different imaging characteristics in the past, now new agents provide truly distinctive characteristics that advance the capabilities in non-invasive disease detection and characterization. The advent of molecular targeted agents is on the horizon for neuro-oncologic cross-sectional imaging that will enable us to further improve imaging capabilities.

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Table 1. Physicochemical characteristics of clinically developed gadolinium-based MR contrast agents

Characteristic	Gd-DTPA *Gadopentate Dimeglumine* Magnevist (0.5 mol/L)	Gd-BOPTA *Gadobenate Dimeglumine* MultiHance (0.5 mol/L)	Gd-EOB-DTPA *Gadoxetate Disodium* Eovist (0.25 mol/L)	*Gadofosveset Trisodium* Ablavar (0.25 mol/L)	Gd-DTPA-BMA *Gadodiamide* Omniscan (0.5 mol/L)	Gd-DTPA-BMEA *Gadoversetamide* OptiMARK (0.5 mol/L)	Gd-DOTA *Gadoterate meglumine* Dotarem (0.5 mol/L)	Gd-HP-DO3A *Gadoteridol* ProHance (0.5 mol/L)	Gd-BT-DO3A *Gadobutrol* Gadovist (1.0 mol/L)
Molecular structure	Linear ionic	Linear ionic	Linear ionic	Linear ionic	Linear non-ionic	Linear non-ionic	Cyclic ionic	Cyclic non-ionic	Cyclic non-ionic
Thermodynamic stability constant (log K_{eq})	22.1	22.6	23.5	22.1	16.9	16.6	25.8	23.8	21.8
Osmolality (Osm/kg)	1.96	1.97	0.69	0.83	0.65	1.11	1.35	0.63	1.60
Viscosity (mPa · s at 37°C)	2.9	5.3	1.2	1.8	1.4	2.0	2.0	1.3	4.96
T1 relaxivity ($L/mmol \cdot s^{-1}$), plasma	4.9	9.7	8.7	Variable	4.8	N/A	4.3	4.6	5.6
N/A = not available									

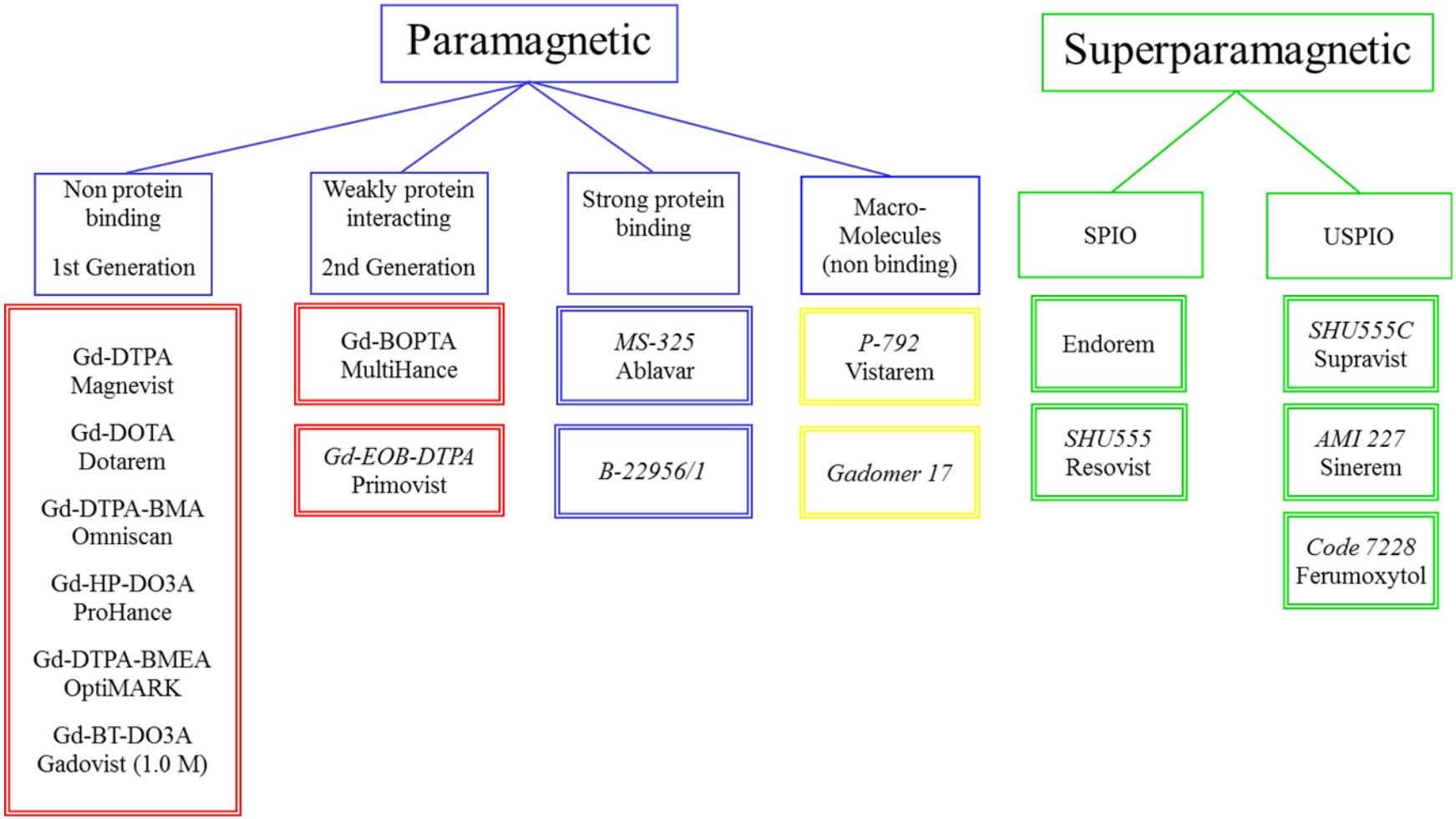

Figure 1. Classification scheme for MR contrast agents that are potentially applicable to cardiovascular imaging. The paramagnetic gadolinium chelates can be classified according to their degree of protein interaction. The ultra small-iron oxide particles are "blood pool agents" which demonstrate long intravascular enhancement