MR Contrast Agents for Cardiac Imaging

Yicheng Ni

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Abstract

Thanks to the ever-advancing technologies, cardiac magnetic resonance imaging (MRI) has become a major diagnostic tool in clinical cardiology for acquisition of morphological, functional and metabolic information. However, it is of no doubt that only when complemented with the use of contrast agents, can cardiac MRI fully play its pivotal roles in clinical diagnosis and therapeutic decision-making. In particular, MR coronary angiography, perfusion mapping, and cellular membrane integrity or myocardial viability assessment rely more on the use of appropriate contrast agents. The current chapter aims to provide an overview on the main topics related to MRI contrast agents including the mechanisms of MRI contrast and contrast agents, classification of both commercially available and preclinically investigational contrast agents useful for cardiac MRI, as well as the general scope of contrast agent applications in relevant clinical practice and experimental research.

1 Introduction

Magnetic resonance imaging (MRI) has rapidly evolved into a major player in the armamentarium of clinical diagnostic imaging. This development is a great symbol of contemporary medicine. Acknowledging its significance, the 2003 Nobel Prize in Physiology or Medicine was awarded jointly to Lauterbur and Mansfield for their pivotal contributions in the discovery and utility of MRI (Gore 2003).

Y. Ni (✉)
Department of Radiology,
Gasthuisberg University Hospital,
Herestraat 49, 3000 Leuven, Belgium
e-mail: yicheng.ni@med.kuleuven.be

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Comparing with any other body structures, the ever-pumping heart in the respiration-tided thorax represents the most difficult organ to image. Nonetheless cardiac MRI is now entirely feasible thanks to the implemented techniques such as ECG triggering, respiration gating, ultrafast or even real-time imaging methods that have efficiently minimized or overcome cardiac and breathing motion artifacts (Kuhl et al. 2004). Over the last decade, there has been tremendous progress in MRI of both cardiac morphology and function. Further advances toward faster acquisition with real-time imaging, higher resolution for plaque imaging and quantitative analysis are taking place at a rapid pace.

Thus, for cardiac imaging, MRI has become advantageous over other modalities due to its versatile strengths, including noninvasiveness; nonionizing safety; superb spatial and temporal resolution; inherent 3D data acquisition with unlimited orientation; intrinsic contrast exploitable for tissue characterization; sensitivity to blood flow and cardiac wall motion; and potential for in vivo measurement of myocardial metabolism by using MR spectroscopy or MRS, as well as any further technical breakthroughs (Van der wall et al. 1996).

Despite all these strengths, it is of no doubt that only when complemented with the use of contrast agents, cardiac MRI can fully play its pivotal roles in clinical diagnosis and therapeutic decision-making. In fact, the potential and necessity of using contrast materials to promote MRI capacity was recognized soon after the invention of this imaging technology (Lauterbur et al. 1978). In particular, MR coronary angiography (MRCA), perfusion mapping and cellular membrane integrity or myocardial viability assessment rely more on the use of appropriate contrast agents for eased imaging acquisition, enhanced image quality and/or improved diagnostic sensitivity and specificity. In addition, contrast agents may be useful for MRI-guided interventional procedures such as angioplasty and localized delivery in gene or other advanced therapies in the future. Further research and development of more targeted MRI contrast agents at the cellular and molecular levels will help to more specifically identify different cardiovascular pathologies including ischemia, atherosclerosis, inflammation, necrosis and angiogenesis. Only by joining together all these indispensable elements, can the comprehensive "one-stop shop" cardiac MRI examination become the reality of clinical cardiology (Ni 1998).

The current chapter aims to provide an overview on the main topics related to MRI contrast agents including the mechanisms of MRI contrast and contrast agents, classification of both commercially available and preclinically investigational contrast agents useful for cardiac MRI, as well as the general scope of contrast agent applications in relevant clinical and experimental research. For the 2nd edition, more information has been updated and incorporated into this chapter since the 1st edition of this book was published 6 years ago.

2 Basic Principle of MR Contrast Agents

2.1 Origins of Imaging Signals for Current Clinical MR

About two-thirds of the human body consists of water that exists either freely or confined within the life molecules. Water is formed by one atom of oxygen bound with two atoms of hydrogen (^{1}H). Another more "MRI-discernible" body constituent is the fat, which is chemically composed of fatty acids such as stearic, palmitic, oleic, etc., covalently bound in various proportions with glyceryl, all are enriched with ^{1}H.

The imaging signals in the clinically applied MRI at present stem from the abundant ^{1}H in the human body, which is inherent in magnetic property due to its single positively charged proton. The similar property is also found in other less abundantly occurring isotopic nuclei such as ^{13}C, ^{19}F, ^{23}Na and ^{31}P with only odd numbers of protons, but not in ^{12}C, ^{14}N and ^{16}O, with even numbers of protons and neutrons.

When the body is exposed to a strong magnetic field, the ^{1}H nuclei in the tissue orient themselves within this magnetic field. While sending in a pulse of radio waves at a certain frequency, the energy content as well as the orientation of the nuclei changes, and, as they relax to their previous states, a resonance radio wave or an MRI signal is emitted. In 1971, Lauterbur pioneered spatial information encoding principles that made image formation possible by utilizing such emitted MRI signals. The further studies of Mansfield on the concept of echo-planar imaging dramatically decreased acquisition time and allowed functional and dynamic imaging (Gore 2003).

The frequencies of electromagnetic waves or radiations used for MRI are from 10^{6} to 10^{9} Hz

approximately, i.e. within radiofrequency range, which are much lower than that of ionizing X-rays (10^{16}–10^{20} Hz) and γ-rays (10^{21}–10^{24} Hz) used for radiography and nuclear medicine, respectively and are therefore considered biologically safe.

Besides ^{1}H, other magnetic nuclei such as ^{23}Na, ^{13}C, ^{19}F and ^{31}P in the human body can also generate MRI signals, though normally with much less intensity but under much more technically demanding conditions and/or at much higher costs (Cannon et al. 1986; Fishman et al. 1987; Friedrich et al. 1995; Kim et al. 1997, 1999; Ardenkjaer-Larsen et al. 2003; Golman et al. 2003; Svensson et al. 2003). Some of these techniques are of particular cardiovascular relevance. The feasibility of obtaining cardiac ^{23}Na MRI at both 4.7 T animal and 1.5 T human scanners has been demonstrated using double-resonant ^{23}Na-^{1}H surface radiofrequency coils for myocardial viability determination (Cannon et al. 1986; Kim et al. 1997; Ouwerkerk et al. 2008). In this context, the dramatic alterations of extra-versus intracellular ^{23}Na concentration during myocardial ischemia or infarction were exploited as intrinsic source of contrast to identify irreversibly damaged myocytes due to disruption of sodium concentration gradient across cellular membranes. However, as the authors admitted, clinical feasibility does not imply clinical utility. Further efforts have to be made before cardiac ^{23}Na MRI can be incorporated as part of the clinical routine (Kim et al. 1999). On the other hand, ^{31}P chemical shift imaging may provide a profile of regional adenosine triphosphate (ATP) and phosphocreatine (PCr) contents, hence an estimation of energy status and viability of the myocardium (Friedrich et al. 1995). Recently a new revolutionary technology that utilizes biomolecules bearing certain prepared hyperpolarized (HP) nucleus such as HP ^{13}C-urea has shown the promise in ultrafast high-resolution MR angiography with unprecedented signal-to-noise (SNR) and contrast-to-noise (CNR) ratios even at very low magnetic field (e.g. 0.01 T). This may also open new horizon for molecular imaging with MRI (Ardenkjaer-Larsen et al. 2003; Golman et al. 2003; Svensson et al. 2003). Despite the high performance of such novel approaches (Bhattacharya et al. 2009), it is likely that conventional ^{1}H MRI will still serve as the mainstream method for providing the basic morphological and functional information of normal and diseased cardiovascular tissues.

2.2 Unique Mechanisms of MRI Contrast Agents

Image contrast is the basis for human visual perception to differentiate between regions on the object. Contrast media or agents denote extrinsic or intrinsic substances that are intended to improve the image contrast of the target tissues by means of increasing or decreasing the attenuation of X-rays in radiography, the signal intensity (SI) in MRI and the echo amplitude in ultrasonography. The radiopharmaceuticals can also be considered as contrast media to a certain extent. Since there is virtually no native radioactivity in the human body, introduction of a radiopharmaceutical into the body always increases positively the contrast of the target tissue over the background. Acceptable biotolerance remains one of the basic requirements for any potential contrast agents.

The main contrast determinants in MRI are ^{1}H proton density, longitudinal (T1) or transverse (T2) relaxation times of ^{1}H protons, and magnetic susceptibility. Since water content or ^{1}H proton density in the tissue is virtually unchangeable, magnetic properties of T1, T2 and susceptibility have therefore been the major parameters dominating the development of MRI contrast agents. Although T1 and T2 are generally prolonged in injured myocardium, there is considerable overlap of relaxation times between normal, reversibly injured and irreversibly damaged myocardium on native MRI, a fact stressing the need of contrast agents for cardiac MRI.

Some paramagnetic transition metal elements such as gadolinium (Gd^{3+}), manganese (Mn^{2+}), dysprosium (Dy^{3+}) and iron (Fe^{3+}) contain in their outer shells of the electron orbit a number of unpaired electron spins, which have relatively long electron spin relaxation time. The magnetic field produced by an electron is much stronger than that by a ^{1}H proton, and therefore these paramagnetic elements are ideal candidates for producing MRI contrast agents that affect T1 and T2 of tissue ^{1}H protons, hence the tissue SI and/or contrast. Contrast enhancement is achieved by either increasing or decreasing the SI of a tissue; thus its signal over background noise ratio (SNR), its contrast relative to another tissue (contrast ratio or CR) and/or to the background noise (contrast-to-noise ratio or CNR) can be enhanced.

Differing from the direct and linear principles of contrast formation with the high-density contrast

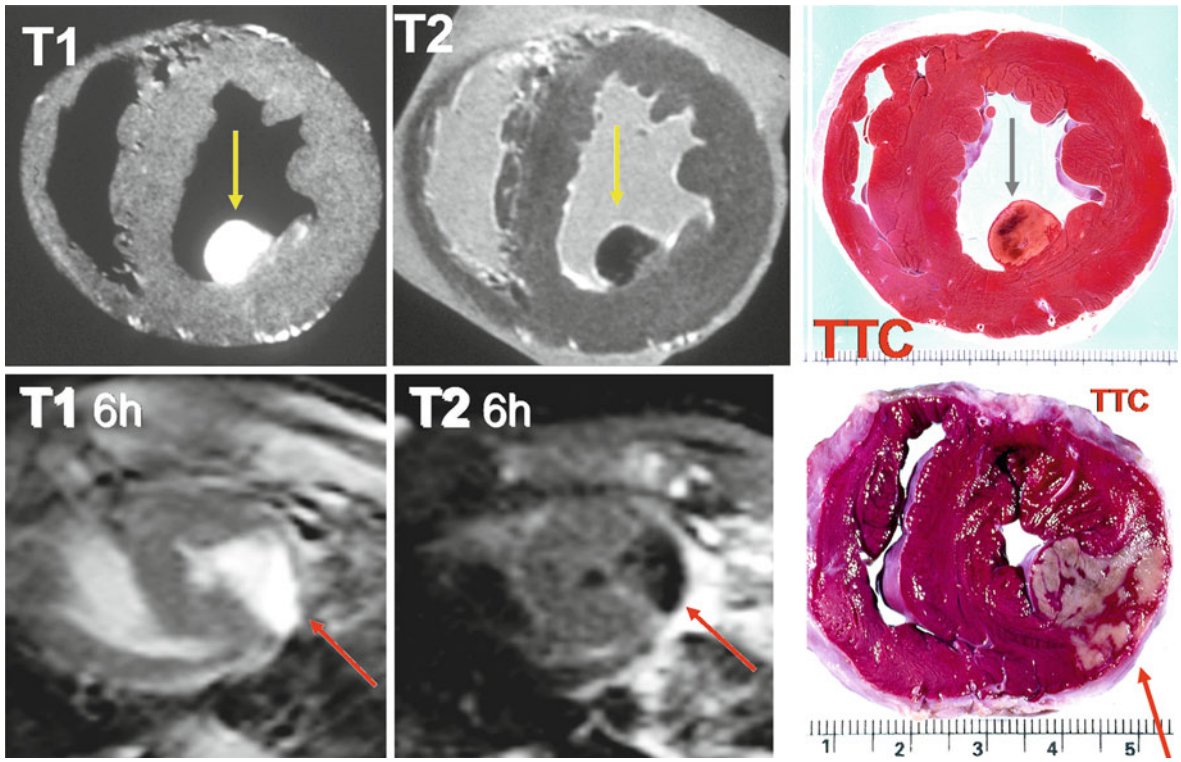

Fig. 1 Nonporphyrin necrosis-avid contrast agents (NACAs) at the same intravenous dose of 0.05 mmol/kg induced both T1 and T2 contrast enhancement (CE) with relevant MRI sequences in reperfused MI (*arrow*) on postmortem images of a dog overnight after injection of *bis*-Gd-DTPA-pamoic acid derivative (ECIII-60; *upper row*) and on in vivo images of a pig 6 h after injection of *bis*-Gd-DTPA-*bis*-indole derivative (ECIV-7; *lower row*), suggesting the chemotactic accumulation of NACAs in the necrotic myocardium as proven by the corresponding TTC stained specimen

media for radiography or the gamma ray emitting isotopes for nuclear scintigraphy, the mechanisms of the current MRI contrast agents are basically indirect and nonlinear, and much more complicated. They rest on the distinct magnetic properties and interactions of native ^{1}H protons toward introduced MRI contrast agents. Depending on influential factors, including the dose of the contrast agent and MRI sequence applied, either T1 shortening (positive) or T2 shortening (negative) contrast effect can be predominant.

The positive contrast agents are typically Gd- or Mn-containing paramagnetic chelates. They shorten both T1 and T2 of the tissue, but since T1 is much longer than T2, their predominant effect at low doses is T1 shortening. Therefore the tissue taking up such contrast agents becomes bright or hyperintense on T1 weighted MRI. However, when the local concentration of a T1 or positive contrast agent becomes very high, its T2 shortening effect appears or becomes even predominant as often seen in the renal pelvis shortly after an intravenous dosage, or as exemplified in the case of experimental acute myocardial infarction (AMI) enhanced with a necrosis-avid contrast agent (NACA; Fig. 1).

The negative contrast agents are often termed superparamagnetic or susceptibility contrast agents that can be created as small Fe_3O_4 particulate aggregates consisting of ferromagnetic or superparamagnetic crystals or particles smaller than 300 nm. They generate local magnetic field gradients that disrupt the homogeneity of the primary magnetic field over the tissue. Besides T2 shortening effect due to the diffusion of water through these field gradients, their more prominent effect is T2* shortening or susceptibility effect, both effects darken the region of interest or produce hypointense signals on T2, T2* and even T1 weighted MR images. However, depending on their particle size and coating, they can also produce substantial T1 shortening effect and function as positive contrast agents used, for example, for MR angiography (MRA).

There are also intrinsic MRI contrast substances such as hemoglobin. The paramagnetic property of deoxyhemoglobin to cause local magnetic field distortion and susceptibility has been exploited as the source of blood oxygen level dependent (BOLD) contrast for functional MRI of the brain (Turner 1997), heart (Manka et al. 2010) and tumor (Padhani 2010).

In principle, it is their magnetic impact on the ^{1}H proton relaxation rather than the MRI contrast agents themselves that create enhanced contrast on MR images. In other words, MRI contrast agents do not generate signals but only modify the amplitude of the signals generated by ^{1}H protons in the presence of magnetic field.

'Because of such an indirect mechanism of action, a lack of linear relation between the SI and the local concentration represents a drawback for accurate quantification of studied MRI contrast agents. Nevertheless, similar to radiopharmaceuticals or radiographic contrast media, in unconventional MRI when the scanner is tuned to the resonant frequencies for nuclei of ^{23}Na, ^{13}C, ^{19}F and ^{31}P, the generated images will only show regions where these nuclei are present, hence feasible for quantitative data analysis with a direct SI and nucleus concentration relationship.

2.3 Dosage in Relation to Contrast Enhancing Efficacy

Normally MRI contrast agents are chemically formulated in a manner similar to that for producing radiopharmaceuticals. Due to the fact that the sensitivity of ^{1}H MRI to detect CA induced effects visible on the image is higher than that of radiography but much lower than that of nuclear scintigraphy, the MRI contrast agents can be given with doses of micromoles per kilogram (about 5–300 μmol/kg), i.e. about 10^{2}–10^{3} times lower than that for radiographic contrast media at a millimoles-per-kilogram level, but 10^{4}–10^{6} times higher than that for radiopharmaceuticals at a nanomole- or even picomole-per-kilogram level. Usually, the physicians' knowledge and experience with CT contrast media can be extended to the use of clinically available MRI extracellular fluid (ECF) space contrast agents. However, as illustrated in Fig. 1, MRI contrast agents possess both T1- and T2-shortening effects and their positive or negative effects of contrast enhancement (CE) depend not only on the total dosage administered but also the local concentration of the accumulated agent in a given target tissue, as well as interaction between the contrast agent and the tissue components. Such a unique phenomenon differing from that with CT and nuclear imaging should be taken into account when contrast enhanced MRI is interpreted.

Based on the diagnostic purpose as well as safety considerations, the exact doses and manners of contrast agent administration vary among different cardiac MRI protocols. For a first-pass myocardial perfusion MRI, a bolus of a contrast agent at a relatively low dose of 0.005–0.05 mmol/kg is intravenously injected at a high speed (e.g. 3–5 ml/s) and flushed with certain volume of 0.9% saline by using a power injector. This is usually followed by another normal dose of contrast agent for delayed CE for estimation of MI or viability (Chiu et al. 2003). To compensate the unstable CE in the AMI due to the use of ECF contrast agents, a constant infusion of Gd-DTPA was recommended for more accurate determination of myocardial necrosis in a clinical setting (Pereira et al. 2000). Diversely, slow intravenous infusion is also a common practice for administration of Mn-based intracellular contrast agents but to avoid acute side-effect caused by calcium disturbance in myocardium (Bremerich et al. 2000; Flacke et al. 2003).

3 Classifications of Contrast Agents for Cardiac MRI

3.1 Extracellular Fluid Space Contrast Agents

The first generation MRI contrast agents including Gd-DTPA and Gd-DOTA (Table 1, Fig. 2) are created by chelating the lanthanide metal element gadolinium with linear or cyclic multidentate ligands (DTPA or DOTA) to form thermodynamically stable and biologically inert complex or coordination compounds so that the paramagnetic properties of gadolinium can be utilized for enhancing MRI contrast, whereas the toxicity of both gadolinium and the

Table 1 Contrast agents that could be used for Cardiac MRI

Category	Short name	Generic name	Trade name	Feature
Extracellular fluid space contrast agents[b]	Gd-DTPA	Gadopentetate dimeglumine	Magnevist	Positive[c]
	Gd-DOTA	Gadoterate meglumine	Dotarem	Positive
	Gd-DTPA-BMA	Gadodiamide injection	Omniscan	Positive
	Gd-HP-DO3A	Gadoteridol injection	ProHance	Positive
	Gd-DTPA-BMEA	Gadoversetamide	Optimark	Positive
	Gd-DO3A-butriol	Gadobutrol	Gadovist	Positive
	Gd-BOPTA	Gadobenate dimeglumine	Multi-Hance	Positive
	Porphyrin and Nonporphyrin NACAs			Positive
Blood pool contrast agents	NC-100150	PEG-feron (USPIO)	Clariscan	Positive
	SH U 555 C	Ferucarbotran (USPIO)	Supravist	Positive
	MS-325		Angiomark	Positive
	B-22956	Gadocoletic Acid		Positive
	Gadomer-17			Positive
	P792	Macromolecular Gd-DOTA derivate	Vistarem	Positive
	AMI-227	Ferumoxtran (USPIO)	Sinerem/combidex	Positive or negative
	Gd-BOPTA	Gadobenate dimeglumine	Multi-Hance	Positive
	Porphyrin and Nonporphyrin NACAs			Positive
Intracellular contrast agents	Mn-DPDP	Mangafodipir Trisodium	Teslascan	Intramyocytic uptake, positive
	$MnCl_2$, MP-680, CVP 1001-1			Experimental, positive
Necrosis-avid contrast agents (NACAs)	Bis-Gd-DTPA-mesoporphyrin		Gadophrin-2 Gadophrin-3[a]	Experimental, positive; Central chelation of Cu[a]
	ECIII-60	Gd-DTPA-pamoic acid derivative	Nonporphyrin NACA	Experimental, positive
	ECIV-7	Gd-DTPA-bisindole derivative	Nonporphyrin NACA	Experimental, positive
	Gadofluorine-M			Experimental, positive
Plaque-specific contrast agents	Gadofluorine-M			Experimental, positive
	Porphyrin and Nonporphyrin NACAs			Experimental, positive

Note

[a] Approved or in development

[b] All ECF space contrast agents are excreted via urine

[c] With high local concentration, negative contrast can be observed, e.g. first-pass perfusion

ligands, if each applied alone, can thus be avoided. After intravenous injection, these contrast agents randomly distribute in intravascular and interstitial ECF spaces, and are eliminated rapidly in their unchanged forms through glomerular filtration in the kidney (Fig. 2), which makes the "renal-specific" property exploitable for evaluation of renal function. These contrast agents also allow possible diagnosis of certain pathological conditions with altered distribution space at vascular level, such as hemangioma and blood–brain-barrier (BBB) breakdown, at interstitial level, such as inflammatory edema and regenerative fibrosis, and at cellular membrane integral level such as tissue necrosis or infarction, e.g. AMI. However, normally they do not allow definite histological diagnoses owing to the intrinsic feature of nonselective distribution over all the above-mentioned pathologies. Alternatively, analyses of enhancement kinetics have been elaborated for differential diagnosis between malignant and benign lesions (Heywang et al. 1989; Kaiser and Zeitler 1989), for quantitative assessment of tumor angiogenesis and microvascular density (Hawighorst et al. 1999), and for determination of cerebral blood flow and volume (Villringer et al. 1988). Lack of real tissue and/or disease specificity of these contrast agents have prompted further research and development of more specific MRI contrast agents. One noteworthy issue is that other, more advanced specific or targeting contrast agents always share more or less the nonspecific properties of the ECF contrast agents especially in their early systemic distribution phase, which has been explored for multipurpose applications of certain organ- or tissue-specific contrast agents such as the hepatobiliary Gd-BOPTA (Cavagna et al. 1997) and necrosis-avid contrast agents (NACAs) (Ni et al. 2002a, b, c, 2005a; Ni 2008) (Table 1).

3.2 Blood-Pool Contrast Agents

This unique type refers to a variety of contrast agents that are confined by purpose to the intravascular space and dedicated exclusively to cardiovascular applications. Such blood-pool (BP) property can be realized by controlling the distribution and elimination of the contrast agents, which in turn is determined by their size relative to the permeability of the capillary endothelium in different organs. Although BP contrast agents are partially or completely limited in passing through the endothelial membrane elsewhere, they can still be excreted by the kidneys (Fig. 2). Usually, the higher the molecular weight of macromolecular compounds, the slower the blood elimination half-life and total blood clearance. In tissues such as myocardium, the lumen of the continuous capillaries is lined with an uninterrupted endothelial layer, which only allow diffusion of drugs with small molecular weight such as Gd-DTPA (590 Da); whereas in the kidneys, glomerular capillaries are fenestrated with pores of 60–70 nm in diameter, which facilitate passage of any drug molecules weighted approximately below 20,000 Da. Above this molecular weight, renal excretion then depends on the lipophilicity and polarity of the agent as well as the pH of the environment. Molecules larger than 70,000 Da cannot pass the glomerular filter, but are metabolized before excretion (Brasch 1991).

Relative to the ECF contrast agents with a short period of peak vascular enhancement, BP contrast agents possess longer plasma half-life and render a higher intravascular signal, and therefore facilitate MR angiography (MRA) with improved flexibility, accuracy and versatility. With the use of BP contrast agents, the time interval between contrast injection and imaging acquisition becomes less crucial due to the resultant optimal imaging window in tens of minutes instead of seconds with the use of ECF contrast agents.

An adequate and uniform particulate size, a high ratio of T1 over T2 relaxivity, an initial intravascular space distribution, a sufficient eventual body clearance and a lack of toxicity and/or immunogenecity are the basic requirements for an ideal BP contrast agent. Several concepts dominate the development of BP contrast agents (Fig. 2). One approach is to synthesize large and median molecules of Gd-containing polymer for prolonged intravascular retention and slower extravasation during renal elimination, as represented by Gd-polylysine (Bogdanov et al. 1993), Gadomer-17 (Misselwitz et al. 2001) and P792 (Port et al. 2001; Taupitz et al. 2001), which may feature rapid urinary clearance kinetics. Another approach utilizes the reversible protein-binding property of certain small molecular Gd chelates to form a type of "semi-endogenous" BP markers, as represented by gadofosveset trisodium (formerly identified asMS-325 or Angiomark) (Lauffer et al.

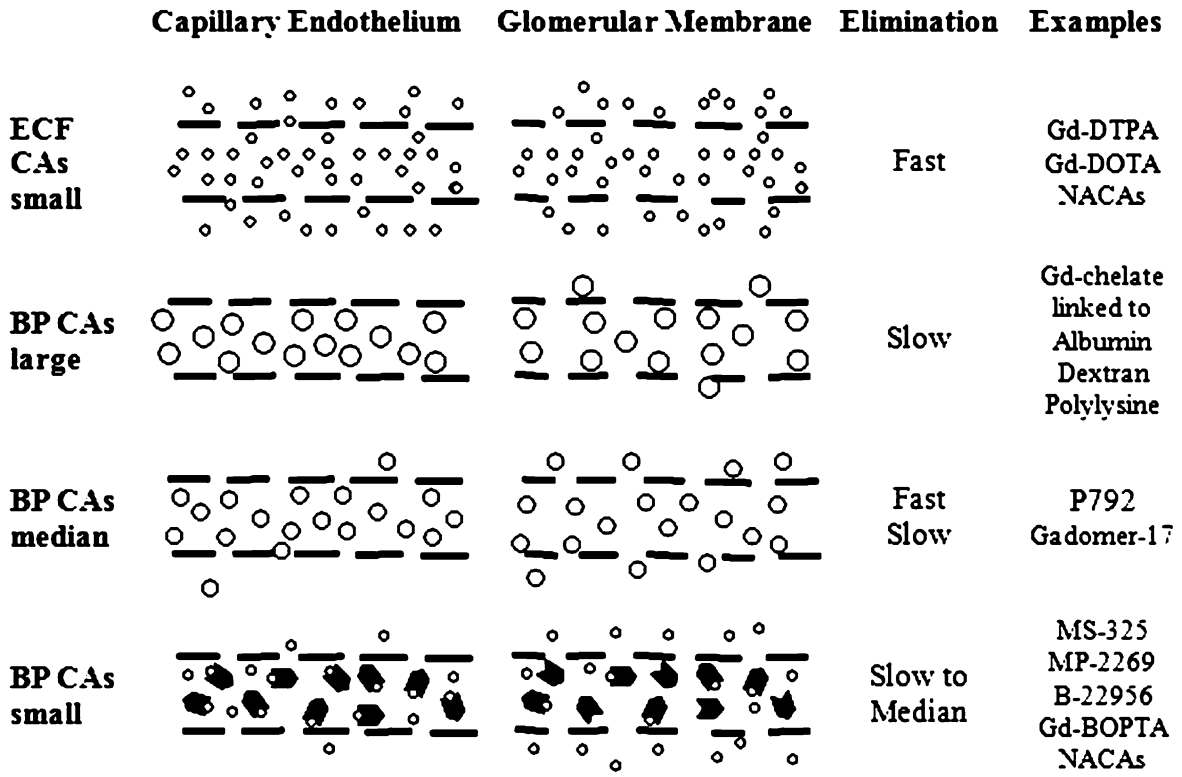

Fig. 2 Extracellular fluid space versus blood-pool contrast agents Note *BP* blood-pool; *CAs* contrast agents; *DTPA* diethylenetriaminepentaacetic acid; *ECF* extracellular fluid space; *Gd* gadolinium; *NACAs* necrosis-avid contrast agents; *DOTA* tetraazacyclododecanetetraacetic acid; *Gd-BOPTA* Gadobenate dimeglumine

1998), MP-2269 (Wallace et al. 1998) and B-22956 (La Noce et al. 2002), as well as other protein-binding (though perhaps somewhat weaker) agents such as Gd-BOPTA (Cavagna et al. 1997) and NACAs (Ni 1998; Ni et al. 2002a, b, c; Ni et al. 2005a; Ni 2008). MS-325 has been the most clinically advanced agent of this class (Lauffer et al. 1998). While all above BP contrast agents are based on paramagnetic gadolinium, the third class is based on small or ultrasmall superparamagnetic iron oxides (USPIO) optimized for blood retention and minimized for susceptibility effects (Chambon et al. 1993; Mayo-Smith et al. 1996; Stillman et al. 1996). Furthermore, clinical trials with starch-coated and stabilized iron oxide particles code-named NC 100150 (Clariscan) have been performed (Ahlstrom et al. 1999). These particulate contrast agents are slowly cleared up from the circulation and recycled through the mononuclear phagacytotic or reticuloendothelial system (MPS or RES), a metabolic route completely different from that used by gadolinium-based contrast agents. The potential cardiovascular applications of BP contrast agents include MRCA, assessment of myocardial perfusion, pulmonary and peripheral MRA, as well as evaluation of microvascular permeability in different pathological conditions. While a slower bolus of BP contrast agents is administered for dynamic arterial phase MRA, higher injection speed as a very fast bolus often necessary for myocardial first-pass perfusion MRI remains one of the safety concerns that have to be taken into account before BP contrast agents can be applied in clinical routine. The speed of injection appears to be crucial in acute toxicity effects of any contrast agents. However, the injection rate at about 1 ml/min used in laboratories to determine LD50 values in experimental animals is probably too slow to detect early deaths (within few minutes after administration), which are mainly caused by osmotic expansion of the plasma volume and failure of the cardiovascular circulation (de Haen et al. 1994). Other factors that are responsible for adverse reactions to contrast agents are chemotoxicity, osmotoxicity, ion toxicity, allergy and dose (Almen 1994).

3.3 Intracellular Contrast Agents

In nuclear scintigraphic tomography, active uptake of radioactive thallium-201 (^{201}Tl) as a potassium analog (Schoeder et al. 1993), and manganese 52 m (^{52m}Mn) and manganese 54 (^{54}Mn) as calcium antagonists (Chauncey et al. 1977; Atkins et al. 1979) by viable myocytes has been applied for assessment of myocardial viability (MV). Similar approach has been adopted in cardiac MRI using cold cation Mn^{2+} preparations as intracellular contrast agents for infarct imaging, since Mn^{2+} is potent for T1 shortening and is taken up only in cells capable of active calcium (Ca^{2+}) transport, and thereby provides an analog to ^{201}Tl imaging in cardiac scintigraphy (Bremerich et al. 2000; Karlsson et al. 2001; Flacke et al. 2003; Storey et al. 2003; Krombach et al. 2004). Mn^{2+} has an ionic radius similar to that of Ca^{2+} and is known to enter myocytes via voltage-facilitated calcium channels. These agents feature bifacial functions, i.e. for myocardial perfusion imaging with the initial blood-pool effect and as viability markers for functional myocytes at the equilibrium phase. Among these preparations, manganese chloride salt ($MnCl_2$) has shown the highest contrast enhancing efficacy with the ability even to identify stunned myocardium (Flacke et al. 2003; Krombach et al. 2004). However, because Mn^{2+} functions as a potent antagonist at the voltage-dependent Ca^{2+} channel across cellular membrane and competes with Ca^{2+} uptake of myocardium, concerns about the potential cardiac toxicity for negative inotropic effects or reduction of myocardial contractility have led to various formulations, all intended to lower cardiac toxicity, such as injection solution of $MnCl_2$ dissolved in calcium gluconate (Flacke et al. 2003) and chelated preparations as slower Mn^{2+} releasers including MP-680 or Mn[EDTA-bis(aminopropanediol)] (Flacke et al. 2003), EVP 1001-1 (Storey et al. 2003), and mangafodipir trisodium (manganese dipyridoxyl diphosphate or Mn-DPDP or Teslascan) (Bremerich et al. 2000; Flacke et al. 2003). The latter is already marketed for liver imaging with a plasma half-life <25 min (Hustvedt et al. 1997) and LD50 about 5.4 mmol/kg in mice (Elizondo et al. 1991).

Interestingly, recent experimental studies in pigs revealed that the metabolite from Mn-DPDP namely manganese dipyridoxyl ethyldiamine (MnPLED) could reduce postischemic reperfusion-induced cardiac dysfunction and infarct size (Karlsson et al. 2001). Therefore, the use of a Mn^{2+}-releasing contrast agents such as Mn-DPDP may be a promising multipurpose approach. In addition to the suggested therapeutic effects of antioxydative myocardial protection (Brurok et al. 1999; Karlsson et al. 2001), with noninvasive MRI, more functional information about myocardial metabolism and MV might be acquired by depicting differential patterns of T1 relaxation changes in relation to regional coronary flow, cellular cation uptake and retention, ion channel function and metabolism in patients with coronary heart disease. However, all these encouraging outcomes are still experimental. Before clinical cardiac MRI might enjoy the CE with an intracellular CA, its formulation, dosage, imaging protocol and especially biotolerance have to be optimized through further strenuous preclinical and clinical research.

3.4 Necrosis-Avid or Multipurpose Contrast Agents?

The ECF contrast agents such as Gd-DTPA have been widely applied to enhance cardiac MRI in both clinical practice and experimental research due to their immediate availability and general safety. Despite the considerable consensus to regard them as viability markers with "necrosis-specific" property to discriminate between viable and nonviable myocardium at delayed phase contrast enhanced MRI (Ramani et al. 1998; Kim et al. 2000; Pereira et al. 2001; Weinmann et al. 2003), inaccuracy, uncertainty, and dependency of using them on multiple influential factors, for imaging interpretation have also been evidenced (Ni et al. 2001b; Oshinski et al. 2001; Saeed et al. 2001; Choi et al. 2002; Judd and Kim 2002; Jin et al. 2007). Particularly, they are still incapable of making explicit distinctions between reversible and irreversible injured myocardium, between acute and chronic infarction, and between ischemic and inflammatory lesions, for which other nonspecific alternatives such as geographic patterns of CE had to be adopted (Hunold et al. 2005). A lack of accuracy in determination of therapeutic tumor necrosis with an ECF contrast agent was also evident in a more recent experimental study (Wang et al. 2011a, b). Therefore, there has been a continuing strategy for searching more specific contrast agents that can offer unambiguous and indisputable imaging diagnosis.

Phosphonate modified Gd-DTPA complexes could produce a persistent and strong CE in diffuse and occlusive MI due to their affinity for calcium-rich tissues and subsequent formation of insoluble calcium phosphate precipitates in the damaged myocardium. However, they may cause disordered calcium-homeostasis and consequently impaired ventricular contractility (Adzamli et al. 1993). Besides, studies with technetium-99 m pyrophosphate, a scintigraphic analogue of this type, showed a lack of specificity between ischemic and necrotic myocardium (Bianco et al. 1983) leading to a significant overestimation of the infarct (Khaw et al. 1987).

Anti-myosin antibody-labeled magnetopharmaceuticals denote an appealing approach. However, possible immunogenic side effects, insufficient expression of antigens or MRI sensitivity to the currently available relaxation enhancers, and complexity in preparation and handling of the agents challenge their clinical applicability (Weissleder et al. 1992).

What do X-rays, nylon, vaccination and penicillin have in common? They were discovered by accident or serendipitously. The word "serendipity" was first introduced in the middle of eighteenth century to express the phenomenon of discovery "by accident and sagacity" (Roberts 1989). What likely also belongs to this type is the discovery of another category of necrosis-targeting contrast agents, which represents an ongoing multiepisode story. To distinguish them from other antibody or receptor-mediated specific contrast agents with better-defined molecular targets, we proposed to nominate these newly discovered porphyrin and nonporphyrin species "necrosis-avid contrast agents" (NACAs) because of their remarkable affinity for necrotic and/or infarcted tissues (Ni et al. 1997a, 1999, 2001a, 2005a; Ni 1998, 2008; Pislaru et al. 1999; Cresens et al. 2001).

Porphyrin derivatives have been investigated for decades in diagnosis and treatment of malignant tumors (Kessel 1984; Gomer 1989; Nelson et al. 1990; Pass 1993). The rationales governing porphyrin-mediated cancer photodynamic therapy are based on "tumor-localizing" and photosensitizing properties of the agents. By analogy, the tumor "preferential uptake" of porphyrins has also been exploited for developing paramagnetic metalloporphyrins as "tumor-seeking" MRI contrast agents (Chen et al. 1984; Ogan et al. 1987; Furmanski and Longley 1988; Bockhorst et al. 1990; Fiel et al. 1990; Van Zijl et al. 1990; Nelson and Schmiedl 1991; Ebert et al. 1992; Place et al. 1992; Hindre et al. 1993; Young et al. 1994; Saini et al. 1995).

However, the research activities in this laboratory have dramatically converted metalloporphyrins from being used as tumor-seeking contrast agents into magnetic markers of MI (Ni et al. 1996; Ni 2008). During the early 1990s, in helping the former Institut für Diagnostikforschung, Berlin, Germany, to screen and confirm a few potentially tumor-specific porphyrin contrast agents, including bis-Gd-DTPA-mesoporphyrin (later named Gadophrin-2) and Mn-tetraphenylporphyrin (Mn-TPP), we conducted experiments on our well-established animal models of primary and secondary liver tumors (Ni et al. 1992). By using the methodologies dissimilar to those in the previous studies, we found that the notified "specific" CE could be attributed only to nonviable (typically necrotic) instead of viable tumor components (Ni et al. 1995), an observation contrary to the assumption raised by an earlier study (Ebert et al. 1992). To support our findings and to convince the believers in tumor-specificity of porphyrins that they are wrong, more metalloporphyrins were assessed in rats with various induced "benign" necroses and the so-called "tumor localizing" phenomenon could be reproduced without exceptions (Ni et al. 1997a). Furthermore, such a specific CE appeared more striking in pure necrosis than in tumors because the latter consist of necrosis only in proportion. Although, unfortunately, these contrast agents can no longer be considered tumor-specific, their superb necrosis targetability has elicited even more exciting, novel applications for MRI visualization of acute MI (Ni et al. 1994, 1998, 2001b Marchal et al. 1996; Herijgers et al. 1997; Pislaru et al. 1999; Marchal and Ni 2000) and brain infarction (Schneider et al. 1995). The local concentration of Gd is frequently over tens of times higher in infarcted compared with normal myocardium. Finally, the potent effects of Gadophrin-2 for labeling spontaneous and therapeutic necroses, including MI and lesions of radiofrequency ablation (RFA) on MRI, have been widely recognized a few years later, after multi-institutional reproducibility studies (Lim and Choi 1999; Saeed et al. 1999; Stillman et al. 1999; Wendland et al. 1999; Choi et al. 2000; Jeong et al. 2001; Saeed et al. 2001; Barkhausen et al. 2002; Ni et al. 2005c; Ni et al. 2006a).

Besides a normal intravenous dose at 0.05–0.1 mmol/kg for cardiac MRI to visualize MI

with an extended imaging window of 3–48 h (Ni et al. 1994; Marchal et al. 1996, 2000; Herijgers et al. 1997; Ni 1998; Pislaru et al. 1999; Lim et al. 1999; Saeed et al. 1999; Stillman et al. 1999; Wendland et al. 1999; Choi et al. 2000; Jeong et al. 2001; Barkhausen et al. 2002), intracoronary delivery of a tiny dose at 0.005 mmol/kg in combination with the percutaneous transcatheter coronary angioplasty (PTCA) procedure served as a diagnostic adjuvant for MV determination and therapeutic assessment (Ni et al. 1998, 2001b; Jin et al. 2007).

So far, triphenyltetrazolium chloride (TTC) staining has been used as the only gold standard for macroscopic identification or quantification of acute MI. However, it is a post-mortem technique and not clinically applicable. Studies with both intravenous and intracoronary NACA injections have revealed that what is specifically enhanced on cardiac MRI corresponds exactly to what TTC dye does not stain on the excised heart, resulting in the same accuracy for MI delineation (Ni et al. 1994, 1998, 2001b; Marchal et al. 1996; Herijgers et al. 1997; Ni 1998; Lim et al. 1999; Pislaru et al. 1999; Saeed et al. 1999; Stillman et al. 1999; Wendland et al. 1999; Choi et al. 2000; Marchal and Ni 2000; Jeong et al. 2001; Jin et al. 2007) (Fig. 1). Experimentally, NACA enhanced MRI has been used as a surrogate of TTC histochemical staining or an in vivo viability gold standard for evaluation of medicinal myocardial protection (Lund et al. 2001), interventional RFA (Ni et al. 1997a, 2005c, 2006a) and drug-effects on inducing tumor necrosis (Wang et al. 2011a). By chelating a copper ion in the center of the cyclic tetrapyrrole ring, Gadophrin-3 has been introduced to improve its structural stability and safety yet still retain its targeting efficacy (Barkhausen et al. 2002; Schalla et al. 2004). Except for slight discoloration that faded considerably over 24 h, during animal experiments no detectable side effects have been reported with porphyrin agents at a 0.05–0.1 mmol/kg dose range (Ni et al. 1994, 1997a, 1998, 2001a Schneider et al. 1995; Marchal et al. 1996; Herijgers et al. 1997; Ni 1998; Lim et al. 1999; Pislaru et al. 1999; Saeed et al. 1999; Stillman et al. 1999; Wendland et al. 1999; Choi et al. 2000; Marchal et al. 2000; Jeong et al. 2001; Saeed et al. 2001). Nevertheless, despite optimistic expectations (Krombach et al. 2002), further commercial development of these colored porphyrin complexes has unfortunately been abandoned by the industry (Weinmann, Schering AG, personal communication) most likely due to the predicted unsatisfactory clinical tolerance resulting from unchangeable nature of dark-colored pigments of this type of chemicals (Fig. 3).

In order to overcome the discoloration, phototoxicity and other side effects related to the use of porphyrin derivatives, we have made continuing efforts to search for more effective, less toxic and less colored compounds. First, to verify whether the cyclic tetrapyrrole structure characteristic of all porphyrins is essential or not for the observed necrosis targeting, we checked more metalloporphyrins and found that four out of nine metalloporphyrins did not prove necrosis avid (Ni et al. 1999). Such unequal performances among different porphyrins, also occurring in cancer photodynamic therapy (Kessel 1984; Pass 1993) and tumor imaging (Ebert et al. 1992), suggest that the tetrapyrrole ring does not appear to be a common structural requirement for the specific targetability. Furthermore, other Gd chelates conjugated to either open-chain tetrapyrroles such as bilirubin and biliverdin or smaller constituents such as mono-, bis- and tri-pyrrole derivatives also failed to reveal a necrosis-specificity (Ni et al. 2002a). These findings not only disprove an inevitable link between porphyrin-related structures and the affinity for necrosis but also imply the possibility to generate totally different nonporphyrin molecules that could be more effective and less colored or even colorless and, therefore, deprived of any unwanted effects associated with porphyrins. Along this line, we have been able to successfully synthesize a few promising leading compounds such as the light yellowish ECIII-60 (bis-Gd-DTPA-pamoic acid) and the colorless ECIV-7 (bis-Gd-DTPA-bisindole) (Marchal et al. 1999; Cresens et al. 2001; Ni et al. 2002a, b; Ni 2008; Wang et al. 2011a), with both featuring extraordinary necrosis-avidity (Figs. 1 and 3). All studied NACAs, whether porphyrin or nonporphyrin species, allow differential diagnoses between reversible ischemic injury and irreversible infarct, acute and healing MI, and occlusive and reperfused MI (Saeed et al. 1999; Choi et al. 2000; Jeong et al. 2001; Ni et al. 2002c; Saeed et al. 2002; Jin et al. 2007). Even negative findings after CE with NACAs help to reliably exclude the presence of necrosis, which would also be of high significance for differential diagnosis (Marchal et al. 1996; Ni 1998, Ni 2008; Ni et al. 2005a).

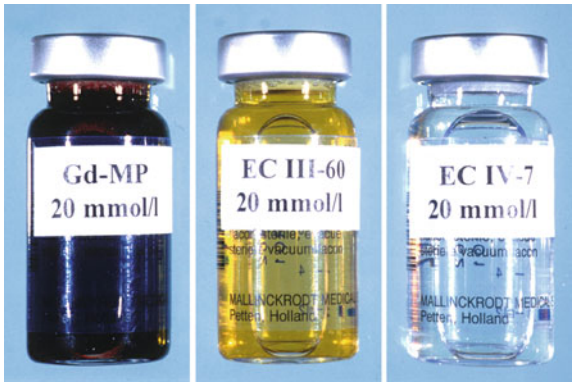

Fig. 3 Vials contain the porphyrin derived NACA Gadophrin-2 on the *left*, the nonporphyrin NACA *bis*-Gd-DTPA-pamoic acid derivative (ECIII-60) in the *middle* and the nonporphyrin NACA *bis*-Gd-DTPA-*bis*-indole derivative (ECIV-7) on the *right* at the same concentration of 20 mmol/L. In contrast to the nontransparent dark-colored pigment-like Gadophrin-2, nonporphyrin NACAs appear as either a transparent light yellowish (ECIII-60) or completely colorless (ECIV-7) water solutions

In a proposed "one-stop-shop" comprehensive package of cardiac MR for MV assessment, the NACA serves as the only key factor that can provide a clear-cut distinction between viable and necrotic myocardium (Ni 1998). In addition to the necrosis-targeting property, NACAs also share some exploitable features commonly seen with other existing contrast agents, for instance their relatively long plasma half-life due to protein binding facilitates their utility as BP contrast agents for MR angiography (Fig. 4) especially of coronary arteries; their amphiphilicity, as well as hepatobiliary and renal pathways, may render applications for liver and kidney specific CE. Therefore, with combined specific and nonspecific capacities, NACAs may serve well as versatile or multipurpose contrast enhancing agents (Ni et al. 2002b, 2005a; Ni 2008). A similar example can be found with Gd-BOPTA or trade-named MultiHance® (Cavagna et al. 1997), which is albeit void of necrosis acidity. (Table 1). Indeed, it appears that both porphyrin and nonporphyrin NACAs exert their necrosis-targeting function only when there exists denatured nonviable tissue debris in a living being, otherwise they just behaved like other less specific contrast agents such as ECF contrast agents used, e.g., for the first-pass myocardial perfusion, BP contrast agents used for MRCA, and hepatobiliary and urinary contrast agents for liver and kidney CE (Ni et al. 2005a; Ni 2008).

Nobel Prize laureate Arthur Kornberg (1918–2007) once thus described that you cannot prove a mechanism but you can only disprove a mechanism, which is exactly reflected by the current status of the mechanism research on NACAs. Hofmann et al. attributed the accumulation mechanism of Gadophrin-2 to its binding to albumin in the plasma and interstitium and subsequent trapping in intratumoral necrotic regions (Hofmann et al. 1999). However, this conclusion was disproved in another study in which only Gadophrin-2 but not the strong albumin-binding BP contrast agent MP2269 revealed in vivo necrosis-avidity (Ni et al. 2001). This finding suggests that only few albumin-binding contrast agents possess the NACA property, although to some extent most of the NACAs tend to bind plasma proteins (typically albumin); in other words, the necrosis-avidity is an outstanding feature beyond the general pharmacological process of albumin-binding-mediated drug transportation (Ni et al. 2005a; Ni 2008).

Hypothetically, NACA-induced necrosis targeting may arise in a seemingly chemotactic fashion as follows. While circulating in the blood pool after administration, the agents approach the necrotic region by a time-consuming process of perfusion through residual vessels, extravasation and interstitial diffusion, wherein reperfused infarction is more favorable than an occlusive one for NACA accumulation due to the ampler access. The disintegrated cell-membrane after autolysis facilitates contact and communication of NACAs with the tissue debris, which in turn may further augment the relaxivity due to macromolecular interactions leading always to a striking CE of the infarct (Lauffer 1991). Our recent studies suggest that such local interaction and retention seems strictly chemo-structure dependent rather than a simple trapping or sluggish wash-in and washout because either a slight modification or even an isomer transformation may drastically switch off the necrosis-targeting effect of certain NACA molecules (Ni et al. 2005a; Ni 2008). With respect to target tissues, the size and site of infarcted areas as well as the presence or absence of postischemic reperfusion determine what the NACA-induced necrosis-specific CE looks like (i.e. patchy or bulky, subendocardial or transmural and complete or rim-like) and how long it may persist. Unlike the "detrapping" process of nonspecific contrast agents in a few hours, the eventual clearance of NACAs from necrotic foci typically takes a few days after administration and parallels the

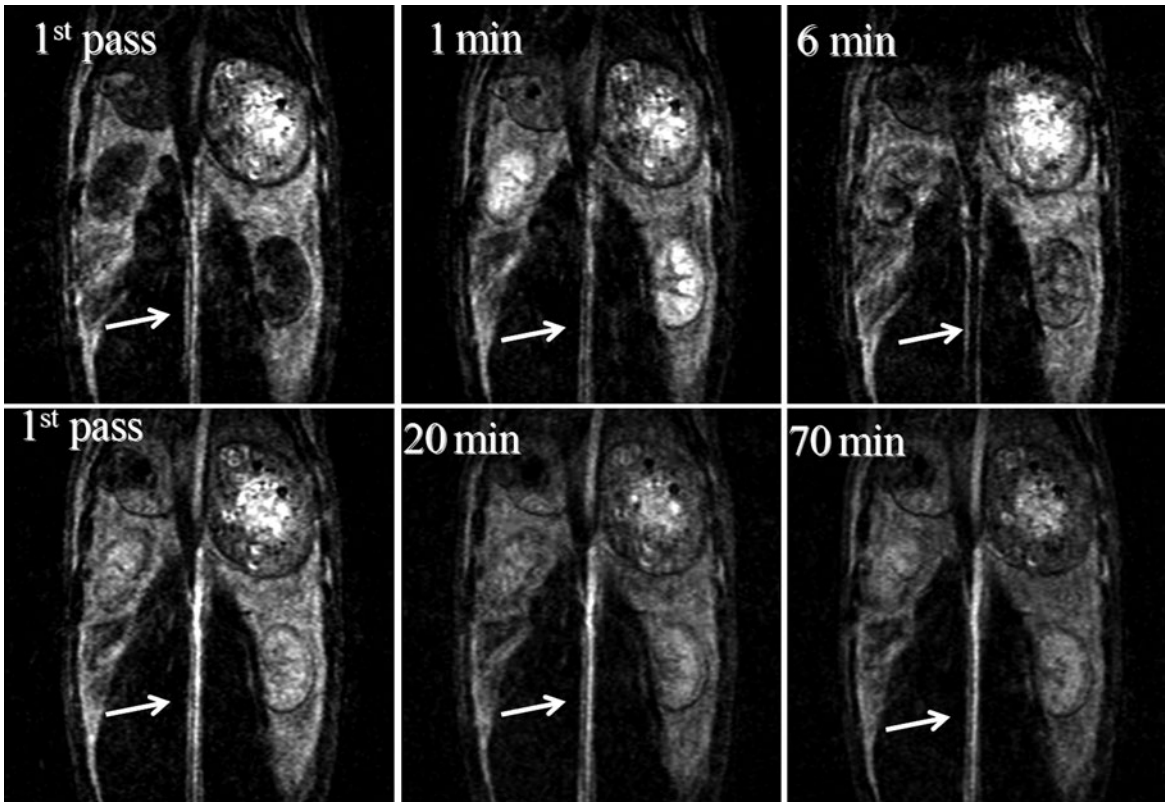

Fig. 4 MR angiography of rabbit aorta (*arrow*) comparing Gd-DTPA at 0.1 mmol/kg (*upper row*) and the nonporphyrin NACA ECIV-7 at 0.05 mmol/kg (*lower row*) display rapid clearance of Gd-DTPA from the circulation and blood-pool (BP) effect of ECIV-7 over 70 min

natural healing process, during which the necrotic tissues are progressively infiltrated and phagocytozed by inflammatory cells (mainly neutrophils, monocytes and/or macrophages) and replaced by the granulation tissue. Therefore the retained NACAs in necrosis are most likely removed together with necrotic materials by phagocytosis, which is supported by more recent results (Ni 2008). Questions remain as to whether the Gd-complex of NACAs is still stable after being taken up by macrophages and what the fate and consequence are of this small necrosis-binding fraction of NACAs in the human body (Ni 1998; Ni et al. 2001a, 2002a, b, 2005a). These have to be further elucidated (Ni 2008). Alternatively, to substitute the bio-incompatible lanthanide element Gd^{3+} with the physiological trace metal element Mn^{2+} in the complex of NACAs may eliminate the concerns about any potential side effects due to gadolinium body retention, which though has proven to be technically challenging until now.

In addition to the above identified porphyrin and nonporphyrin NACAs, there appears to be a large variety of synthetic or natural, endogenous or exogenous substances such as the organic dye Evans blue used for intravital staining (Hamer et al. 2002), the botanical extract hypericin derived from St. Johns Wort (Ni et al. 2005a, 2006b, 2007a, b; Ni 2008; Van de Putte et al. 2008a, b), the heme-related cofactor hematoporphyrin for oxygen transportation (Kessel 1984; Gomer 1989; Nelson et al. 1990; Nelson et al. 1991; Pass 1993), and the urinary-excretable glucarate catabolized from UDP (uridine diphosphate)-glucose (Orlandi et al. 1991), which all seem to share a common necrosis-avidity (Ni 2008). They may firmly bind to the denatured nonviable tissue components or subcellular organelle proteins found in necrotic debris (Ni et al. 2005a). However, unless being inherently colored or fluorescent, their existence can hardly be discerned prior to their labeling with detectable markers as to form radiopharmaceuticals (Ni et al. 2006b; Ni 2008),

magnetopharmaceuticals (Ni et al. 1994, 1998, 2001a, b; Schneider et al. 1995; Marchal et al. 1996, 2000; Herijgers et al. 1997; Ni 1998; Lim et al. 1999; Pislaru et al. 1999; Saeed et al. 1999; Stillman et al. 1999; Wendland et al. 1999; Choi et al. 2000; Jeong et al. 2001; Saeed et al. 2001) and optical contrast media (Ni 2008; Van de Putte et al. 2008a, b).

Furthermore, such generally perceived structural diversity versus functional similarity supports our hypothesis that the avidity of certain chemicals to necrotic debris in the living body is an ever existing phenomenon as part of the natural wound healing process, which has never been well recognized yet deserves to be wisely exploited for medical purposes (Ni et al. 2002a, b, c; Ni et al. 2005a, b; Ni 2008). The key steps to realize this more close-to-nature strategy include understanding the underlying mechanisms of necrosis-avidity and identifying the exact local structural configuration responsible for such a strong physicochemical reaction through careful analyses on the structure–function relationship among all available NACA-like substances. Then, it might be possible to create dedicated, all-in-one, multifunctional contrast agents by purposely tailoring the chemical structures. In contrary to more aggressive and sophisticated approaches such as transgenic or cloning techniques that are prone to potential ecological hazards, such more biocompatible molecular engineering may render additional NACA targetability onto any known nontoxic substances that could be the more physiological life molecules such as vitamins, simple carbohydrates and amino acids, and/or even existing medications already in use such as anti-ischemic and thrombolytic drugs (Ni 2008).

Although side effects and adverse reactions from MRI CAs are much less common than their CT counterparts, one extremely rare adverse reaction from gadolinium-based contrast agents called nephrogenic systemic fibrosis (NSF), a disease of the skin and internal organs that could be debilitating and even fatal (Perazella 2007; Wang et al. 2011b), has drawn public attention and may hinder further development of Gd-based MRI contrast agents including NACAs. Alternatively, taking the advantage of high sensitivity and low toxicity of nuclear medicine, a necrosis-avid tracer agent based on the natural compound hypericin has been developed and validated for MV determination by combined use of single photon emission computed tomography (SPECT) and positron emission tomography (PET) (Ni et al. 2006b; Fonge et al. 2008). The strong affinity of hypericin to necrosis appears to be a few orders of magnitude higher than that of monoclonal antibodies and therefore has been further exploited for developing a novel targeted radiotherapy for the treatment of solid malignancies (Ni et al. 2007a; Li et al. 2011).

Development in this promising direction may open a new horizon certainly for the diagnosis and treatment of diseases including those in clinical cardiology, wherein interdisciplinary collaborations from both academics and industries are warranted. The ultimate beneficiaries would be the entire human society (Ni 2008).

3.5 Potential Plaque- and Thrombus-Specific Contrast Agents

Atherosclerosis and thrombosis are two sequential, interdependent processes causative for acute coronary syndrome (ACS) in patients with chronic cardiovascular disease. Noninvasive, high-resolution MRI may depict 3D microanatomy of the lumen and the vascular wall, characterize the composition of the atherosclerotic plaque, identify lesions vulnerable to erosion or rupture, and therefore provide information about not only the individual high-risk plaques but also overall plaque burden in each patient. These diagnostic messages are critical for making decisions in emergent therapeutic interventions and monitoring progression and regression of atherosclerosis during preventive treatment with, e.g., lipid-lowering drug regiments. It is believed that the high resolution of MRI in combination with sophisticated contrast agents under development may offer the promise of in vivo molecular imaging of the plaque (Fayad 2003).

There have been some developments in favor of plague and thrombus-specific contrast agents that can target either matrices or cellular compositions of the lesion (Table 1).

Fibrin-specific paramagnetic nanoparticles formulated with Gd-DTPA-bis-oleate (BOA) or Gd-DTPA-phosphatidylethanolamine (PE) are reported to have high affinity for fibrin-rich thrombus and the potential to sensitively detect active vulnerable plaques on T1 weighted MRI (Flacke et al. 2001).

Macrocyclic gadolinium-based Gadofluorines prone to form nanomicelles were originally intended for intravenous MR lymphography but have been found also to be able to accumulate in the deeper-

layer intima (rich in foam cells and cellular debris) of the atherosclerotic aorta, leading to a strong positive CE in a genetically hyperlipidemic rabbit model one day after intravenous injection (Barkhausen et al. 2003). Gadofluorine B can also be regarded as another nonporphyrin NACA because of characteristic pharmacodynamic behaviors similar to those commonly seen with other NACAs (Misselwitz, Schering AG, personal communication).

Interestingly, porphyrins and an expanded porphyrin target atherosclerotic plaques too (Spokojny et al. 1986; Vever-Bizet et al. 1989; Young et al. 1994; Woodburn et al. 1996; Barkhausen et al. 2003). Given the clues collected in the studies on porphyrin and nonporphyrin species of NACAs as described in detail above, their multiple pyrrole ring structures are unlikely essential for their preferential accumulation in the nonviable matrices of the plaques. A secondary macrophage uptake following NACA-necrosis binding may also count for their local enrichment. Further studies may reveal that plaque-targeting could well be one of the NACAs' versatile functions.

Besides functioning as positive BP contrast agents for MR angiography and negative contrast agents for lesion delineation in the lymph node, liver and spleen, long-circulating USPIOs also accumulate in atherosclerotic plaques due to active uptake by localized monocytes and macrophages. At a relatively high intravenous dose (e.g., 1 mmol/kg), persistent hypointense signals could be detected over a few days in the wall of atherosclerotic arteries from the same rabbit atherosclerotic models (Schmitz et al. 2000; Ruehm et al. 2001; Kooi et al. 2003). Nonetheless, from the viewpoints of dose efficacy and safety, so far none of these agents have convincingly shown even their remote clinical feasibility.

3.6 Emerging Molecular Imaging Contrast Agents

Molecular imaging can be typically defined as the technology that is established for developing targeted and activatable imaging agents to exploit specific molecular markers, pathways or cellular processes to generate image contrast with appropriate imaging modalities (Jaffer and Weissleder 2004). Strictly speaking, what also fall well into this plausible definition would be many already existing MRI contrast agents, including albumin targeting BP contrast agents, Mn-based intracellular contrast agents and even NACAs that are involved in several pathophysiological processes such as protein binding, chemotactic interaction with necrotic tissues as well as hepatobiliary and renal pathways.

The underpinning hypothesis of this newer approach to imaging is that most disease processes have a molecular basis that can be exploited to (1) detect disease earlier, (2) stratify disease subsets (e.g., active versus inactive), (3) objectively monitor novel therapies by imaging molecular biomarkers and (4) prognosticate disease (Jaffer et al. 2004).

Although still far from the clinical reality in cardiac MRI, the research in this discipline is rapidly advancing with a few leading molecular probes already emerging from laboratory experiments for MRI monitoring cardiovascular pathologic processes or consequences such as atherosclerosis (Winter et al. 2003), thrombosis (Johansson et al. 2001) and heart failure (Schellenberger et al. 2002) as well as therapeutic intervention (Kraitchman et al. 2003; Yang 2010). It has been predicted that in the ensuing years fundamental aspects of cardiovascular biology will be detectable in vivo and that promising molecular imaging agents will be translated into the clinical arena to guide diagnosis and therapy of human cardiovascular illness (Jaffer et al. 2004). For an overview of the fundamentals of cardiovascular molecular imaging approaches, the latest advances in the areas of atherosclerosis, heart failure, and stem cell therapy, the future prospects of translational molecular imaging in the clinical cardiology, as well as future directions that will shape molecular imaging in the postgenomics era, the readers are directed to the details in a recent review article (Chen and Wu 2011). This would again offer opportunities for us to witness whether such anticipations could bring about the breakthroughs that are really beneficial to patients suffering from, and to clinicians fighting against, cardiovascular diseases.

4 Application Scopes of MR Contrast Agents for Cardiac Imaging

As demonstrated in many chapters throughout the contents in this book, the use of contrast agents has undoubtedly become an integral part of the daily practice

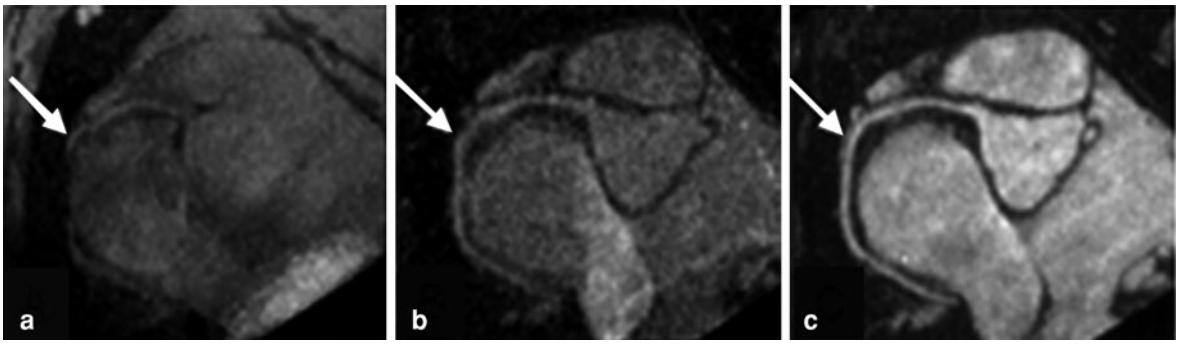

Fig. 5 Comparison of MR angiography of the right coronary artery (*arrow*) in the same pig without contrast agent injection (**a**), with an ECF agent Gd-DTPA at 0.2 mmol/kg (**b**) and with a blood-pool contrast agent Gadomer-17 at 0.1 mmol/kg (**c**) demonstrate the indispensable role of contrast agents especially the blood-pool contrast agent in MR coronary angiography. The images are displayed after multiplanar reconstruction. (by courtesy of Debiao Li, Biomedical Engineering Department, Northwestern University, Evanston, IL, USA; now Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, University of California, Los Angeles, CA, USA)

of cardiac MRI because of their efficacy and their excellent tolerance profile. Their application scopes cover almost all aspects of cardiac MRI, including noninvasive depiction of cardiac anatomy ("Cardiac Anatomy") and real-time monitor of cardiac function ("Cardiac Function"), in particular myocardial perfusion ("Myocardial Perfusion") and cardiac output quantification. The indispensable role of contrast agents is exemplified in comprehensive diagnoses of ischemic ("Ischemic Heart Disease") and nonischemic ("Heart Muscle Diseases") heart diseases as well as heart failure ("Heart Failure and Heart Transplantation") and neoplasms ("Cardiac Masses"). More delicate evaluations with CE MRI on pericardial diseases and valvular heart diseases are addressed in "Pericardial Disease" and Chapter entitled "Valvular Heart Disease", respectively. The state-of-the-art techniques for MR coronary artery imaging is introduced in "Coronary Artery Disease". The images by courtesy of Dr. Debiao Li illustrate well the crucial added value of contrast agents by comparing MRCA in a swine without contrast agent, with an ECF contrast agent and with a BP contrast agent injection (Fig. 5). In addition, the usefulness of contrast agents has also been proven for clinical diagnoses of congenital heart diseases ("Congenital Heart Disease") and abnormalities in great vessels ("Great Vessels"). Similarly, it proves crucial to apply a contrast agent for MR guided catheterized cardiac interventions ("MR-Guided Cardiac Catheterization") and for studying cardiac modeling ("Cardiac Modelling–Future Perspectives").

5 Conclusion

Despite the appreciable maturity with continuing excellence over 30 years of age, it is encouragingly evident that MRI would still have its best years to come toward a "one-stop shop" final solution of noninvasive, 3D, high-resolution real-time imaging of the cardiovascular system particularly boosted by the new inventions and applications of MRI contrast agents.

References

Adzamli IK, Blau M, Pfeffer MA, Davis MA (1993) Phosphonate-modified Gd-DTPA complexes. III: The detection of myocardial infarction by MRI. Magn Reson Med 29:505–511

Ahlstrom KH, Johansson LO, Rodenburg JB, Ragnarsson AS, Akeson P, Borseth A (1999) Pulmonary MR angiography with ultrasmall superparamagnetic iron oxide particles as a blood pool agent and a navigator echo for respiratory gating: pilot study. Radiology 211:865–869

Almen T (1994) The etiology of contrast medium reactions. Invest Radiol 29(suppl 1):S37–S45

Ardenkjaer-Larsen JH, Fridlund B, Gram A et al (2003) Increase in signal-to-noise ratio of >10, 000 times in liquid-state NMR Molecular imaging with endogenous substances. Proc Natl Acad Sci U S A 100:10158–10163

Atkins H, Som LP, Fairchild RG et al (1979) Myocardial positron tomography with manganese-52 m. Radiology 133(3 Pt 1):769–774

Barkhausen J, Ebert W, Debatin JF, Weinmann HJ (2002) Imaging of myocardial infarction: comparison of magnevist and gadophrin-3 in rabbits. J Am Coll Cardiol 39(8):1392–1398

Barkhausen J, Ebert W, Heyer C, Debatin JF, Weinmann HJ (2003) Detection of atherosclerotic plaque with Gadofluorine-enhanced magnetic resonance imaging. Circulation 108(5):605–609

Bhattacharya P, Ross BD, Bunger R (2009) Cardiovascular applications of hyperpolarized contrast media and metabolic tracers. Exp Biol Med (Maywood) 234:1395–1416

Bianco JA, Kemper AJ, Taylor A, Lazewatsky J, Tow DE, Khuri SF (1983) Technetium-99m(Sn2+)pyrophosphate in ischemic and infarcted dog myocardium in early stages of acute coronary occlusion: histochemical and tissue-counting comparisons. J Nucl Med 24:485–491

Bockhorst K, Hohn-Berlage M et al (1990) Proton relaxation enhancement in experimental brain tumors–in vivo NMR study of manganese(III)TPPS in rat brain gliomas. Magn Reson Imaging 8(4):499–504

Bogdanov AA Jr, Weissleder R, Frank HW et al (1993) A new macromolecule as a contrast agent for MR angiography: preparation, properties, and animal studies. Radiology 187: 701–706

Brasch RC (1991) Rationale and applications for macromolecular Gd-based contrast agents. Magn Reson Med 22: 282–287 discussion 300–303

Bremerich J, Saeed M, Arheden H, Higgins CB, Wendland MF (2000) Normal and infarcted myocardium: differentiation with cellular uptake of manganese at MR imaging in a rat model. Radiology 216:524–530

Brurok H, Ardenkjaer-Larsen JH, Hansson G et al (1999) Manganese dipyridoxyl diphosphate: MRI contrast agent with antioxidative and cardioprotective properties? Biochem Biophys Res Commun 254:768–772

Cannon PJ, Maudsley AA, Hilal SK, Simon HE, Cassidy F (1986) Sodium nuclear magnetic resonance imaging of myocardial tissue of dogs after coronary artery occlusion and reperfusion. J Am Coll Cardiol 7:573–579

Cavagna FM, Maggioni F, Castelli PM et al (1997) Gadolinium chelates with weak binding to serum proteins. A new class of high-efficiency, general purpose contrast agents for magnetic resonance imaging. Invest Radiol 32:780–796

Chambon C, Clement O, Le Blanche A, Schouman-Claeys E, Frija G (1993) Superparamagnetic iron oxides as positive MR contrast agents: in vitro and in vivo evidence. Magn Reson Imaging 11:509–519

Chauncey DM Jr, Schelbert HR, Halpern SE et al (1977) Tissue distribution studies with radioactive manganese: a potential agent for myocardial imaging. J Nucl Med 18:933–936

Chen IY, Wu JC (2011) Cardiovascular molecular imaging: focus on clinical translation. Circulation 123:425–443

Chen CW, Cohen JS, Myers CE, Sohn M (1984) Paramagnetic metalloporphyrins as potential contrast agents in NMR imaging. FEBS Lett 168:70–74

Chiu CW, So NM, Lam WW, Chan KY, Sanderson JE (2003) Combined first-pass perfusion and viability study at MR imaging in patients with non-ST segment-elevation acute coronary syndromes: feasibility study. Radiology 226:717–722

Choi C (2002) Contrast washout by MRI identifies stunned myocardium in patients after reperfused myocardial infarction. J Cardiovasc Mag Res 4:19 (Abstract)

Choi SI, Choi SH, Kim ST et al (2000) Irreversibly damaged myocardium at MR imaging with a necrotic tissue-specific contrast agent in a cat model. Radiology 215:863–868

Cresens E, Ni Y et al (2001). Substituted bis-indole derivatives useful as contrast agents, pharmaceutical compositions containing them and intermediates for producing them. Patent Application number PCT/BE01/00192, USA patent 7081472

de Haen C, Morisetti A, Bertani F, Tirone P (1994) The factor time in acute intravenous toxicity studies of contrast media. Invest Radiol 29(suppl 2):S108–S110

Ebert E, Hofmann S (1992) Metallopophyrins: tumor-specific contrast agents? European Magnetic Resonance Forum Foundation. Hamburg, Germany

Elizondo G, Fretz CJ, Stark DD et al (1991) Preclinical evaluation of MnDPDP: new paramagnetic hepatobiliary contrast agent for MR imaging. Radiology 178:73–78

Fayad ZA (2003) MR imaging for the noninvasive assessment of atherothrombotic plaques. Magn Reson Imaging Clin N Am 11:101–113

Fiel RJ, Musser DA, Mark EH, Mazurchuk R, Alletto JJ (1990) A comparative study of manganese meso-sulfonatophenyl porphyrins: contrast-enhancing agents for tumors. Magn Reson Imaging 8:255–259

Fishman JE, Joseph PM, Floyd TF, Mukherji B, Sloviter HA (1987) Oxygen-sensitive 19F NMR imaging of the vascular system in vivo. Magn Reson Imaging 5:279–285

Flacke S, Fischer S, Scott MJ et al (2001) Novel MRI contrast agent for molecular imaging of fibrin: implications for detecting vulnerable plaques. Circulation 104:1280–1285

Flacke S, Allen JS, Chia JM et al (2003) Characterization of viable and nonviable myocardium at MR imaging: comparison of gadolinium-based extracellular and blood pool contrast materials versus manganese-based contrast materials in a rat myocardial infarction model. Radiology 226:731–738

Fonge H, Vunckx K, Wang H et al (2008) Non-invasive detection and quantification of acute myocardial infarction in rabbits using mono-[123I]iodohypericin microSPECT. Eur Heart J 29:260–269

Friedrich J, Apstein CS, Ingwall JS (1995) 31P nuclear magnetic resonance spectroscopic imaging of regions of remodeled myocardium in the infarcted rat heart. Circulation 92:3527–3538

Furmanski P, Longley C (1988) Metalloporphyrin enhancement of magnetic resonance imaging of human tumor xenografts in nude mice. Cancer Res 48:4604–4610

Golman K, Ardenkjaer-Larsen JH, Petersson J, Mansson S, Leunbach SI (2003) Molecular imaging with endogenous substances. Proc Natl Acad Sci U S A 100:10435–10439

Gomer CJ (1989) Photodynamic therapy in the treatment of malignancies. Semin Hematol 26:27–34

Gore J (2003) Out of the shadows—MRI and the Nobel Prize. N Engl J Med 349:2290–2292

Hamer PW, McGeachie JM, Davies MJ, Grounds MD (2002) Evans blue dye as an in vivo marker of myofibre damage: optimising parameters for detecting initial myofibre membrane permeability. J Anat 200(Pt 1):69–79

Hawighorst H, Knapstein PG, Knopp MV, Vaupel P, van Kaick G (1999) Cervical carcinoma: standard and pharmacokinetic analysis of time-intensity curves for assessment of tumor angiogenesis and patient survival. Magma 8:55–62

Herijgers P, Laycock SK, Ni Y et al (1997) Localization and determination of infarct size by Gd-Mesoporphyrin enhanced MRI in dogs. Int J Card Imaging 13:499–507

Heywang SH, Wolf A, Pruss E, Hilbertz T, Eiermann W, Permanetter W (1989) MR imaging of the breast with Gd-DTPA: use and limitations. Radiology 171:95–103

Hindre F, Le Plouzennec M, de Certaines JD, Foultier M, Patrice TT, Simonneaux G (1993) Tetra-p-aminophenylporphyrin conjugated with Gd-DTPA: tumor-specific contrast agent for MR imaging. J Magn Reson Imaging 3:59–65

Hofmann B, Bogdanov A Jr, Marecos E, Ebert W, Semmler W, Weissleder R (1999) Mechanism of gadophrin-2 accumulation in tumor necrosis. J Magn Reson Imaging 9:336–341

Hunold P, Schlosser T, Vogt FM et al (2005) Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. AJR Am J Roentgenol 184:1420–1426

Hustvedt SO, Grant D, Southon TE, Zech K (1997) Plasma pharmacokinetics, tissue distribution and excretion of MnDPDP in the rat and dog after intravenous administration. Acta Radiol 38(4 Pt 2):690–699

Jaffer FA, Weissleder R (2004) Seeing within: molecular imaging of the cardiovascular system. Circ Res 94: 433–435

Jeong AK, Choi SI, Kim DH et al (2001) Evaluation by contrast-enhanced MR imaging of the lateral border zone in reperfused myocardial infarction in a cat model. Korean J Radiol 2:21–27

Jin J, Teng G, Feng Y et al (2007) Magnetic resonance imaging of acute reperfused myocardial infarction: intraindividual comparison of ECIII-60 and Gd-DTPA in a swine model. Cardiovasc Intervent Radiol 30:248–256

Johansson LO, Bjornerud A, Ahlstrom HK, Ladd DL, Fujii DK (2001) A targeted contrast agent for magnetic resonance imaging of thrombus: implications of spatial resolution. J Magn Reson Imaging 13:615–618

Judd RM, Kim RJ (2002) Imaging time after Gd-DTPA injection is critical in using delayed enhancement to determine infarct size accurately with magnetic resonance imaging. Circulation 106 (e6) author reply e6

Kaiser WA, Zeitler E (1989) MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. Radiology 170(3 Pt 1):681–686

Karlsson JO, Brurok H, Eriksen M et al (2001) Cardioprotective effects of the MR contrast agent MnDPDP and its metabolite MnPLED upon reperfusion of the ischemic porcine myocardium. Acta Radiol 42:540–547

Kessel D (1984) Porphyrin localization: a new modality for detection and therapy of tumors. Biochem Pharmacol 33:1389–1393

Khaw BA, Strauss HW, Moore R et al (1987) Myocardial damage delineated by indium-111 antimyosin Fab and technetium-99m pyrophosphate. J Nucl Med 28:76–82

Kim RJ, Lima JA, Chen EL et al (1997) Fast ^{23}Na magnetic resonance imaging of acute reperfused myocardial infarction. Potential to assess myocardial viability. Circulation 95:1877–1885

Kim RJ, Judd RM, Chen EL, Fieno DS, Parrish TB, Lima JA (1999) Relationship of elevated 23Na magnetic resonance image intensity to infarct size after acute reperfused myocardial infarction. Circulation 100:185–192

Kim RJ, Wu E, Rafael A et al (2000) The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 343:1445–1453

Kooi ME, Cappendijk VC, Cleutjens KB et al (2003) Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. Circulation 107:2453–2458

Kraitchman DL, Heldman AW, Atalar E et al (2003) In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction. Circulation 107:2290–2293

Krombach GA, Higgins CB, Gunther RW, Kuhne T, Saeed M (2002) MR contrast media for cardiovascular imaging. Rofo 174:819–829

Krombach GA, Saeed M, Higgins CB, Novikov V, Wendland MF (2004) Contrast-enhanced MR delineation of stunned myocardium with administration of MnCl(2) in rats. Radiology 230:183–190

Kuhl HP, Spuentrup E, Wall A et al (2004) Assessment of myocardial function with interactive non-breath-hold real-time MR imaging: comparison with echocardiography and breath-hold Cine MR imaging. Radiology 231:198–207

La Noce A, Stoelben S, Scheffler K et al (2002) B22956/1, a new intravascular contrast agent for MRI: first administration to humans—preliminary results. Acad Radiol 9(suppl 2):S404–S406

Lauffer RB (1991) Targeted relaxation enhancement agents for MRI. Magn Reson Med 22:339–342 (discussion 343–346)

Lauffer RB, Parmelee DJ, Dunham SU et al (1998) MS-325: albumin-targeted contrast agent for MR angiography. Radiology 207:529–538

Lauterbur P, Mendonca Dias H, Rudin A (1978) Augmentation of tissue proton spin-lattice relaxation rates by in vivo addition of paramagnetic ions. In: LJ Dutton PO, Scarpa A (eds) Frontiers of biological energetics. Academic Press, New York, pp 752–759

Li J, Sun Z, Zhang J, et al (2011) A dual targeting anticancer approach: soil and seed principle. Radiology, published online before print on June 28, doi:10.1148

Lim TH, Choi SI (1999) MRI of myocardial infarction. J Magn Reson Imaging 10:686–693

Lund GK, Higgins CB, Wendland MF, Watzinger N, Weinmann HJ, Saeed M (2001) Assessment of nicorandil therapy in ischemic myocardial injury by using contrast-enhanced and functional MR imaging. Radiology 221: 676–682

Manka R, Paetsch I, Schnackenburg B, Gebker R, Fleck E, Jahnke C (2010) BOLD cardiovascular magnetic resonance at 3.0 tesla in myocardial ischemia. J Cardiovasc Magn Reson 12:54

Marchal G and Ni Y (2000) Use of porphyrin-complex or expanded porphyrin-complex as an infarction localization diagnosticum. US patent No. 6,013,241

Marchal G, Ni Y, Herijgers P et al (1996) Paramagnetic metalloporphyrins: infarct avid contrast agents for diagnosis of acute myocardial infarction by MRI. Eur Radiol 6:2–8

Marchal G, Verbruggen A, Ni Y, Adriaens P, Cresens E (1999) Non-porphyrin compounds for use as a diagnosticum and/or pharmaceutical, Belgium, International application No. PCT/BE99/00104

Mayo-Smith WW, Saini S, Slater G, Kaufman JA, Sharma P, Hahn PF (1996) MR contrast material for vascular enhancement: value of superparamagnetic iron oxide. Am J Roentgenol 166:73–77

Misselwitz B, Schmitt-Willich H, Ebert W, Frenzel T, Weinmann HJ (2001) Pharmacokinetics of Gadomer-17, a new dendritic magnetic resonance contrast agent. Magma 12:128–134

Nelson JA, Schmiedl U (1991) Porphyrins as contrast media. Magn Reson Med 22:366–371 (discussion 378)

Nelson JA, Schmiedl U, Shankland EG (1990) Metalloporphyrins as tumor-seeking MRI contrast media and as potential selective treatment sensitizers. Invest Radiol 25(suppl 1):S71–S73

Ni Y (1998) Myocardial viability. In: Bogaert JDA, Rademakers FE (eds) Magnetic resonance of the heart and great vessels: clinical applications. Medical Radiology—diagnostic imaging and radiation oncology. Springer, Berlin, pp 113–132

Ni Y (2008) Metalloporphyrins and functional analogues as MRI contrast agents. Curr Med Imaging Rev 4:96–112

Ni Y, Marchal G, van Damme B et al (1992) Magnetic resonance imaging, microangiography, and histology in a rat model of primary liver cancer. Invest Radiol 27:689–697

Ni Y, Marchal G, Petré C et al (1994) Metalloporphyrin enhanced magnetic resonance imaging of acute myocardial infarction (abstract). Circulation 90:I–468

Ni Y, Marchal G, Yu J et al (1995) Localization of metalloporphyrin-induced "specific" enhancement in experimental liver tumors: comparison of magnetic resonance imaging, microangiographic, and histologic findings. Acad Radiol 2:687–699

Ni Y, Marchal G, Herijgers P et al (1996) Paramagnetic metalloporphyrins: from enhancers of malignant tumors to markers of myocardial infarcts. Acad Radiol 3(suppl 2): S395–S397

Ni Y, Miao Y, Bosmans H et al (1997a) Evaluation of interventional liver tumor ablation with Gd-mesoporphyrin enhanced magnetic resonance imaging (abstract). Radiology 205(P):319

Ni Y, Petre C, Miao Y et al (1997b) Magnetic resonance imaging-histomorphologic correlation studies on paramagnetic metalloporphyrins in rat models of necrosis. Invest Radiol 32:770–779

Ni Y, Pislaru C, Bosmans H et al (1998) Validation of intracoronary delivery of metalloporphyrin as an in vivo "histochemical staining" for myocardial infarction with MR imaging. Acad Radiol suppl 5(1):S37–S41 (discussion S45–S46)

Ni Y, Miao Y, Cresens E et al (1999) Paramagnetic metalloporphyrins: there exist necrosis-avid and non-avid species. 7th Annual Scientific Meeting for ISMRM, Philadelphia, Pennsylvania, USA

Ni Y, Adzamli K, Miao Y et al (2001a) MRI contrast enhancement of necrosis by MP-2269 and gadophrin-2 in a rat model of liver infarction. Invest Radiol 36:97–103

Ni Y, Pislaru C, Bosmans H et al (2001b) Intracoronary delivery of Gd-DTPA and Gadophrin-2 for determination of myocardial viability with MR imaging. Eur Radiol 11:876–883

Ni Y, Cresens E, Adriaens P et al (2002a) Necrosis-avid contrast agents: introducing nonporphyrin species. Acad Radiol 9(suppl 1):S98–S101

Ni Y, Cresens E, Adriaens P et al (2002b) Exploring multifunctional features of necrosis avid contrast agents. Acad Radiol 9(suppl 2):S488–S490

Ni Y, Dymarkowski S, Chen F, Bogaert J, Marchal G (2002c) Occlusive myocardial infarction enhanced or not enhanced with necrosis-avid contrast agents at MR imaging. Radiology 225:603–605

Ni Y, Bormans G, Chen F et al (2005a) Necrosis avid contrast agents: functional similarity versus structural diversity. Invest Radiol 40:526–535

Ni Y, Huyghe D, Chen F, Bormans G, Verbruggen G, Marchal G (2005b) Research on necrosis avid contrast agents: further expansion of scope. Acad Radiol 12(suppl 5):55–56

Ni Y, Mulier S, Miao Y, Michel L, Marchal G (2005c) A review of the general aspects of radiofrequency ablation. Abdom Imaging 30:381–400

Ni Y, Chen F, Mulier S et al (2006a) Magnetic resonance imaging after radiofrequency ablation in a rodent model of liver tumor: tissue characterization using a novel necrosis-avid contrast agent. Eur Radiol 16:1031–1040

Ni Y, Huyghe D, Verbeke K et al (2006b) First preclinical evaluation of mono-[^{123}I]iodohypericin as a necrosis-avid tracer agent. Eur J Nucl Med Mol Imaging 33:595–601

Ni Y, Van de Putte M, de Witte P, Verbruggen A, Marchal G, Sun Z (2007a) Targeted radiotherapy. Patent application PCT/BE2008/000099

Ni Y, Van de Putte M, Fonge H, Verbruggen A, de Witte P, Marchal G (2007b) Necrosis avid contrast agents (NACAs): evidence in favour of hypothetical mechanisms and new potential applications. Contrast Media Mol Imaging 2:276

Ogan MD, Revel D, Brasch RC (1987) Metalloporphyrin contrast enhancement of tumors in magnetic resonance imaging. A study of human carcinoma, lymphoma, and fibrosarcoma in mice. Invest Radiol 22:822–828

Orlandi C, Crane PD, Edwards DS et al (1991) Early scintigraphic detection of experimental myocardial infarction in dogs with technetium-99 m-glucaric acid. J Nucl Med 32:263–268

Oshinski JN, Yang Z, Jones JR, Mata JF, French BA (2001) Imaging time after Gd-DTPA injection is critical in using delayed enhancement to determine infarct size accurately with magnetic resonance imaging. Circulation 104:2838–2842

Ouwerkerk R, Bottomley PA, Solaiyappan M et al (2008) Tissue sodium concentration in myocardial infarction in humans: a quantitative ^{23}Na MR imaging study. Radiology 248:88–96

Padhani A (2010) Science to practice: what does MR oxygenation imaging tell us about human breast cancer hypoxia? Radiology 254:1–3

Pass HI (1993) Photodynamic therapy in oncology: mechanisms and clinical use. J Natl Cancer Inst 85:443–456

Perazella MA (2007) Nephrogenic systemic fibrosis, kidney disease, and gadolinium: is there a link? Clin J Am Soc Nephrol 2:200–202

Pereira RS, Wisenberg G, Prato FS, Yvorchuk K (2000) Clinical assessment of myocardial viability using MRI during a constant infusion of Gd-DTPA. MAGMA 11:104–113

Pereira RS, Prato FS, Wisenberg G, Sykes J, Yvorchuk KJ (2001) The use of Gd-DTPA as a marker of myocardial viability in reperfused acute myocardial infarction. Int J Cardiovasc Imaging 17:395–404

Pislaru SV, Ni Y, Pislaru C et al (1999) Noninvasive measurements of infarct size after thrombolysis with a necrosis-avid MRI contrast agent. Circulation 99:690–696

Place DA, Faustino PJ, Berghmans KK, van Zijl PC, Chesnick AS, Cohen JS (1992) MRI contrast-dose relationship of

manganese(III)tetra(4-sulfonatophenyl) porphyrin with human xenograft tumors in nude mice at 2.0 T. Magn Reson Imaging 10:919–928

Port M, Corot C, Rousseaux O et al (2001) P792: a rapid clearance blood pool agent for magnetic resonance imaging: preliminary results. MAGMA 12:121–127

Ramani K, Judd RM, Holly TA et al (1998) Contrast magnetic resonance imaging in the assessment of myocardial viability in patients with stable coronary artery disease and left ventricular dysfunction. Circulation 98:2687–2694

Roberts R (1989) Serendipity: accidental discoveries in science. Wiley, New York

Ruehm SG, Corot C, Vogt P, Kolb S, Debatin JF (2001) Magnetic resonance imaging of atherosclerotic plaque with ultrasmall superparamagnetic particles of iron oxide in hyperlipidemic rabbits. Circulation 103:415–422

Saeed M, Bremerich J, Wendland MF, Wyttenbach R, Weinmann HJ, Higgins CB (1999) Reperfused myocardial infarction as seen with use of necrosis-specific versus standard extracellular MR contrast media in rats. Radiology 213:247–257

Saeed M, Lund G, Wendland MF, Bremerich J, Weinmann H, Higgins CB (2001) Magnetic resonance characterization of the peri-infarction zone of reperfused myocardial infarction with necrosis-specific and extracellular nonspecific contrast media. Circulation 103:871–876

Saeed M, Wendland MF, Bremerich GL, Weinmann HJ, Higgins CB (2002) Assessment of myocardial viability using standard extracellular and necrosis specific MR contrast media. Acad Radiol 9(suppl 1):S84–S87

Saini SK, Jena A, Dey J, Sharma AK, Singh R (1995) MnPcS4: a new MRI contrast enhancing agent for tumor localisation in mice. Magn Reson Imaging 13:985–990

Schalla S, Wendland MF, Higgins CB, Ebert W, Saeed M (2004) Accentuation of high susceptibility of hypertrophied myocardium to ischemia: complementary assessment of Gadophrin-enhancement and left ventricular function with MRI. Magn Reson Med 51:552–558

Schellenberger EA, Bogdanov A Jr, Hogemann D, Tait J, Weissleder R, Josephson L (2002) Annexin V-CLIO: a nanoparticle for detecting apoptosis by MRI. Mol Imaging 1:102–107

Schmitz SA, Coupland SE, Gust R et al (2000) Superparamagnetic iron oxide-enhanced MRI of atherosclerotic plaques in Watanabe hereditable hyperlipidemic rabbits. Invest Radiol 35:460–471

Schneider G, Hayd C, Mühler A et al (1995) Contrast enhanced MRI of experimentally induced brain infarctions in rabbits using Bis-Gd-MP as MR contrast agent. 3rd Annual Scientific Meeting. Society of Magnetic Resonance, Nice, France. Society of Magnetic Resonance, p 1144

Schoeder H, Friedrich M, Topp H et al (1993) Myocardial viability: what do we need? Eur J Nucl Med 20:792–803

Spokojny AM, Serur JR, Skillman J, Spears JR (1986) Uptake of hematoporphyrin derivative by atheromatous plaques: studies in human in vitro and rabbit in vivo. J Am Coll Cardiol 8:1387–1392

Stillman AE, Wilke N, Li D, Haacke M, McLachlan S (1996) Ultrasmall superparamagnetic iron oxide to enhance MRA of the renal and coronary arteries: studies in human patients. J Comput Assist Tomogr 20:51–55

Stillman AE, Wilke N, Jerosch-Herold M (1999) Myocardial viability. Radiol Clin North Am 37:361–378 vi

Storey P, Danias PG, Post M et al (2003) Preliminary evaluation of EVP 1001–1: a new cardiac-specific magnetic resonance contrast agent with kinetics suitable for steady-state imaging of the ischemic heart. Invest Radiol 38:642–652

Svensson J, Mansson S, Johansson E, Petersson JS, Olsson LE (2003) Hyperpolarized ^{13}C MR angiography using true-FISP. Magn Reson Med 50:256–262

Taupitz M, Schnorr J, Wagner S et al (2001) Coronary magnetic resonance angiography: experimental evaluation of the new rapid clearance blood pool contrast medium P792. Magn Reson Med 46:932–938

Turner R (1997) Signal sources in bold contrast fMRI. Adv Exp Med Biol 413:19–25

Van de Putte M, Wang H, Chen F, de Witte PA, Ni Y (2008a) Hypericin as a marker for determination of tissue viability after intratumoral ethanol injection in a murine liver tumor model. Acad Radiol 15:107–113

Van de Putte M, Wang H, Chen F, de Witte PA, Ni Y (2008b) Hypericin as a marker for determination of tissue viability after radiofrequency ablation in a murine liver tumor model. Oncol Rep 19:927–932

van der Wall EE, Vliegen HW, de Roos A, Bruschke AV (1996) Magnetic resonance techniques for assessment of myocardial viability. J Cardiovasc Pharmacol 28(suppl 1): S37–S44

van Zijl PC, Place DA, Cohen JS, Faustino PJ, Lyon RC, Patronas NJ (1990) Metalloporphyrin magnetic resonance contrast agents. Feasibility of tumor-specific magnetic resonance imaging. Acta Radiol (suppl) 374:75–79

Vever-Bizet C, L'Epine Y, Delettre E et al (1989) Photofrin II uptake by atheroma in atherosclerotic rabbits. Fluorescence and high performance liquid chromatographic analysis on post-mortem aorta. Photochem Photobiol 49:731–737

Villringer A, Rosen BR, Belliveau JW et al (1988) Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. Magn Reson Med 6:164–174

Wallace RA, Haar JP Jr, Miller DB et al (1998) Synthesis and preliminary evaluation of MP-2269: a novel, nonaromatic small-molecule blood-pool MR contrast agent. Magn Reson Med 40:733–739

Wang H, Miranda Cona M, Chen F et al (2011a) Comparison between nonspecific and necrosis-avid gadolinium contrast agents in vascular disrupting agent-induced necrosis of rodent tumors at 3.0T. Invest Radiol May 13. (Epub ahead of print). PMID: 21577133

Wang Y, Alkasab TK, Narin O et al (2011b) Incidence of nephrogenic systemic fibrosis after adoption of restrictive gadolinium-based contrast agent guidelines. Radiology 260:105–111

Weinmann HJ, Ebert W, Misselwitz B, Schmitt-Willich H (2003) Tissue-specific MR contrast agents. Eur J Radiol 46:33–44

Weissleder R, Lee AS, Khaw BA, Shen T, Brady TJ (1992) Antimyosin-labeled monocrystalline iron oxide allows detection of myocardial infarct: MR antibody imaging. Radiology 182:381–385

Wendland MF, Saeed M, Lund G, Higgins CB (1999) Contrast-enhanced MRI for quantification of myocardial viability. J Magn Reson Imaging 10:694–702

Winter PM, Morawski AM, Caruthers SD et al (2003) Molecular imaging of angiogenesis in early-stage atherosclerosis with alpha(v)beta3-integrin-targeted nanoparticles. Circulation 108:2270–2274

Woodburn KW, Fan Q, Kessel D et al (1996) Phototherapy of cancer and atheromatous plaque with texaphyrins. J Clin Laser Med Surg 14:343–348

Yang X (2010) Interventional molecular imaging. Radiology 254:651–654

Young SW, Sidhu MK, Qing F et al (1994) Preclinical evaluation of gadolinium (III) texaphyrin complex. A new paramagnetic contrast agent for magnetic resonance imaging. Invest Radiol 29:330–338