

# The Future of Magnetic Resonance Imaging Contrast Agents

## Description

Gadolinium (Gd)-based contrast agents (GBCAs) dominate the current contrast-enhanced magnetic resonance imaging (CE-MRI) market and are proven to increase the efficacy of diagnostic magnetic resonance imaging (MRI) scans. However, in the future it is likely that a personalized combination of contrast enhancement and image processing techniques will be used to optimize diagnosis and treatment planning while minimizing risk and cost. This activity is designed to educate radiologists about the future of MRI contrast agents, including high relaxivity macrocyclic GBCAs, alternatives to GBCAs, and imaging processing techniques.

## Learning Objectives

Upon completing this activity, the reader should be able to:

- Identify potential limitations of current gadolinium contrast agents;
- Recognize possible advantages and disadvantages of alternative metal-based paramagnetic contrast agents and metal-free contrast agents; and,
- Explain how image analysis methods may provide radiologists the information they need to make accurate clinical assessments without contrast agents.

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## Target Audience

- Radiologists
- Related Imaging Professionals

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# The Future of Magnetic Resonance Imaging Contrast Agents

Laura E Minton; Renu Pandit; WR Willoughby, PhD; Kristin K Porter, MD, PhD

*Editor's note: This is the second part of a two-part series. The first part appeared in the November–December 2021 issue of Applied Radiology.*

Gadolinium (Gd)-based contrast agents (GBCAs) dominate the current contrast-enhanced magnetic resonance imaging (CE-MRI) market and are proven to increase the efficacy of diagnostic magnetic resonance (MR) scans.<sup>1</sup> Adverse side effects of GBCAs are uncommon,<sup>2</sup> and the reported GBCA-associated incidence of nephrogenic systemic fibrosis (NSF) has declined due to pre-MR patient screening and replacement of linear GBCAs with macrocyclic compounds.<sup>3</sup> Recently, however, there has been concern about Gd de-chelation from GBCAs and possible effects of bioaccumulation in the central nervous system.<sup>4-7</sup>

The future of MR contrast may see a replacement of Gd with alternative metals, such as manganese (Mn) or iron-based agents. Metal-based paramagnetic contrast agents are limited by the intrinsic toxicity of many metal ions, their persistence in tissue, and their ability to provide only one type of contrast.<sup>8</sup> This has led researchers to pursue contrast mechanisms that do not require metals. A promising example is chemical exchange dependent saturation transfer (CEST) MRI, which can generate clinically useful contrasts using diamagnetic molecules with exchangeable protons in amine, amide and hydroxyl groups.<sup>9-15</sup>

Recent work has also been done to improve the relaxivity and in vivo

lifetime of metal-free, nitroxide-based contrast agents.<sup>16</sup> Alternatively, the development of sequences, arrays of coils, k-space strategies, stochastic imaging, and machine learning-based image analysis procedures<sup>17</sup> have provided numerous opportunities to improve image contrast in MRI.<sup>18</sup> MRI sequences and post-processing techniques may be developed to replace or decrease the use of contrast agents (for example 4D MRI instead of MRA and CEST imaging) or hybrid technologies such as PET/MR may rely on radiotracers in lieu of MR contrast agents.<sup>19</sup>

## Higher-relaxivity Gadolinium agents

Given the history of NSF and Gd retention in the brain and other organs, the lowest GBCA dose should be used that provides enough enhancement for diagnosis in routine

practice.<sup>20</sup> Thus, the development of next-generation high-relaxivity GBCAs meets a real medical need. By revisiting the GBCA dose-response relationship, such agents would allow reduction of the injected Gd dose with the same efficacy or improvement in the rate of lesion detection and characterization with the usual dose.

An example of a high-relaxivity GBCA is the blood pool agent gadofosveset trisodium, which non-covalently binds to human serum albumin at the proportion of 80% to 90%.<sup>21</sup> Gadofosveset trisodium was indicated for MRA; however, after poor sales, production was discontinued in 2017. Another high-relaxivity macrocyclic agent, Gadopiclenol, is currently in phase III clinical trials.<sup>22</sup> With its higher relaxivity, Gadopiclenol may only require half of a standard Gd dose to reach the same efficacy compared to agents already available.<sup>23</sup>

## Manganese-based agents

Manganese (Mn)-based products have been identified as a potential alternative to GBCAs.<sup>24</sup> Two Mn-based agents, commercially sold as Teslascan (Mangafodipir) and LumenHance, have been available in the past,<sup>25</sup> but were withdrawn from the US market due to toxicity concerns and poor

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**Table 1. Next-generation MR contrast imaging enhancement mechanisms**

CLASS	PROS	CONS	EXAMPLES
Gd-based, high relaxivity	<ul style="list-style-type: none"> <li>Lower dosages for relaxivity comparable to GBCAs</li> <li>Improved lesion detection</li> </ul>	<ul style="list-style-type: none"> <li>Possible Gd accumulation</li> </ul>	<ul style="list-style-type: none"> <li>Gadofosveset trisodium (discontinued)</li> <li>Gadopicleenol (phase III trials)</li> </ul>
Mn-based	<ul style="list-style-type: none"> <li>Comparable relaxivity, CE-MRA to GBCAs</li> </ul>	<ul style="list-style-type: none"> <li>Possible neurotoxicity</li> <li>Not commercially available</li> </ul>	<ul style="list-style-type: none"> <li>Mn-DPDP (discontinued)</li> <li>Mn-PyC3A (preclinical trials)</li> </ul>
Fe-based	<ul style="list-style-type: none"> <li>Favorable for imaging metastatic disease</li> <li>Long intravascular half-life</li> <li>Superior CE-MRA</li> </ul>	<ul style="list-style-type: none"> <li>Possible hypersensitivity reactions</li> </ul>	<ul style="list-style-type: none"> <li>Ferrotran (approved in Netherlands)</li> <li>Ferumoxtyol (not FDA approved for CE-MRI)</li> </ul>
CEST	<ul style="list-style-type: none"> <li>Metal-free</li> <li>Can be non-invasive</li> <li>Molecular imaging applications</li> </ul>	<ul style="list-style-type: none"> <li>Longer imaging times</li> <li>Specialized, high-SAR sequences</li> <li>Under active development</li> </ul>	<ul style="list-style-type: none"> <li>Iopamidol, iopromide (pHe)</li> <li>Endogenous lactate (phenotype tumors)</li> <li>Dextrans + PSMA ligands (prostate cancer)</li> </ul>
ORCAs	<ul style="list-style-type: none"> <li>Metal-free</li> <li>ROS imaging</li> </ul>	<ul style="list-style-type: none"> <li>Limited lifetime</li> <li>Limited relaxivity</li> <li>In preclinical trials</li> </ul>	<ul style="list-style-type: none"> <li>BASP-nitroxide</li> <li>TMV nitroxyls</li> </ul>
Image processing	<ul style="list-style-type: none"> <li>Metal-free</li> <li>Non-invasive</li> </ul>	<ul style="list-style-type: none"> <li>Reproducibility under investigation</li> </ul>	<ul style="list-style-type: none"> <li>Generative adversarial networks (segmentation)</li> </ul>

sales. As of 2021, no Mn-based contrast agent is currently commercially available, and it is unknown whether Mn products will become a safer alternative to GBCAs as approved MR contrast agents.

Manganese dipyridoxildiphosphate (Mn-DPDP), marketed as Teslascan (Mangafodipir), was first used in humans as an intravenous, paramagnetic, hepatobiliary MR contrast agent for the detection and characterization of liver lesions.<sup>25</sup> This water-soluble molecule was taken up selectively by hepatocytes; it dissociated in vivo into the metal and chelate. The Mn was absorbed intra-cellularly and excreted in bile, while the chelate was eliminated via renal filtration.<sup>25</sup> More recently, Mn-PyC3A was shown in studies with baboons and mice to provide comparable relaxivity and contrast enhanced MR angiography to GBCAs.<sup>26,27</sup> The PyC3A component serves as a chelator, which helps to prevent hepatic uptake and optimize elimination.<sup>26</sup>

These studies demonstrate that Mn-PyC3A is excreted both renally

and partially by the hepatobiliary system, with near complete elimination (>99.5% after 24 hours).<sup>28</sup> This partial hepatobiliary elimination allows for delayed phase visualization of liver metastases in mouse models.<sup>28</sup> PET-MRI studies in rat models with renal impairment showed that Mn-PyC3A was eliminated more completely from nephrectomy rats than gadoterate meglumine was, and that this was the result of increased hepatobiliary excretion.<sup>29</sup> Although more studies are needed, these studies indicate that Mn-PyC3A has potential as a contrast agent in humans.

Studies of industrial workers exposed to Mn-containing fumes, suggest that Mn may induce neurotoxicity in human brains with behavioral consequences and cognitive deficits because of decreased globus pallidus and cerebellar volume.<sup>30</sup> This is an important consideration, given that the Gd retention in the brain has, as of yet, not shown neurotoxicity. As such, it is uncertain whether the benefit-risk balance of Mn-based agents will ultimately reach or exceed that of GBCAs.

## Iron-based agents

The identification of iron-based agents as a potential alternative to GBCAs has led to extensive preclinical and clinical research, although the only MR contrast agent commercially available is Ferrotran (formerly Combidex, ferumoxtran-10), an iron oxide nanoparticle approved in the Netherlands for detection of metastatic disease in lymph nodes.<sup>31</sup> Iron oxide is a super-paramagnetic agent that leads to a disproportionate shortening of the T2 time, resulting in a strong decrease in the MR signal and thus producing a negative contrast in vivo. Additionally, when iron oxide particles are present at low concentration in the blood stream, they can also produce a signal enhancement on T1 sequences with very short echo times and produce positive contrast. After intravenous administration, the ultra-small formulations of superparamagnetic particles of iron oxide are removed from the blood by the reticuloendothelial system in the liver, spleen, and lymph nodes, a helpful distribution when considering imaging metastatic

disease. These agents also have an extremely long intravascular half-life, making iron-based agents an attractive choice for MRA.<sup>32</sup>

Feraheme (ferumoxytol) has been approved for iron supplementation in patients with end-stage renal disease. While it has been used to visualize the vasculature in children and adults with MR, it is not FDA approved as an MRI contrast agent. Moreover, its labeling includes a boxed warning concerning the risk of fatal and serious hypersensitivity reactions as well as a contraindication for patients who have had an allergic reaction to any intravenous iron replacement product.<sup>33</sup> In a 2015 study with 15 renal transplant participants, ferumoxytol was shown to deliver superior vessel sharpness with high-resolution steady state MRA and equivalent signal to noise ratio when compared to standard first-pass MRA. Because it is not Gd based, ferumoxytol can be used without concern for NSF or Gd retention.<sup>34</sup>

### Chemical exchange saturation transfer (CEST) imaging

A relatively new class of contrast agents known as CEST agents have been studied and developed since 2000. In a process similar to magnetization transfer contrast (MTC), these agents provide contrast via selective radiofrequency (RF) saturation of the nuclear magnetization of protons on the agent molecules and subsequent chemical exchange of these saturated protons with water protons. After many successive saturation pulses and exchanges, a detectable decrease in the nearby water signal accumulates and generates contrast enhancement.

An appealing advantage of many of these contrast agents is the lack of paramagnetic metal that may lead to side effects or lasting health effects. Other promising features of the technique are its ability to provide molecularly specific information and

its wide applicability. However, CEST imaging sequences are currently limited by long acquisition times, increased specific absorption of radiation (SAR), and strong dependence on experimental factors like field inhomogeneities.<sup>35</sup>

The CEST technique using contrast agents like iopamidol and iopromide has been successful in measuring extracellular pH (pHe) for the detection and characterization of tumors and even for the evaluation of tumor acidosis.<sup>9,10,13</sup> Since the only requirement for a compound to be utilized for CEST contrast is having a proton that is exchangeable with water, the CEST technique can be used for clinically relevant molecular imaging with MRI.<sup>36</sup> For example, extracellular lactate, a diamagnetic CEST (diaCEST) agent was successfully imaged using a paramagnetic shift reagent.<sup>37</sup> This technique could eventually be used to detect not only the presence of tumors, but also their specific phenotypes. Diamagnetic dextran, a glucose polymer that is already clinically indicated as a plasma volume expander, has been modified with prostate-specific membrane antigen (PSMA) targeting ligands to provide MRI contrast specifically for prostate cancer without metals or radiotracers.<sup>38</sup>

The CEST technique also opens the door to theranostic applications without the use of radiotracers. Many pharmaceuticals cannot be imaged directly with MRI but contain exchangeable protons. This provides the possibility of image-guided drug delivery and pharmacokinetic studies without the risks associated with ionizing radiation.<sup>36</sup> CEST contrast, however, requires specialized MR sequences that can increase SAR and prolong clinical examination times.

### Organic radical contrast agents (ORCAs)

Another class of metal-free contrast agents uses the magnetic interaction of unpaired electrons

on organic radical moieties and nearby water protons to modulate MR contrast. These organic radical contrast agents (ORCAs) provide another avenue to metal-free MR contrast enhancement, and since they are paramagnetic, do not require specialized pulse sequences with long, adiabatic RF pulses to provide contrast enhancement, like CEST agents. However, the stable organic radical nitroxide has only one unpaired electron, compared to the seven unpaired electrons on the Gd<sup>3+</sup> ion or five unpaired electrons on the Fe<sup>3+</sup> ion, which limits the relaxivity and contrast enhancement provided by the molecule.<sup>39</sup>

The appeal of metal-free organic contrast agents has led to broad interest in addressing the limitations of nitroxide-based MR contrast, which include the relatively low relaxivity and rapid metabolic reduction of nitroxide to molecules that do not enhance contrast.<sup>39</sup> Rajca, et al, demonstrated that nitroxide radicals on polymeric scaffolds can increase the lifetime of ORCAs in vivo and provide proton relaxivity  $r_1$  close to that of GBCAs, about  $5 \text{ mM}^{-1} \text{ s}^{-1}$ . Nguyen, et al, showed that synthesizing nitroxide radicals into brush-arm star polymeric (BASP) structures substantially increases both the relaxivity due to a larger concentration of paramagnetic species and the half-life of ORCAs in vivo. MR contrast enhancement with  $r_2$  relaxivities greater than  $1000 \text{ mM}^{-1} \text{ s}^{-1}$  in rodents was observed up to 24 hours post-injection of BASP-ORCAs.<sup>40</sup>

Nguyen, et al, also showed the usefulness of BASP-ORCAs as theranostic agents, where the relaxivity could be modulated with drug-activated triggers.<sup>41</sup> Dharmawardana, et al, synthesized nitroxyl groups onto rigid tobacco mosaic virus (TMV) protein coats to achieve  $r_1$  relaxivity of  $1.5 \text{ mM}^{-1} \text{ s}^{-1}$  and  $r_2$  relaxivity of  $4.5 \text{ mM}^{-1} \text{ s}^{-1}$  at 1.5 T, which is on the order of relaxivities of GBCAs.<sup>42</sup> TMV-based contrast agents could also be

used to image superoxide production in cases of deep tissue injury due to their unique structure that prevents the quenching of fluorophores by nearby free radicals.<sup>42</sup> None of these compounds have progressed further than preclinical testing, however, and further developments need to be made before ORCAs are approved for clinical use.

### Contrast Without the Agents

Ongoing research makes contrast agents safer, more effective, and more biochemically specific for precision diagnoses. On the other hand, recent developments in the field of radiomics, machine learning, and image processing algorithms are taking steps toward lessening or even eliminating the need for intravenous injection of foreign materials into the body to improve the diagnostic efficacy of MRI. Advanced machine learning algorithms based on generative adversarial networks have been developed that, when trained, provide approximately the same segmentation information from non-CE MRI of liver lesions and cardiac cine imaging without the use of contrast agents compared to the gold-standard CE-MRI.<sup>17,43</sup> These image analysis methods can provide radiologists with the information they need to make accurate clinical assessments without expensive, potentially unsafe use of GBCAs. However, more work needs to be done to evaluate the reproducibility of radiomic data provided by such algorithms across a broader population.

### Conclusion

Despite significant efforts in pre-clinical, translational, and clinical research to identify and develop alternative Gd-free diagnostic agents, it is most probable that the next generation of MRI contrast agents will still include Gd, suggesting that true high relaxivity macrocyclic GBCAs may be

at least in the near future. Looking forward, a personalized combination of contrast enhancement and image processing techniques is likely to be used to optimize diagnosis and treatment planning while minimizing risk and cost.

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