College of Health and
Medical Technologies
Department of Radiology
Technologies

CONTRAST AGENTS IN MRI

2nd stage

By
MSc. Ahmed Salman Jasim

2023

HISTORICAL DEVELOPMENT

Shortly after the introduction of clinical MRI, the first contrast enhanced human MRI studies were reported in 1981 using ferric chloride as a contrast agent in the gastrointestinal tract. In 1984, Carr et al. were the first to demonstrate the use of a gadolinium compound as a diagnostic intravascular MRI contrast agent. Currently, around one-quarter of all MRI examinations are performed with contrast agents.

MECHANISM OF ACTION

- MRI contrast agents act indirectly by altering the magnetic properties of hydrogen ions (protons) in water and lipid, which form the basis of the image in MRI. It is the paramagnetic effect of the contrast agent rather than the agent itself which is imaged. To increase the inherent contrast between tissues, MRI contrast agents must alter the rate of relaxation of protons within the tissues. The changes in relaxation vary, and therefore different tissues produce differential enhancement of the signal (Figs 2.2 and 2.3).
- These figures show that, for a given time t, if the T1 relaxation is more rapid, then a larger signal is obtained (brighter images), but the opposite is true for T2 relaxation, where more rapid relaxation produces reduced signal intensity (darker images). There are different means by which these effects on protons can be produced using a range of MRI contrast agents.

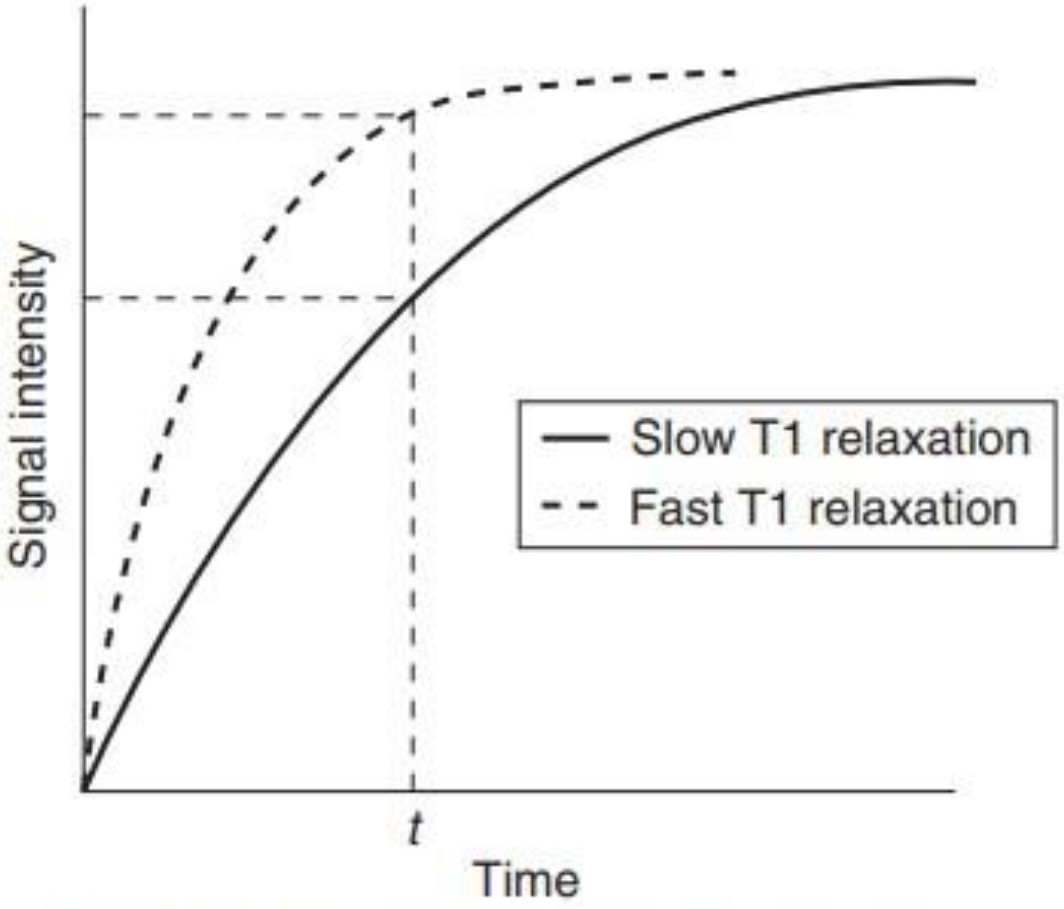

Fig. 2.2 Signal intensity and T1 relaxation time.

MRI contrast agents interact with the magnetic moments of the protons in the tissues by exerting a large magnetic field density (aproperty imparted by their unpaired electrons) and thereby altering their T1 relaxation time (longitudinal relaxation rate), producing a change in signal intensity (see Fig. 2.2). The electron magnetic moments also cause local changes in the magnetic field, which promote more rapid proton dephasing and therefore shorten the T2 relaxation time (transverse relaxation rate). All contrast agents shorten both T1 and T2 relaxation times, but some will predominantly affect T1 and others predominantly T2

Agents with unpaired electron spins are potential contrast material for use in MRI. These may be classified under three headings:

1. **Ferromagnetic**—These retain magnetism even when the applied field is removed. This may cause particle aggregation and interfere with cell function, and are therefore unsafe for clinical use as MRI contrast agents.
2. **Paramagnetic**—e.g. gadolinium contrast agents are by far the most widely used MRI contrast agents. Their maximum effect is on protons in the water molecule, shortening the T1 relaxation time and hence producing increased signal intensity (white) on T1 images (see Fig. 2.2).
3. **Superparamagnetic**—e.g. particles of iron oxide (Fe_3O_4). These cause abrupt changes in the local magnetic field, which results in rapid proton dephasing and reduction in the T2 relaxation time, and hence producing decreased signal intensity (black) on T2 images (see Fig. 2.3). Superparamagnetic compounds are available in preparations for providing gastrointestinal contrast.

GADOLINIUM

Gadolinium (Gd) is a toxic heavy metal with seven unpaired electrons. It is rendered nontoxic and soluble by chelation with large organic molecules, forming a stable complex around the gadolinium. Gadolinium chelates represent the largest group of MRI contrast media and can either be injected intravenously or used as an oral preparation.

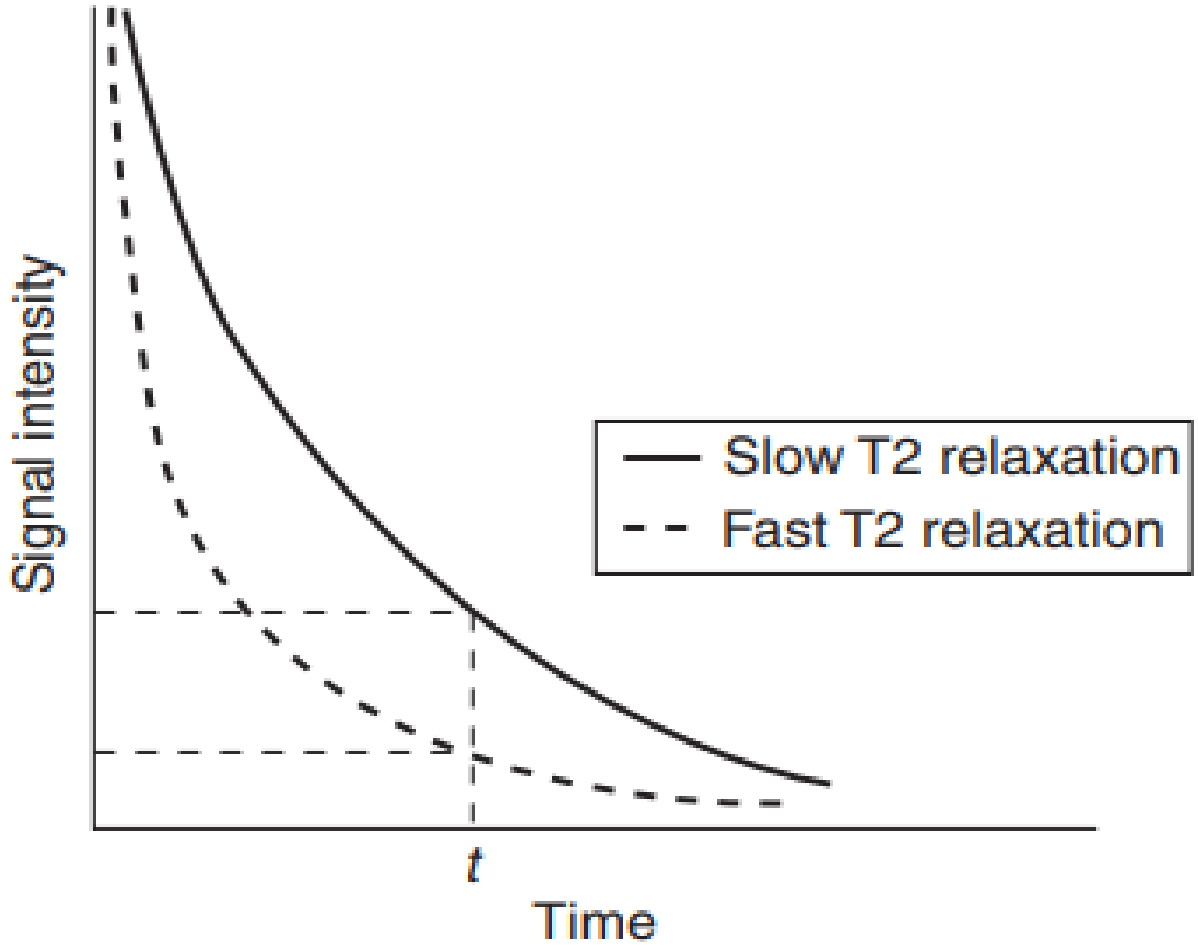

Fig. 2.3 Signal intensity and T2 relaxation time.

Gd contrast agents are available in three forms:

1. Extracellular fluid (ECF) agents—By far the most commonly used form of gadolinium. Includes:

(a) Gd-diethylenetriaminepenta-acetic acid (DTPA),
Gadopentetatedimeglumine (Magnevist)

(a) (b) Gd-DTPA-bismethylamide, Gadodiamide (Omniscan)

(b) (c) Gd-DO3A, Gadoteridol (ProHance).

These all contain a central, strongly paramagnetic gadolinium ion within an eight-coordinate ligand and a single water molecule forming a stable nine-coordinate complex. After intravenous injection, they circulate within the vascular system and are excreted unchanged by the kidneys. There is a wide range of indications for ECF agents, including improved detection rates and more accurate delineation and characterization of tumours. The ECF agents do not cross the normal, intact blood–brain barrier, but will extravasate across where it is abnormal, and thus they are very effective in demonstrating many forms of CNS pathology. ECF agents are used for angiography but rapidly leak out of the vascular space into the interstitial space, and thus are used only for dynamic arterial studies.

2. Liver agents—The excretion pathway of the gadolinium chelates can be modified to produce compounds such as Gd-BOPTA, Gadobenate (Multihance) and Gd-DTPA, and Gadoxetate disodium (Primovist), which are taken up by hepatocytes and excreted intact via the hepatobiliary system. These agents are used to (a) improve the detection of liver lesions that do not contain hepatocytes (and therefore do not take up the contrast), such as liver metastases; and (b) to characterize lesions that do take up the contrast, such as hepatocellular carcinoma. They can also be used to provide positive contrast (T1 weighted) imaging of the hepatobiliary system.

3. Blood pool agents—These bind reversibly to human albumin, forming large molecules with higher relaxivity and longer persistence in the vascular space than ECF agents, allowing a wider range of vascular imaging (e.g. Gadofosvesettrisodium; Vasovist).

Dose

For ECF gadolinium agents, usually 0.1 mmolkg−1 body weight; up to 0.2 mmolkg−1 when used in low-field magnets.

Adverse Reactions

Gadolinium contrast agents are very safe and well tolerated; they have a lower incidence of adverse reactions than iodinated contrast agents. Adverse reactions to gadolinium are mostly mild and selflimiting. **These can be divided into acute and delayed reactions.**

Table 2.5 Acute Adverse Reaction Rates for Gadolinium Contrast Agents

Study	Number of Examinations	Mild (%)	Moderate (%)	Severe (%)	Fatal
Morgan et al.[2]	28,078	0.63	0.02	0.014	None
Abujudeh et al.[3]	32,659	0.13	0.018	0.006	None
Dillman et al.[4]	78,353	0.05	0.012	0.005	None
Hunt et al.[5]	158,439	0.03	0.007	0.0025	None

Acute adverse reactions

1.**mild—**e.g. nausea, vomiting, headache, dizziness, shaking, altered taste, itching, rash, facial swelling

2.**moderate**—e.g. tachycardia or bradycardia, hypertension, generalized erythema, dyspnoea, bronchospasm, wheezing, mild hypotension

3.**severe**—e.g. laryngeal oedema (severe or rapidly progressive), unresponsiveness, cardiopulmonary arrest, convulsions, clinically manifest cardiac arrhythmias.

Patients with a history of previous adverse reaction to gadolinium contrast agents have an increased likelihood of experiencing adverse reactions, with a 30% recurrence rate of hypersensitivity reactions in those with previous reactions.6 Those with asthma, documented allergies, or

Delayed adverse reactions

1.Renal impairment—When used at the standard doses listed previously, gadolinium contrast agents do not cause significant impairment of renal function.

2. **Nephrogenic systemic fibrosis (NSF)—**This rare but significant systemic disorder, first described in 2000, is characterized by increased deposition of collagen with thickening and hardening of the skin, contractures, and in some patients, clinical involvement of other tissues. Most cases are mild, but an estimated 5% have a progressive debilitating course. NSF occurs in patients with renal disease, and almost all patients with NSF have been exposed to gadolinium-based contrast agents within 2–3 months prior to the onset of the disease.

The mechanism by which renal failure and gadolinium-based contrast agents trigger NSF is not known

In 2009 the European Medicines Agency Committee for Medicinal Products for Human Use Scientific Advisory Group categorized gadolinium products according to risk of causing nephrogenic systemic fibrosis:

1. **Low risk**—Macrocyclic chelates including gadoteratemeglumine (Dotarem), gadoteridol (Prohance), gadobuterol (Gadovist).

2. **Medium risk**—Linear ionic chelates including gadoxetic acid (Primovist), gadobenatedimeglumine (Multilane).

3. **High risk**—Linear non-ionic chelates including gadodiamide (Omniscan) and linear ionic chelates including gadopentetatedimeglumine (Magnevist). Preventative guidelines have been shown to be

Precautions for prevention of adverse reactions

Detailed guidelines are available from the American College of Radiology, Royal College of Radiologists, and the European Society of Urogenital Radiology .These form the basis for the following advice.

Acute adverse reactions

1. Identify patients at increased risk of reaction because of previous gadolinium reaction, asthma, allergies, or previous adverse reaction to iodinated contrast.

2. For those at increased risk, consider an alternative test not requiring a gadolinium agent.

3. If proceeding with i.v. gadolinium contrast:

(a) Patients who have previously reacted to one gadolinium-based contrast agent should be injected with a different agent if they are restudied.

(b) Those with an increased risk of adverse reaction should be monitored more closely after injection.

Delayed adverse reactions

1. Identify patients at risk of NSF—particularly patients with renal impairment, patients in the perioperative period after liver transplant, infants, neonates, and the elderly.

2. For patients at increased risk, consider an alternative test not requiring .

3.If proceeding with gadolinium contrast, the use of high-risk gadolinium contrast medium is contraindicated (see previous notes). The lowest possible dose of low- or medium-risk gadolinium-based contrast agent should be used.a gadolinium agent

GASTROINTESTINAL CONTRAST AGENTS

MR enteroclysis is increasingly widely used in the evaluation of the small bowel. During this examination, 1–3 L of 0.5% methylcellulose solution in water, infused via a nasogastric tube, is used as the gastrointestinal tract contrast agent.

Other contrast materials can be used to distinguish the bowel from adjacent soft-tissue. As with CT, bowel contrast agents must be palatable and need to mix readily with the bowel contents to ensure even distribution.

They can be divided into two groups: positive agents and negative agents.

Positive Agents

These include fatty oils and gadolinium. They act by T1 shortening effects and appear white on T1 images.

Negative Agents

These include ferrite and barium sulphate (60%–70% w/w). These act by T2 shortening effects and appear black on T2 images

CONTRAST AGENTS IN ULTRASONOGRAPHY

- Since the first reported use of ultrasound (US) contrast was published in the late 1960s, describing the intracardiac injection of agents during echocardiography, considerable progress has now been made in the development and clinical application of US contrast agents, and these are now used increasingly to assess vascularity and tissue perfusion. US contrast agents contain **microbubbles of air**, nitrogen, or fluorocarbon gas coated with a thin shell of material **such as albumin, galactose, or lipid**.
- The contrast is usually injected intravenously, but in order to cross the pulmonary capillary bed and reach the systemic arterial circulation, the microbubbles must be 3–5 μm diameter, approximately the size of a red blood cell. Bubbles of this size only remain intact for a very short time in blood. The bubbles do not pass through the vascular endothelium and therefore provide pure intravascular contrast. The effect of a bolus injection is to increase the echo signal from blood by a factor of 500–1000. After about 5 min, the gas from the bubbles diffuses into the blood, and the very small mass of shell material is then metabolized.1

Clinical applications of US contrast agents include the following:

1.Identification and characterization of solid lesions, particularly in the liver,4 but also in the spleen, pancreas, kidney, prostate, ovary, and breast.

2. To assist US-guided interventions such as biopsy.

3. Voiding urosonography can be used to detect vesico-ureteric reflux in children; here US contrast is administered directly into the bladder.

4. Assessment of fallopian tubal patency at hysterosonosalpinography.

5. Determination of disease activity in patients with inflammatory bowel disease.

There are a number of different microbubble contrast agents available. Levovist is one of the most widely used; it consists of microbubbles of air enclosed by a thin layer of palmitic acid in a galactose solution and is stable in blood for 1–4 min. SonoVue, another microbubble contrast agent, is an aqueous suspension of stabilized sulphur hexafluoride microbubbles. The US agents in clinical use are well tolerated, and serious adverse reactions are rarely observed. These agents are not nephrotoxic and may be used in patients with any level of renal function.5 Allergic-type reactions occur rarely, and adverse events are usually mild and self-resolving.

reference

Watson, N. & Jones, H. chapman& Nakielnys ‘’Guide to Radiological procedures’’ , 7th edition, Elsevier Health Sciences, 2017.