Contrast agents and molecular imaging

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Outline

- Contrast agents
  - Definition and classification
  - Design requirements
  - MR contrast mechanisms
  - Relaxivity theory of CA
  - Gadolinium complex
  - Tissue specific contrast agents(application)
- MR Molecular imaging

Definition and classificaiton

- Contrast agents (CA) are chemical substances introduced to the anatomical or functional region being imaged, to increase the differences between different tissues or between normal and abnormal tissue, by altering the relaxation times.
- Classification
  - paramagnetic, superparamagnetic
  - Extracellular, introcellular
  - Positive (shortening T1), Negative (shortening T2)

Design requirements

- The ability to alter the parameters responsible for image contrast
- Some specificity in vivo and stay localized for reasonable period of time.
- Substantially cleared from the targeted tissue.
- Low toxicity and stable in vivo
- Suitable shelf life for storage.

MR contrast mechanisms

- Parameters determining MR signal intensity and contrast:
  - Density, relaxivity (T1,T2,T2*), magnetic susceptibility, diffusion, perfusion.
- Spin echo $$I \sim \rho(1-e^{-TR/T1})(e^{TE/T2})$$
- Gradient echo $$I \sim \frac{\rho \sin\theta(1-e^{-TR/T_1})(e^{-TE/T_2^*})}{1-\cos\theta e^{-TR/T_1}}$$
- Diffusion and perfusion?

Magnetic susceptibility

- Susceptibility describes the ability of substance to become magnetized in an external magnetic field.
- Four categories:
  - Diamagnetic substances
  - Paramagnetic
  - Superparamagnetic and ferromagnetic materials

Magnetic susceptibility

- Diamagnetic substances (most organic compounds) -> small negative magnetic susceptibility.
- A paramagnetic ion can strongly influence the relaxation rate of nearby protons
  - Paramagnetic agents positive T1 relaxation, little effect on T2 relaxation.

Magnetic susceptibility

- Superparamagnetic substance
  - Directly influence tissue contrast.
  - Large enough to be an domain.
  - External field ->align with the field -> large net positive magnetization.
  - Removal of field->return to random orientation->loss positive magnetization

Magnetic susceptibility

- Ferromagnetic compounds:
  - Large collection of interacting domains in a crystalline matrix.
  - Extremely large net positive magnetization in external field and remain this when removal of external field.
- Superparamagnetic and ferromagnetic compound function as negative agents.
  - Large net positive magnetic moments induce spin dephasing in tissue.

Relaxivity theory

- The contribution of a paramagnetic species to T1,T2 relaxation times arises as
  - Interaction between the unpaired electrons of the paramagnetic ion and the hydrogen nuclei of water molecules.
- Interactions between paramagnetic agent and protons of water
  - Inner-sphere relaxation
  - Out-sphere relaxation
- Solomon-Bloembergen equation

Inner-sphere relaxation

- The formation of a coordinate covalent molecular bond between a water molecule and the paramagnetic ion.
- Lead to enhanced relaxation of the water protons on the basis of the magnetic influences and efficiency of chemical exchange.
- The more water molecules bond with paramagnetic ion, the greater its influence on relaxation enhancement.
- The shorter the residence time of water molecule with paramagnetic ion, the greater the relaxation enhancement effect (bond with other H2O)

Outer-sphere relaxation

- No direct bonding
- Relative rotational and translational diffusion of water molecules and paramagnetic ion
- The more and closer the water molecules approach (pass) the paramagnetic ion, the more efficient the relaxation enhancement.
- Dipole-dipole relaxation process

Solomon-Bloembergen equation

$$\frac{1}{T1} = \frac{2}{15}\left[\frac{S(S+1)\gamma^2 g^2 \beta^2}{r^6}\left(\frac{3\tau_c}{1+\omega_I^2\tau_c^2} + \frac{7\tau_c}{1+\omega_S^2\tau_c^2}\right)\right] + \frac{2}{3}\left[\frac{S(S+1)A^2}{h^2}\left(\frac{\tau_e}{1+\omega_S^2\tau_c^2}\right)\right]$$

dipole-dipole terms scalar terms

$$\frac{1}{T2} = \frac{1}{15}\left[\frac{S(S+1)\gamma^2 g^2 \beta^2}{r^6}\left(4\tau_c + \frac{3\tau_c}{1+\omega_I^2\tau_c^2} + \frac{13\tau_c}{1+\omega_S^2\tau_c^2}\right)\right] + \frac{1}{3}\left[\frac{S(S+1)A^2}{h^2}\left(\tau_e + \frac{\tau_e}{1+\omega_S^2\tau_c^2}\right)\right]$$

Dipole-dipole term

- Express a distance factor, dependent on $1/r^6$ (r = radius)
- The net magnetic moment of an unpaired electron spin is 657 times greater than that of a proton.
- The more closely the water molecule can approach the paramagnetic ion species, the more efficient the relaxation enhancement effect on the paramagnetic ion.
- The optimal relax enhancement occurs when molecules bearing nuclear spins have fast access to as many sites near the paramagnetic molecule as possible -> inner-sphere relaxation.
- Important to use carrier ligands minimizing the distance effects.

Scalar term

- Summarize the probability that a transient coincidence of an unpaired electron of the paramagnetic ion and the proton nucleus of nearby water molecule.
- The probability is defined by τ_c

$$\frac{1}{\tau_c} = \frac{1}{\tau_r} + \frac{1}{\tau_s} + \frac{1}{\tau_m}$$

- The correlation time of the interacting spins is dominated by the fastest of the three rate terms

Scalar term

- If higher-molecular-weight ligands surround the paramagnetic metal ions

  -> $+\tau_r$ -> $+\tau_c$ -> - T1, T2 -> more efficient relaxation.

$$\frac{1}{\tau_c} = \frac{1}{\tau_r} + \frac{1}{\tau_s} + \frac{1}{\tau_m}$$

- τ_r: paramagnetic tumbling motion
- τ_s: electron spin flip
- τ_m: chemical exchange

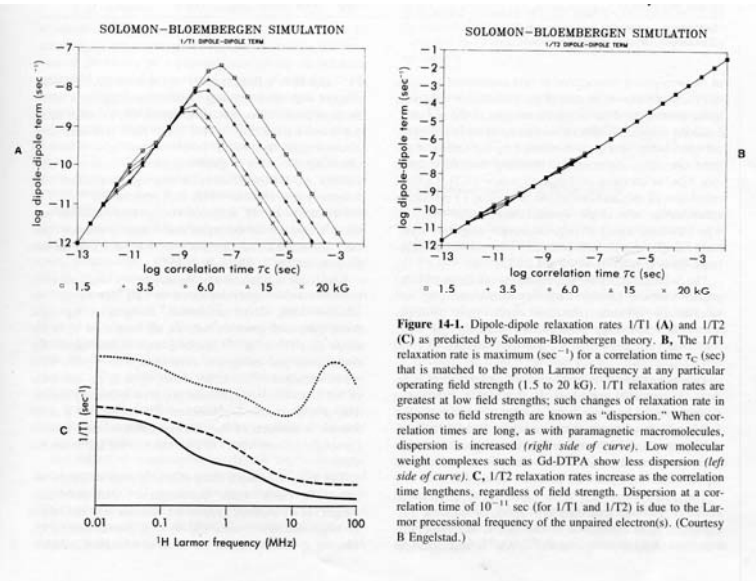


Figure 14-1. Dipole-dipole relaxation rates 1/T1 **(A)** and 1/T2 **(C)** as predicted by Solomon-Bloembergen theory. **B,** The 1/T1 relaxation rate is maximum (sec^{-1}) for a correlation time τ_C (sec) that is matched to the proton Larmor frequency at any particular operating field strength (1.5 to 20 kG). 1/T1 relaxation rates are greatest at low field strengths; such changes of relaxation rate in response to field strength are known as "dispersion." When correlation times are long, as with paramagnetic macromolecules, dispersion is increased *(right side of curve)*. Low molecular weight complexes such as Gd-DTPA show less dispersion *(left side of curve)*. **C,** 1/T2 relaxation rates increase as the correlation time lengthens, regardless of field strength. Dispersion at a correlation time of 10^{-11} sec (for 1/T1 and 1/T2) is due to the Larmor precessional frequency of the unpaired electron(s). (Courtesy B Engelstad.)

Strength field and dispersion

- Lamor frequency (field strength) influence relaxation rate.
  - If + ω -> - RR -> + T1, T2(?)
  - Dispersion
  - + τ_c -> + dispersion (?)
  - Lower molecular weight complex, Gd-DTPA show less dispersion

Relaxivity

- With the presence of the paramagnetic compound:

$$\frac{1}{T1_{(observed)}} = \frac{1}{T1_{(intrinsic)}} + \frac{1}{T1_{(paramagnetic)}}$$

$$\frac{1}{T2_{(observed)}} = \frac{1}{T2_{(intrinsic)}} + \frac{1}{T2_{(paramagnetic)}}$$

- The concentration (*c*) of paramagnetic species is critical to the degree of the observed relaxation enhancement:

$$\frac{1}{T1,2_{(observed)}} = \frac{1}{T1,2_{(intrinsic)}} + R1,2 \cdot c$$

- Relaxivity (*R1*,*R2*) : is a measurement of a paramagnetic species to influence relaxation.
  - $mM^{-1}s^{-1}$
  - Measured experimentally

Effectiveness of metal ion

- Relaxivity depends on:
  - Number of the unpaired electrons
  - Spin relaxation time.
- Relaxation agents
  - Gadolinium, manganese, high-spin ferric ion, and nitroxide radicals
    - Large number of unpaired electrons
    - Long τ_s : 10^{-8}~10^{-10}
  - lanthanides like dysprosium and europium
    - 7 unpaired electrons, shortτ_s : 10^{--12}~10^{-13}
    - Poor relaxation agents
    - Resonance frequency shift agents

Signal intensity versus concentration of CA

- Paramagnetic species reduce T1 and T2
  - Low concentration, T1 shortening
  - High concentration, T2 shortening
- Signal intensity is consequence of:
  - Biexponential signal intensity equation
  - Choice of TR and TE.
  - R2/R1
- The relation between the signal intensity to the concentration of CA is nonlinear

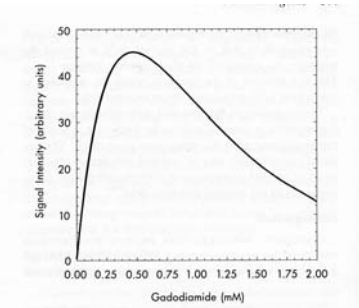


Figure 14-2. Change in signal intensity versus concentration (mM or mmol/L) of gadodiamide injection calculated using the equation, $SI = 100\ (1 - e^{-TR/T1})e^{-TE/T2}$. T1 and T2 values were measured in vitro at 10 MHz. Within clinical dosage ranges (0.01 to 0.3 mmol/kg) currently used for paramagnetic agents, the reduction in T2 (which results in a loss of signal intensity) is dominated by T1 reduction, leading to an overall increase in signal intensity.

Choice of pulse sequence

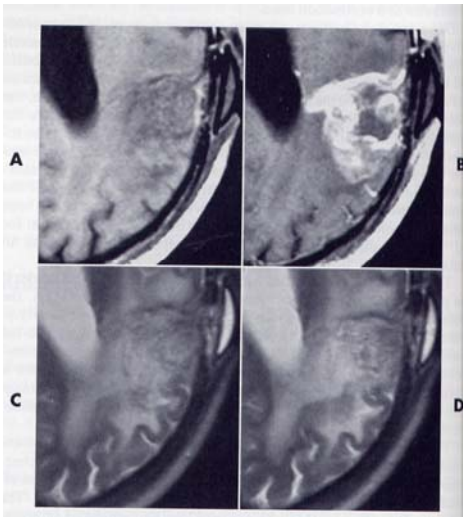
- Depend on the type of contrast agent chosen.
  - Paramagnetic materials, strong effect on T1, T1-weighted imaging protocols.
  - Ferromagneitc, superparamagnetic, and susceptibility (T2*) enhancing agents, T2-weighted imaging sequences to maximize contrast agents.

Development of CA

- Metal salts ($MnCl_2$)- > metal chelates (Gd-EDTA) -> particulate agents (SPIO)->nanoparticles (USPIO).
- Nonspecific agents ->specific organ function or disease ->functional and metabolic imaging.

Gadolinium complex

- Approved by FDA for use in cranial disease diagnostics in mid-1988.
- Gadolinium chelates (like Gadolinium DTPA) provides greater contrast between normal tissue and abnormal tissue in the brain and body.
- Gadolinium chelates was developed because of:
  - High relaxivity of the gadolinium ion
  - Relax low toxicity of the complex
- Gd-DTPA, Gd-DTPA-BMA, Gd-HP-DO3A, others like Gd-DOTA
- Gadolinium chelates is eliminated through the urinary system with in six hours of the first injection



Nonspecific MR contrast agents

- allow measurement of vascular permeability, blood flow, and blood volume.
- Poorly suited to characterize tumor microvessels.
- differentiation of benign from malignant tissues is problematic.

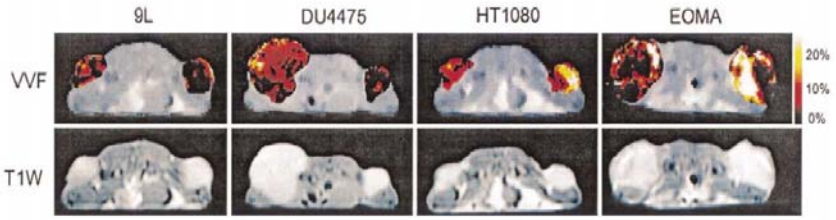


Fig. 3. Nonspecific MR contrast agents for steady-state imaging of tumor vascularization. MR images of four tumors (9L, DU4475, HT 1080, and EOMA) with significantly different microvessel density as a surrogate parameter for tumor angiogenesis. **Top** Grey scale-coded vascular volume fraction (VVF) maps of contrast-induced susceptibility changes ($\Delta R2^*$) using a USPIO. Note the heterogeneity of the VVF among the different tumor models. **Bottom** Different tumors in T1-weighted spin-echo MR images. MR-derived VVF maps correlated well with different microvessel densities and vascular endothelial growth factor expression of different tumor types. (Reprinted with permission from Bremer et al. [4])

Targeted MR contrast agents

- Many molecular targets are overexpressed in tumors and can be targeted by attaching an affinity ligand to the MR reporter.

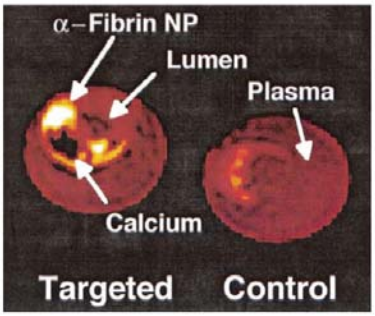


Fig. 4. Fibrin-targeted MRI contrast agent. Fibrin-targeted and control carotid endarterectomy specimens in enhanced MRI show contrast enhancement (*white areas*) of a small fibrin deposit on symptomatic ruptured plaque. Targeting of the contrast agent was done by a specific antibody linked to a perfluorocarbon nanoparticle, which is loaded with multiple gadolinium chelates. (Reprinted with permission from Flacke et al. [24])

Smart MR contrast agents

- Smart MR contrast agents (i.e., agents that can be activated) undergo conformational changes upon target interaction, which significantly alter their signal properties (e.g., shortening of T1 relaxation time).

Tissue specific contrast agents

- compounds with a tissue-specific distribution to detect focal anomalies or evaluate tissue function may be desirable to improve diagnostic accuracy.

Liver-specific agents

- (Gd) chelates improve the diagnosis of focal liver lesions. (not really specific to the liver tissue).
- Hepatocyte-specific compounds
  - Specific uptake in the hepatocyte
  - paramagnetic chelates
  - superparamagnetic iron oxide (SPIO)(preclinically)
- RES-specific compounds
  - SPIO nanoparticles

Blood-pool agents

- MR angiography (MRA)
- fast imaging technologies were further improved by using relaxation enhancers
- Since imaging is still time consuming, compounds that remain in the intravascular space are desirable.
- Several paramagnetic and superparamagnetic agents are now in clinical development.

Lymph node-specific agents

- Low-molecular weight Gd chelates, as well as polymeric agents, also used as blood pool agents, can be used for this indication
- Ultrasmall superparamagnetic iron oxides
  - darkening of the lymphatic vessels and lymph nodes
  - poor transport kinetics from the injection side, which creates a tattooing effect.

Tumor-specific agents

- nontoxic, tumor-specific agents are somewhat misleading.
- Monoclonal antibodies labeled with paramagnetic atoms or superparamagnetic nanoparticles are believed to be the ultimate tumor-seeking materials.
- However, the required dose of the labeled antibody is still too high to make commercial development realistic.

Molecular imaging

- Molecular imaging is a growing research discipline aimed at developing and testing novel tools, reagents, and methods to image specific molecular pathways in vivo, particularly those that are key targets in disease processes.

Current Imaging Developments

- **Radionuclide Imaging**
  - **PET (Positron Emission Tomography) scan**
  - **SPECT (Single Photon Emission Computed Tomography) Scan**
  - **Quantitative Autoradiography**
  - **Radionucleotide imaging combined with a computed tomography**
  - **(CT) or a nuclear resonance imaging (NRI) scan**
- **MRI:** uses paramagnetic-labeled CA or other CA to produces high imaging resolution
- **Optical Imaging**

Potential of imaging techniques for MI

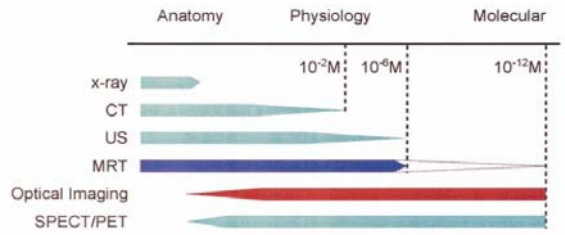


Fig. 2. Potential of different imaging techniques for molecular imaging. Due to their high SNRs, optical imaging and nuclear imaging techniques can detect molecular structures in picomolar (10^{-12}) concentrations within a given voxel. This is about three to six orders of magnitude more sensitive than currently available MRI techniques. However, innovative MR contrast agents may change MRI into a truly molecular imaging modality. (Modified from Weissleder and Mahmood [1])

CA for MR molecular imaging

- Ligands are needed for selective binding.
- Gadolinium may be used, but
  - Low relaxivities; not biocompatible; potential toxicity following cellular dechelating over time
- Superparamagnetic iron oxide (SPIO) particles is preferred.
  - Provide most change signal (esp, T2* weighted)
  - Composed of biodegradable iron
  - Surface coating (dextran) allows directly linkage to functional groups and ligands
  - Easily detected by light and electron microscopy
  - Can be magnetically manipulated and change their magnetic properties according size, with potential to reveal their structural conformation
  - Problem:
    - Prevent direct anatomical MR evaluation of tissue
    - Difficult to discriminate between targeted molecules and cells and image artifacts

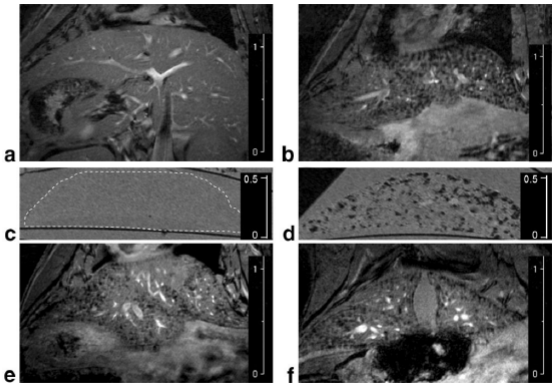


FIG. 2. In vivo MRI slice of (a) a control liver and (b) a liver from an animal whose spleen was injected with labeled hepatocytes 1 month prior to imaging. c and d: In vitro MRI slices of the same samples shown in a and b. The dotted outline in c delineates the liver boundary. e and f: In vivo MRI slices from two other animals that received live labeled hepatocytes. Scale bars are in centimeters.

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