Contrast Agents
Rad 226

Mike Moseley, Ph.D.
Department of Radiology
Stanford University
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MR Contrast Review
Get it going...
“Water Proton Density, T1, and T2*”
Isn't Gadolinium the alpha-dog of MR contrast?

Or...Is Chaos Approaching?

Mad Max - Warner Bros 2015
Challenges in contrast agents
T1 agents
T2 agents
Gradients
Novel ideas

Approaching the storm
Can Contrast Be a “Bad” Thing?
Recent reports of Gd accumulation and “NSF”

Gadodiamide-Associated Nephrogenic Systemic Fibrosis: Why Radiologists Should Be Concerned
Dale R. Broome, Mark S. Girguis, Pedro W. Baron, Alfred C. Cottrell, Ingrid Kjellin and Gerald A. Kirk

Rare multisystemic fibrosing disorder, 12/575 pts. All patients had renal insufficiency. Developed NSF post-Gd (Omniscan) despite early dialysis... Conclusion: NSF “strongly associated” with Gd administration.
FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI)

About one-third of the 20 million MRIs in the United States each year use one of nine gadolinium-based contrast agents.
Recent reports on potential genotoxic effects of strong and fast switching electromagnetic gradients such as used in cardiac MR (CMR) have raised safety concerns. The aim of this study was to analyse DNA double-strand breaks (DSBs) in human blood lymphocytes before and after CMR examination.

The present findings indicate that CMR should be used with caution and that similar restrictions may apply as for X-ray-based and nuclear imaging techniques in order to avoid unnecessary damage of DNA integrity with potential carcinogenic effect.
Isolated lymphocytes were exposed to 0.2–1.2 mM of Gd only or in combination with a 60-Hz ELF-EMF of 0.8-mT field strengths.

**ELF-EMF (0.8 mT)** exposure also increased cell death, MN frequency, olive tail moment, and apoptosis induced by Gd treatment alone. These results suggest that Gd induces DNA damage and apoptotic cell death in human lymphocytes and that ELF-EMF enhances the cytotoxicity and genotoxicity of Gd.
The Impact will be loud...

Ferumoxytol: Gad-killer or just killer?

K. Yeom, T. Christen, S. Holdsworth, Stanford
FDA Drug Safety Communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol)

How Did It All Start?

Mad Max - Warner Bros 2015
Why Alter MR Tissue Contrast?

1. Proton Relaxation
2. 1.5 Proton Density
3. Proton Exchange
4. Proton Frequency
5. Polarization
6. Chemical Shift metabolism
7. Magnetization transfer
8. Other nuclei, F19, C13, O17
9. Other nuclei exchange O17
10. Proton Diffusion
11. Magnetic Susceptibility
12. Tissue conductivity

Who Are the Front Runners?

Mad Max - Warner Bros 2015
Why Alter MR Tissue Contrast?

1. Nuclei (proton) density - PD
2. Spin lattice Relaxation – T1
3. Susceptibility – T2, T2*

Are amenable for pharmacologic perturbation...

\[ SI = PD \left[ 1 - e^{-\frac{TR}{T1} - \frac{TE}{T2}} \right] e \]

Unpaired Electrons in MR

\[ \frac{2 \mu_B B}{h} = \frac{2 \cdot \frac{1}{2} \left( 5.79 \times 10^{-3} \text{eV} / \text{fT} \right)}{6.58 \times 10^{-16} \text{eV} \cdot \text{s}} = 1.7608 \times 10^{11} \text{A}^{-1} \]

\[ v = \frac{\gamma}{2\pi} = 28.025 \text{GHz}; \quad \text{Larmor frequency} \]

\[ \frac{2 \mu_B B}{h} = \frac{2 \left( 2.79 \times 3.15 \times 10^{-8} \text{A} / \text{T} \right) (\pi)}{6.58 \times 10^{-16} \text{eV} \cdot \text{s}} = 2.6753 \times 10^{8} \text{A}^{-1} \]

\[ v = \frac{\gamma}{2\pi} = 42.5781 \text{MHz}; \quad \text{Larmor frequency} \]

Basic Arrangement of Electrons in Iron (Fe)
1. T1-shortening on T1w images*.
   Paramagnetic agents (Gd-DTPA).
   Coated supermagnetic irons (iron particles).
2. T2 (or T2*) shortening on T2*w images.
   Para-/superparamagnetic agents (iron particles).
   Paramagnetic agents (Gd or Dy-DTPA)

\[ SI = N(H) \left[ 1 - e^{-\frac{TR}{T1}} \right] e^{-\frac{TE}{T2}} \]

1. T1-shortening agents on T1w images.
   Paramagnetic agents (Gd is best).
   Coated supermagnetic irons (iron particles).
2. Chemical-shifting on T2 or CEST images.
   Chemical shift (Pr, Eu, Tb, Dy, Tm, Yb).
Unpaired Electrons in MR

MR relaxation enhancement ("relaxivity") is a question of unpaired electrons...

- **Diamagnetic agents**: no unpaired e-; no effect on T1, T2. PD only
  - T1 - T2* - Oils, PFOB
  - 10

- **Paramagnetic agents**: unpaired e-; noninteracting domains
  - 10
  - T1↓ T2*↓ Gd³⁺, Fe³⁺

- **Superparamagnetic**: unpaired e- pools; noninteracting domains
  - +2
  - T1↓ T2*↓ Fe particle

- **Ferromagnetic**: unpaired e- oceans; strongly interacting domains
  - +4
  - (>$0.035\mu m$) threshold...
  - T1 - T2↓↓ Fe particle

*cm / gauss

Artifacts…
Why Gadolinium?

Gd-DTPA: Berlex – Magnevist™
Gd-DTPA-BMA: “Omniscan™”
Nycomed-Amersham-GE Healthcare
Gd-DOTA: Geurbet – DOTAREM™
**Gadolinium an MR Agent - Why chelate a good thing?**

The chelate binds the metal tightly…
Excreted renally (>99.9%).
Occupies space and coordination sites…
A necessary evil.

**Unpaired e⁻ and “T1 Relaxivity”**

Unpaired electron clouds fluctuate around metal.
\( e^- \) create fluctuation in local B0 - *interactions with protons.*
Fluctuating B0 fields – *Acts as magnetization sink.*
Randomizes magnetization.
Result looks like T1 relaxation –  
Fast relaxation = *Shortened T1.*

**Apparent shortening of T1**

at a given B0 and temperature...

\[
\frac{1}{T1} \text{ (observed)} = \frac{1}{T1} \text{ (intrinsic)} + r1 [\text{Conc}]
\]

\[
(200 \text{ msec} = 1000 \text{ msec} + 3.8^{*}[0.1\text{mmol/kg}])
\]

\(*\text{mmol}^{-1} \text{ L sec}^{-1}\)
Proton spins near metal sees fluctuating B₀ caused by the electron spins near proton frequency. 637,000 x more effective! Any proton magnetization is damped by the oscillations of the electron spins. Result is “relaxed” protons.

\[
\frac{1}{T₁} \approx \frac{1}{\tau_S} + \frac{1}{\tau_m} + \frac{1}{\tau_R}
\]

Unpaired e⁻ and “T₁ Relaxivity”

Good Stuff:
Positive effect on T₁-weighted MRI.
T₁w MRI typically rapid.
Doesn’t cross intact BBB.
Relatively rapid, safe.
Patents nearing end...

However:
MW a bit small (MW~500au).
Extravasates too easily.
Clears with 17 min plasma T₁/₂
Too expensive !?
T1 Relaxivity – T1 Shortening!

Short TR

Long TR

Gd-DTPA Enhances BBB Breakdowns

Pre

Post
Advanced Options for MRA

In-plane (coronal) images saturate in-flow...

Poor SNR
Not used...

Fast SPGR
30 seconds/
16 slices
3DFT.

Advanced Options for MRA

Contrast shortens T1.

No saturation of vascular spins.
Not flow, but anatomy...

Fast SPGR
30 seconds/
16 slices
3DFT.

0.1 mmol/kg Gd DTPA
MIP'ping works.

New area of fast vascular MRI.

Fast SPGR
30 seconds/
16 slices
3DFT.
0.1 mmol/kg Gd DTPA
Lanthanide Chelated Agents

**CNS:**
BBB leakage – tumors, etc.
T1-enhanced MRA.
Bolus dynamics.

**Cardiac, Cardiovascular:**
Delayed enhancement!
Wall actions, Bolus dynamics.
T1-enhanced MRA.

**Non-neuro:**
Tumor update and leakage.
MSK tears.
Blood pool issues.
Lanthanide Chelated Agents

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**Lanthanide Chelated Agents**

**CNS:**
- BBB leakage – tumors, etc.
- T1-enhanced MRA.
- Bolus dynamics.

**Cardiac, Cardiovascular:**
- Delayed enhancement!
- Wall actions, Bolus dynamics.
- T1-enhanced MRA.

**Non-neuro:**
- Tumor update and leakage.
- MSK tears.
- Blood pool issues.
- Liver...

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**Proton Relaxation by Paramagnetic Metal Ions.**

*Unpaired electrons relax protons Much more efficient...*

Number of unpaired electrons -
- Gd, Dy = 7 unpaired electrons.
- Fe, Mn = 5 unpaired electrons.
- Fe domains create big magnetic moments.

Electron-spin (esr) relaxation times - \( ts \)
- Gd - long esr T1 = good T1-shortening.
- Dy - short esr T1 = poor T1-shortening.

Proton near paramagnetic centers- \( tm \)
- Coordination sites and placement critical.
- DTPA occupies more than EDTA, unfortunately...

Paramagnetic correlation times - \( tr \)
- Gd-DTPA-albumin increases T1 relaxivity 10 fold.
T1 Relaxivity – *Why Gd-DTPA?*

Magnetic moment (# unpaired electrons)
- Gd has 7 unpaired e-
- OxyHb (Fe $^{+2}$) vs. DeOxyHb (Fe $^{+3}$)

Electron relaxation rate (near that of protons?)
- Gd-DTPA vs. Dy-DTPA

Tumbling of the cloud (exposure time to protons)
- Gd-DTPA-binding

Approach of water to the unpaired electrons...
- MetHb

$$\frac{1}{T1_{\text{observed}}} = \frac{1}{T1_{\text{intrinsic}}} + R1 \ [\text{Conc}]$$

(200 msec = 1000 msec + 3.8[0.1mmol/kg])
MR Contrast Domination

Gd-DTPA
The Best?

Not so fast...

T1 Relaxivity – Better than Gd-DTPA?

Magnetic moment (# unpaired electrons)
OxyHb vs. MetHb

Electron relaxation rate (near that of protons?)
Gd-DTPA vs. Dy-DTPA

Tumbling of the cloud (exposure time to protons)
Gd-DTPA-binding

Approach of water to the unpaired electrons...
MetHb

T1 Relaxivities mmol⁻¹ L sec⁻¹:
Gd-DTPA ~ 4
Gd-dimers ~ 10
Gd-Dextrans ~ 40
MS-325-HSA ~ 45
Iron oxides ~ 20
**Paramagnetics - Blood Pool Agents**

*Gd-phostriamine MS-325 - Epix - Schering*

**T1-shortening agents:**
- Affinity to HSA
- 80-90% labeled
- $R_1 \sim 40-50$
- $T_{1/2} \sim 60$ minutes

- **Gd-phostriamine**
- **MS-325**
- **Epix**
- **Schering**

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**Blood Volume from T1-Contrast**

**ABLAVAR**
- Enhanced Blood Pool
- CBV Mapping
- Functional MRI

- **3D SPGR (DISCO)**
- 0.03 mmol/kg
- $T_{1/2} = 19$ minutes
**T1 Relaxivity – *Not just Gd-DTPA*…**

- Magnetic moment (# unpaired electrons)
- OxyHb vs. MetHb
- Electron relaxation rate (near that of protons?)
- Gd-DTPA vs. Dy-DTPA
- Tumbling of the cloud (exposure time to protons)
- Gd-DTPA-binding

**Approach of water to the unpaired electrons…**

<table>
<thead>
<tr>
<th>MetHb</th>
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**T1 Relaxivity – *Natural Iron Contrast***

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Molecular Imaging Using "Relaxivity"?

**Hint 1**

**Hint 2**

Fe(II)  Fe(III)
OxyHb  MetHb

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**H1 T1 and "Relaxivity"**

MR Functional Reporter agents for Enzyme activity "Egadme"

Blocked with galactopyranose

Cleavage of the Egadme by β-galactosidase
Creates increase in R1

Stealing Even More New Ideas

Contrast: Conformation and Relaxivity

Sensing agents
(a) glucose-sensitive
(b) lactate-sensitive.
How to Make a Killer T1 Agent…

Pick a big # unpaired electrons – *big moment*
- Gd has 7 unpaired electrons... *hard to beat that…*

Pick a long e- relaxation time – *ts*
- Gd - long esr T1 = good T1-shortening.

Let water get into the mix - *tm*
- Open metal to protons w/o becoming toxic...
- Ligand chemists make $$$. 

Slow the metal down - *tr*
- Add stuff to Gd...

*Hmmm…*
- *Buckeyballs…*
- *Aerogels…*
- *Liposomes…*
- *Proteins…etc*
Ligands design and R1 relaxivity.
Kinetics of biodistribution.
Plasma retentions.
Wash-out, elimination routes.
Osmolality and viscosity.

**Gd-DTPA**
ECF
renal clearance ~ 100 minutes.
plasma half-life ~ 18 minutes.

*(Gd-DTPA)*-albumin
Plasma retention agent.
renal clearance ~ days.
plasma half-life ~ 45 minutes.

**Particulate iron (e.g., AMI-227)**
Plasma retention agent.
liver half-life ~ 6 months-1 year.
plasma half-life ~ 90 minutes.
Plasma Retention

Physiologic Parameters

BBB disruptions – “ECF” agent
Lack of BBB - tumors
Vascular permeability
Renal retention / collection

Does All T1 Contrast Need to be Gadolinium?
Proton Magnetic Susceptibility

Quantitative Susceptibility Mapping

*What and Why*

- QSM natural extension of GRE and SWI and is both bleed/WM sensitive.
Why Alter MR Tissue Contrast?

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2. Spin lattice Relaxation – T1
3. Susceptibility – T2, T2*

Are amenable for pharmacologic perturbation...

\[ SI = PD \left( 1 - e^{-\frac{TR}{T1}} \right) e^{-\frac{TE}{T2}} \]

Magnetic Susceptibility

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- **Diamagnetic agents**
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- **Superparamagnetic**
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  - noninteracting domains

- **Ferromagnetic**
  - unpaired e- oceans
  - strongly interacting domains

\( T1 \ll T2^* \)

- **T1**
- **T2**
- **Oils, PFOB**
- **Gd^{3+}, Fe^{3+}**
- **Fe particle**
- **Metal Artifacts...**
**Unpaired e- and “T2* Relaxivity"**

*Local gradients (unpaired e-).*
*Local environment (clots, packed RBC).*
*Enhanced by proton diffusion.*
*Increased spin dephasing = T2* decreased.*

**Magnetic susceptibility reduces T2***

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**Unpaired e- and “T2* Relaxivity"**

*Magnetic susceptibility factors*

- Magnetic moment (# unpaired electrons) – Fe°3 > Fe°2
- Size of “domains” – Fe-oxide > FeCl
- Size and concentration of particle – SPIO (RES capture) > USPIO (blood pool)

**T2* Effects (in order):**

- Iron oxides (SPIO)
- Iron oxides (USPIO)
- FeCl
- DyDTPA
- GdDTPA
- DeOxyHb
- OxyHb

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*Feridex-enhanced MR “USPIO”*
Can Gd- or Fe Be Both a T1 and T2* Agent?

“Concentration’ is the key to alterations of T1 and T2*.

Superparamagnetics

Alterations of T1 and T2

Particulates (superparamagnetic irons):
Possesses mild T1-shortening at low [Fe].
Large T2* effect at higher [Fe].
Biodistribution vary depending on size:

- >20 nm size: Liver (RES) uptake agents
- 20 nm: Oral (gut) agents
- 10-20 nm: Lymph nodes, blood pool
- 4-6 nm: Hepatocytes, targets

Size is the most important aspect of biodistribution. All particles must be < 5 µm to avoid entrapment in lung.
Nanoparticles!
Magnetic susceptibility factors

Particulates (superparamagnetic irons):
- Possesses mild T1-shortening at low [Fe].
- Large T2* effect at higher [Fe].
- Biodistribution vary depending on size:
Iron T2* “Ferumoxytol”

**Feraheme**
Enhanced Blood Pool
CBV Mapping
Functional MRI

3D EPI
3 minutes
7mg/kg
$T_{1/2} = 19$ hours
Blood = Ideal MR Contrast Agent?

Oxyhemoglobin

- Diamagnetic
- Low $\chi$

Deoxyhemoglobin

- Paramagnetic
- High $\chi$

Balance of HbO2 → Hb affects T2*. T2* effects extend beyond vascular space.

Blood flow

T2* image
Surplus of HbO2 → to Hb → leads to an increase in T2*-weighted image intensity...

**Blood flow**

1.5T vs. 3.0T Motor Task Finger Apposition

Spiral 2D single shot, 200 frames, TR 1000ms, TE 40ms
3T 60°; 1.5T 70° (T1@3T: T1@1.5T~900ms; T1@3.0T~1400ms)
20cm FOV, 5mm/skip 0, 90x90, 6 slices

G. Glover, Dept. of Radiology
Reduced posterior cingulate cortex (PCC) activity is among the most common findings in early AD.

PCC hypometabolism found in many cognitive diseases...

“Default-mode network” from fMRI in healthy young adults scanned on a 3T magnet at Stanford University. Arrows indicate the PCC.
“Brain Noise” – Resting State fMRI ~2015

Volkow and Tomasi, NIDA

Resting State fMRI “Connectivity Mapping”

Cole, et al. Center for the Neural Basis of Cognition
Neurotransplantation of magnetically labeled oligodendrocyte progenitors: MR tracking of cell migration and myelination

J. W. M. Bulte†‡, S.-C. Zhang§, P. van Gelderen¶, V. Herynek, E. K. Jordan†, I. D. Duncan§**, and J. A. Frank

PNAS, 96, 1999

50 mg MION-46L-OX-26
Cell Density 2.5–3.0 x 10^5 per 15 cm² surface area

Mapping the Brain Neural Fiber Pathways

*Inject MR-iron labeled stem cells*
*Stem cells migrate to injury via white matter tracts*
*Use DTI as delivery roadmap!*

**Stem cell implant colony**

**Stroke in brain**

**Migration of colony along white matter to repair stroke**

Guzman, Bammer, Moseley, Steinberg
Stanford
MR can haz more?

Iron nanoparticles in MRI
Blood pool T2*
Long retention times
Iron is taken up by macrophages!
MR Agents in Disguise…

Paramagnetic Lanthanide Complexes as “PARACEST” Agents

• Lanthanide metals either:
  • shorten proton T1 (Gd does this…) or
  • shift their Larmor frequency (+ or -)

• Shift agents very old idea
• New novel applications
• $T^0C$, pH sensitive

Imaging the Tissue Distribution of Glucose in Livers Using A PARACEST Sensor

Jimin Ren,1 Robert Trokowski,2 Shanrong Zhang,1 Craig R. Malloy,1,3 and A. Dean Sherry1,2*

*Corresponding author.

[Images and graphs related to the research are shown here.]
What Does MR Offer?

It is a major “clinical endpoint”.
Near-ideal “translational” tool.
DWI, FLAIR, SWI

Nex-Gen MR Ideas for MI:
- High-field – SNR and T2* (BOLD)
- New contrast agents – ParaCEST
- New add-ons – MR/PET
- Multi-nuclear – Hyper…!