

ISMRM Joint Study Group Virtual Meeting
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Relaxometry for Detection and Quantification of Iron and Iron Oxides with MRI

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ISMRM ONE
COMMUNITY FOR CLINICIANS AND SCIENTISTS

Big Thanks



Yuxin (Annie) Zhang Diego Hernando TJ Colgan Ante Zhu Gesine Knobloch

Disclosures

No relevant conflicts
Unrelated conflicts:

- Ownership in Calimetrix, Elucent, Reveal, and Collectar
- UW-Madison receives research support from GE Healthcare

Off-label use of ferumoxytol

Objectives

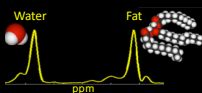
- Methods for detection and quantification of endogenous and exogenous iron
- Basic principles of relaxometry
- Contrast mechanisms for quantifying iron
- Ferumoxytol and clinical / research applications

Iron is Special

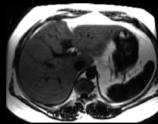
- Essential element needed to sustain life
- **Only** naturally occurring high susceptibility element in the body detectable by MRI
- Endogenous
 - Ferritin, hemosiderin, myoglobin, hemoglobin ...
- Exogenous
 - Iron-based contrast agents

Fat vs Iron Quantification

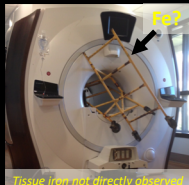
Fat as seen on MR



Water Fat ppm



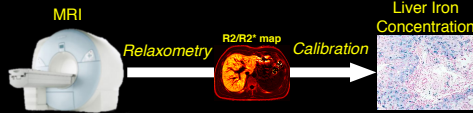
Iron as seen on MR



Tissue iron not directly observable
<http://imgur.com/pS1pec>

Liver Iron Quantification: Indirect Approach

- Do not measure iron directly
- Observe the effects of iron deposition on proton signal



How do we detect and quantify iron?

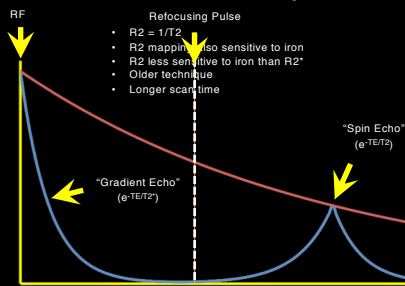
- Rely on iron's unique magnetic properties!
- How do iron oxides modulate the MRI signal?
 - Susceptibility of course ... but much more

$R2$ χ
 $T1$ $R2^*$

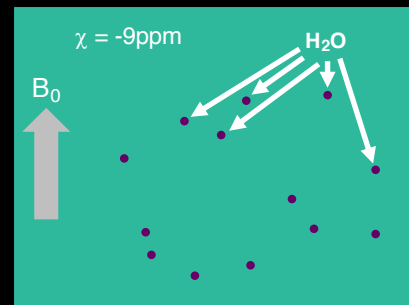
Weighted imaging ("qualitative")
 or
 Relaxometry ("quantitative")

Fancy methods ...

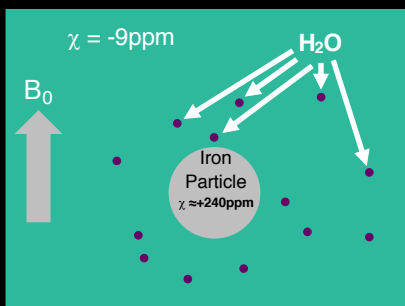
Gradient Echo vs Spin-Echo



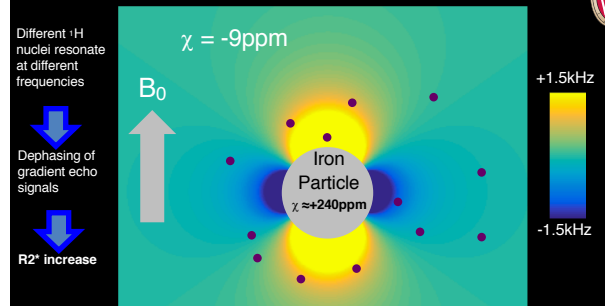
Effect of Iron on MR Signals: Gradient Echo

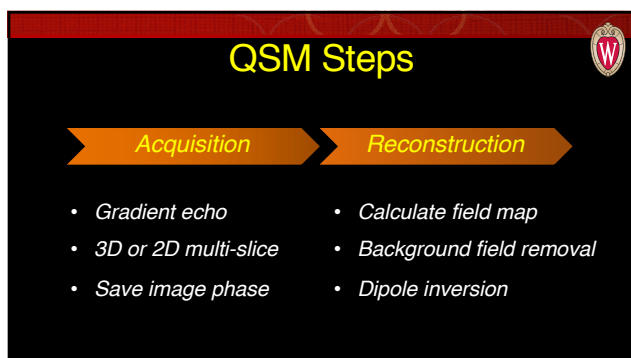
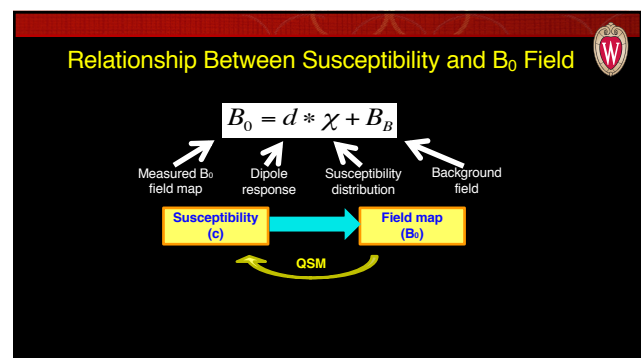
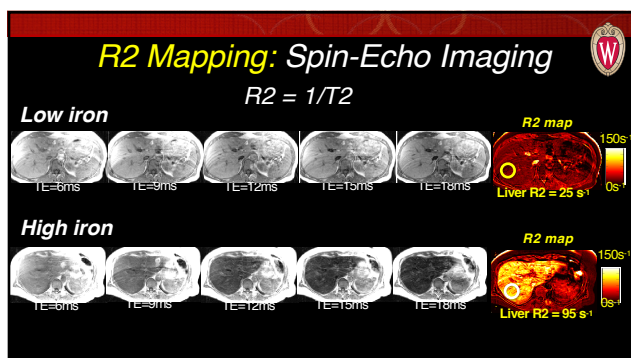
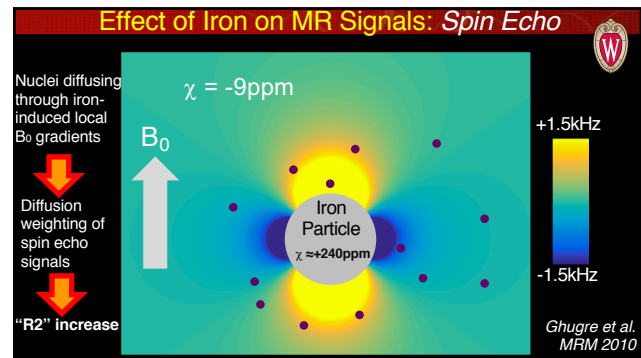
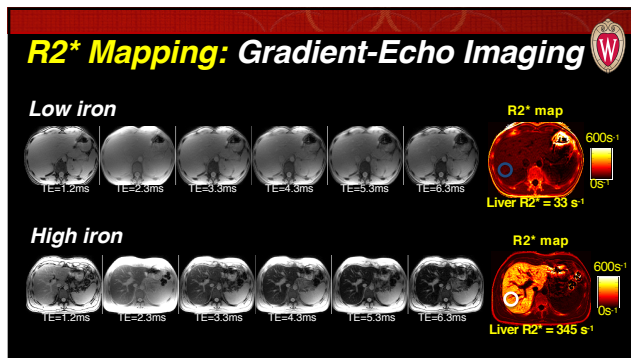


Effect of Iron on MR Signals: Gradient Echo



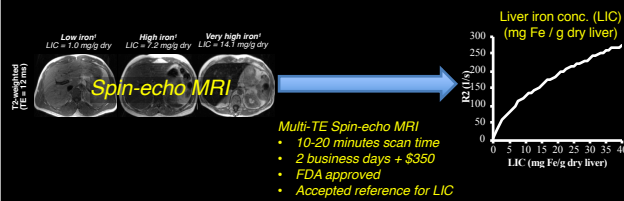
Effect of Iron on MR Signals: Gradient Echo





- ### Liver Iron Overload
- Two main causes:
 - *Hemochromatosis* (hereditary)
Excess intestinal absorption
 - *Hemosiderosis* (transfusional)
Repeated blood transfusions for anemias, SCD, MDS,...
 - Excess body iron is highly toxic, can lead to
 - Liver damage (cirrhosis, liver failure, cancer)
 - Pancreatic dysfunction (diabetes, exocrine insufficiency)
 - Heart failure (cardiomyopathy, sudden death)

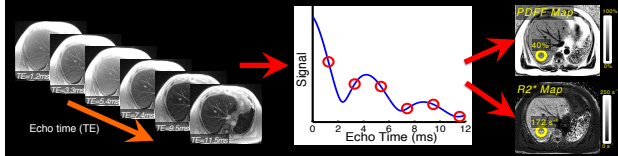
Liver Iron Quantification with R2 Mapping



¹FerriScan (St Pierre TG et al, Blood 2005)

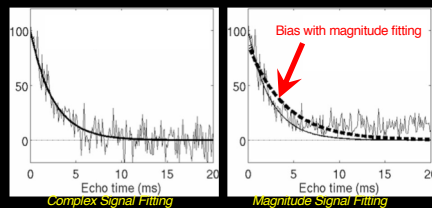
Complex Fat-Corrected R2* Mapping

Multi-echo CSE-MRI acquisition



Complex fat-corrected R2* mapping

Why Complex R2* Mapping?



Hernando et al MRM 2012

Why Iron Oxides?

- Exciting new ways to label cells
 - inject labeled cells into the body
 - inject iron oxide into the body
- Track cells over days, weeks, or months
- Magnetic activity does not decay
- Characterize the activity of cells (phagocytic)
- Track migrating cells to key tissues of interest

What is Ferumoxytol?

- Super-paramagnetic iron oxide (magnetite)
- Strong alignment with B₀ field leading to **very** strong paramagnetic effect
- Coated in polyglucose sorbitol carboxymethylether for biocompatibility
- Intravascular for 14 hours
- Uptake into the reticuloendothelial system (RES)
 - Liver, spleen, bone marrow ... lymph nodes (?)

What is Ferumoxytol?

- Clinically approved for IV treatment of iron deficient anemia
- Favorable MRI properties for clinical and research applications

Safety and Technique of Ferumoxytol Administration for MRI

Shreyas S. Vasanawala,^{1*} Kim-Lien Nguyen,² Michael D. Hope,³ Mellena D. Bridges,⁴ Thomas A. Hope,³ Scott B. Reeder,⁵ and Mustafa R. Bashir⁶

MRM 2016

Commercially Available Contrast Agents

| Generic Name | Brand Name | Manufacturer | Conc. (M) | Dose (mmol/kg) | Pharmaco-kinetics | Protein Binding | Chemical Structure | 1.5T | | 3.0T | | ACR NSF Safety Group |
|---------------------------|------------|--------------|-----------|----------------|----------------------------|-----------------|--------------------|--|--|--|--|----------------------|
| | | | | | | | | r_1 (s ⁻¹ mol ⁻¹) | r_2 (s ⁻¹ mol ⁻¹) | r_1 (s ⁻¹ mol ⁻¹) | r_2 (s ⁻¹ mol ⁻¹) | |
| gadopentabate dimeglumine | Magnevist | Bayer | 0.5 | 0.1 | ECF | no | Linear | 3.941 | 4.653 | 3.327 | 5.2 | 1 |
| gadodiamide | Omniscan | GEHC | 0.5 | 0.1 | ECF | no | Linear | 4.3 | 5.2 | 4.0 | 5.6 | 1 |
| gadoteridol | ProHance | Bracco | 0.5 | 0.1 | ECF | no | Macrocyclic | 4.1 | 5.0 | 3.7 | 5.7 | 2 |
| gadoterate meglumine | Dotarem | Guertel | 0.5 | 0.1 | ECF | no | Macrocyclic | 3.6 | 4.3 | 3.5 | 4.9 | 2 |
| gadobutol | Gadavist | Bayer | 1.0 | 0.1 | ECF | no | Macrocyclic | 4.752 | 6.148 | 3.650 | 6.371 | 2 |
| gadobenate meglumine | Multihance | Bracco | 0.5 | 0.05-0.1 | ~60% ECF, ~5% HB, ~50% ECF | no* | Linear | 6.341 | 8.748 | 5.543 | 11.075 | 2 |
| gadoteric acid | Eovist | Bayer | 0.25 | 0.05* | ~60% ECF, ~5% HB, ~50% ECF | yes | Linear | 6.9 | 8.7 | 6.2 | 11.0 | 3 |
| ferumoxytol* | Feraheme | Ammag | 30 mg/mL | 3.0mg/kg* | IV, RES | no | nta | 19.0 | 64.9 | 9.5 | 65.2 | nta |

Pharmacokinetics

- Extracellular fluid
- Hepatobiliary
- Intravascular

Formulation

- 0.5M
- 0.25M
- 1.0M

Safety

- macrocyclic vs linear
- NSF Safety

Relaxivity

- Standard
- "High" relaxivity

What is Relaxivity?

$\Delta R_1 = r_1 [C]$

Change in T_1 → $\Delta R_1 = r_1 [C]$ ← Contrast concentration

↑ r_1 (s⁻¹mol⁻¹) ← Gd, Mn, Fe, ...

Bang for your Buck!
(amount of T1 shortening per contrast molecule)

What is Relaxivity?

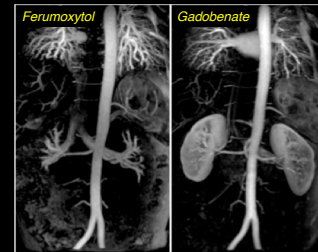
$$\Delta R_1 = r_1 [C]$$

$$\Delta R_2 = r_2 [C]$$

$$\Delta R_2^* = r_2^* [C]$$

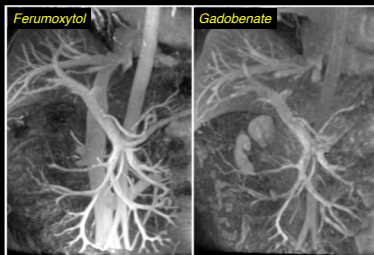
Relaxivity isn't just for T1 anymore!

Ferumoxytol: MR Angiography



Schubert et al JMIR 2017

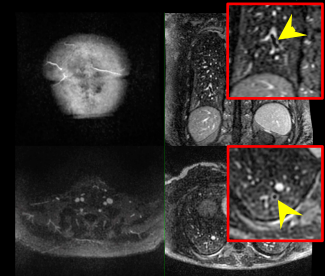
Ferumoxytol: MR Angiography



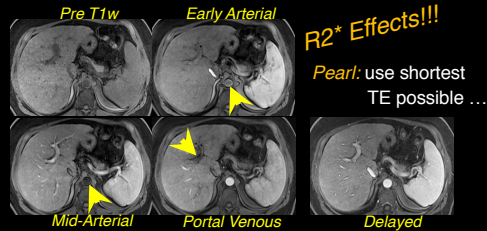
Schubert et al JMIR 2017

Ferumoxytol and Pulmonary MRA

- Viable alternative to gadolinium
 - Infuse prior to arrival in Radiology
 - 1 breath-hold MRA!!
- Good alternative in pregnancy
 - 1-2 mg/kg, diluted, slow infusion
- Expensive (\$600 / bottle)



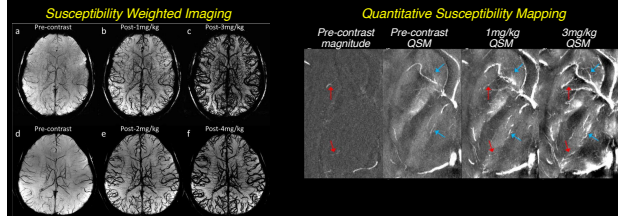
Ferumoxytol: Pitfall



Case courtesy Mustafa Bashir, MD; Reeder et al, Magnetic Resonance in Medicine, 2015

Susceptibility Weighted Imaging and Quantitative Susceptibility Mapping of the Cerebral Vasculature Using Ferumoxytol

Saileng Liu, PhD,^{1*} Jean-Christophe Brisset, PhD,² Jiani Hu, PhD,²
E. Mark Haacke, PhD,^{1,2} and Yulin Ge, MD²

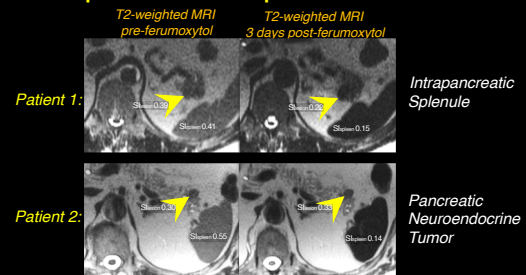


Ferumoxytol: Uptake in RES



Abdominal R2* mapping
pre- and post-ferumoxytol

Intrapancreatic Splenule vs PNET?



Rendell et al J Gastrointest Surg 2019

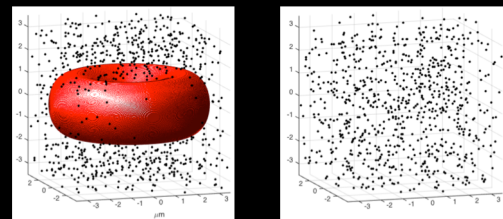
Relaxivity of Ferumoxytol at 1.5T and 3.0T

- Medium is critical
- May be non-linear!
- T1 effects lower at 3T
- No change in r_2 and r_2^* with field strength
- Saturation effects



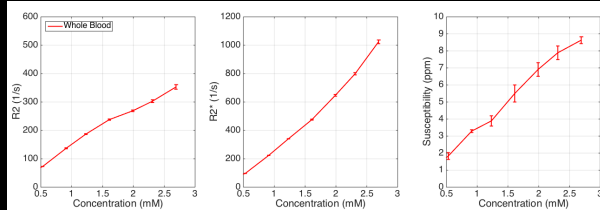
Knobloch et al Investigative Radiology 2018

Distribution Matters!



Colgan et al MRM 2019

Distribution Matters!



*Opportunities to characterize how iron is stored
... and where it's located ...*

Colgan et al MRM August 2019

Summary and Take Away Points

- Measurement of iron content
 - Basic principles of MRI, including relaxometry
 - Quantitative biomarkers
- Endogenous and exogenous sources of iron
- Ferumoxytol, other iron based contrast agents
- Many exciting clinical and research applications
- Many fundamental unsolved problems to tackle

Related Papers

- McCullough BJ, et al. J Magn Reson Imag (2013) DOI: 10.1002/jmri.23879
- Knobloch G, et al. Invest Radiol (2018) DOI: 10.1097/RLI.0000000000000434
- Tan H., et al. Invest Radiol (2014) DOI: 10.1097/RLI.0000000000000043
- Colgan TJ, et al. Magn Reson Imag (2019) DOI: 10.1002/mrm.27946
- Storey P, et al. Invest Radiol (2012) DOI: 10.1097/RLI.0b013e31826dc151
- Liu S., et al. J Magn Reson Imag (2017) DOI: 10.1002/jmri.25809
- Hsieh MC., et al. Trans Japanese Society for medical and Biological Engineering (2016) DOI: 10.11239/jmbe.51.R-240
- Lu X., et al. Magn Reson Med (2018) DOI: 10.1002/mrm.27062
- Bjornerud A., et al. Magn Reson Med (2002) DOI: 10.1002/mrm.10066
- Rad AM., et al. J Magn Reson Imag (2007) DOI: 10.1002/jmri.20978
- Li W., et al. Radiology (2015) DOI: 10.1148/radiol.2015150315
- Kokony, et al. Magn Reson Imag (2018) DOI: 10.1016/j.mri.2017.12.019
- Kokony, et al. Magn Reson Imag (2019) DOI: 10.1016/j.mri.2019.05.006
- Xie H., et al. Magn Reson Imag (2016) DOI: 10.1002/mrm.26035
- Zhu A., et al. J Magn Reson Imag (2019) DOI: 10.1002/jmri.26849
- Ludwig KD., et al. Magn Reson Med (2018) DOI: 10.1002/mrm.27548

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