Imaging inflammation and tracking macrophages with MRI using USPIO

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Magnetic Resonance Imaging (MRI)
MORE PROTONS
MORE SIGNAL
FASTER DECAY
It’s a magnet!
PRESENCE OF IRON GIVES SMALLER SIGNAL, FASTER DECAY
Iron nanoparticle MRI contrast agents

- Small and ultrasmall super-paramagnetic particles of iron oxide (SPIO and USPIO) typically 10-200 nanometres in diameter. Tiny ‘iron filings’
- Engulfed by inflammatory cells “macrophages”
- MRI signal changes caused by presence of iron correlate with macrophage density

Morishige et al. Circ. 122, 1707-15, 2010
Multi-modal imaging

Sinusas et al. Circ Cardiovasc Imaging 1, 244-56, 2008)
“Targeted” nanoparticles

Fig. 1 Schematic representation of advances in magnetic nanoparticle (MNP) design. MNP agents currently under development will have significantly higher relaxivities than earlier generations of MNP, and will also have improved synthetic coats for targeted imaging.

Sosnovik et al. Basic Res Cardiol 103, 122-30, 2008)
1. iv administration - USPIO
2. Cell labelling - SPIO
Abdominal Aortic Aneurysms
12 hours!

- LUNG
- DIAPHRAGM
- HEART
- HEAD
- FEET
- BOWEL
AAA Pathophysiology

“Biological Hotspots”
Neovascularisation
Inflammation
Proteolytic activity
Oxidative stress

Reduced tensile strength
Potential site of rupture
The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study
Evaluation Using Ultrasmall Superparamagnetic Iron Oxide-Enhanced Magnetic Resonance Imaging in Carotid Disease

Tang et al. JACC 2009;53:2039-2050
USPIO Imaging

3T MRI Imaging of AAA

USPIO

Pre-contrast

Post-contrast
Methods: Image Analysis

MRI scans (x2)

Sequences:

- T2W: TSE
- T2*W: multiecho, gradient echo (TE 4.9, 7.4, 10.7, 13.3 ms)
USPIO Imaging

**Multiecho T2* Sequences**

Signal Intensities for echo times to derive T2*
exponential decay:

\[ S(t) = S(0) \exp\left(-\frac{t}{T2^*}\right) \]

Time constant (T2*)

Time (t)

% of signal intensity at 6.9 ms

Echo time (ms)

Tom MacGillivray, WTCRF

Jenny Richards, BHF Clinical PhD Fellow
Region of Interest

Blue – wall
Green – thrombus
Red – blood pool

Yolanda Sorgia-Koutraki, UoE fellowship PhD student
Olivia Berry, BHF Clinical PhD Fellow
Registration

- Purpose-written software used for spatial registration of data
- Manual validation of registration is performed
Output images: %ΔT2* colour maps

a. T2W image

b. Per cent ΔT2* value (no threshold)

c. Per cent ΔT2* value (threshold 59 %)
USPIO Uptake
AAA Histology

USPIOs

AAA Uptake Patterns

USPIO Uptake

Abdominal Aortic Aneurysm Growth Rate

Magnetic Resonance Imaging Using Ultrasmall Superparamagnetic Particles of Iron Oxide in Patients Under Surveillance for Abdominal Aortic Aneurysms to Predict Rupture or Surgical Repair

MRI for Abdominal Aortic Aneurysms to predict Rupture or Surgery: The MA³RS trial +300 patients
Olivia Berry and Jenny Richards
Inflammation after MI

- Damaged myocardium
- Neutrophils
- Efferocytosis
- Angiogenesis
- Fibrosis
- Myofibroblast activation

- Day 1-4: Pro-inflammatory M1 Mo/Mφ
- Day 5 onwards: Pro-reparative M2 Mφ (Ym1)

Modified from: F. van der Akker et al; 2013
Patients with Myocardial Infarction

LGE-Gadolinium

USPIO
Patients with Myocardial Infarction
Patients after Myocardial Infarction Or CABG Surgery (R2*=1/T2*)

Alam et al. Circ Cardiovasc Imaging 2011;5:559-565
Myocardial Measurements After USPIO Infusion

Absolute R2* Value Increase Post USPIO Infusion

- Healthy Volunteer Myocardium
- Remote Myocardium post MI
- Myocardium post CABG
- Infarct Zone post MI
Elafin Myocardial Protection from Ischaemia Reperfusion (EMPIRE) injury
Shirjel Alam & Peter Henriksen

Metabolism and Inflammation in Carotid Atherosclerosis (MICA) Study
Alex Vesey

Cardiac Sarcoidosis, Myocarditis and Transplant Rejection
Colin Stirrat & Shirjel Alam
SPIOs and Cell Labelling
SPIO-Labelled Cells
‘The Arbab Method’

Arbab et al. Blood 2011;104:1217-1223
Magnetic Resonance Imaging Of SPIO-Labelled Cells *Embedded in Agarose*

$1.25 \times 10^5$ cells

$x 10^4$

$x 10^3$

$x 10^2$
SPIO-Labelled Cells

*In Vitro Viability*

Richards et al. *Circ Cardiovasc Imaging* 2012;5:509-517
SPIO-Labelled Cells

In Vitro Function

Transwell Migration Assay

Modified Boyden Chamber

Upper chamber: cell suspension (~ 250,000 cells) in RPMI

Microporous (5 μm) membrane

Lower chamber: 600 μL RPMI +/- MCP-1
Migration Assay

Clumping

Original Method

Edinburgh Method
SPIO-Labelled Mononuclear Cells

*In Vitro Characterisation*

Richards et al. *Circ Cardiovasc Imaging* 2012;5:509-517
SPIO-Labelled Cells

Liver take up of SPIO-labelled mononuclear cells

In Vivo Intravenous Administration in Mice
No Toxicity Noted
Venesection & Leukapheresis

Richards et al. *Circ Cardiovasc Imaging* 2012;5:509-517
SPIO-Labelled Mononuclear Cells

Intravenous Administration in Man

Richards et al. *Circ Cardiovasc Imaging* 2012;5:509-517
SPIO-Labelled Mononuclear Cells

Summary

- USPIO – iv administration
- Cardiovascular non-invasive assessment of AAA and myocardium
- Other applications?

- SPIO – cell labelling
- Non-invasive assessment of inflammation
- Chronic pathology?
- Validation in murine models
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