Superparamagnetic iron oxide-enhanced magnetic resonance for imaging cardiac inflammation. A minireview

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Background. Advances in nanotechnology have lead to the development of a novel contrast media for Magnetic Resonance Imaging (MRI) – the superparamagnetic iron oxide nanoparticle (SPIO). SPIO nanoparticles are used to image inflammation on the cellular level in various settings.
This review covers the physicochemical characteristics of SPIO particles as well as relevant animal and clinical studies and discusses the potential of SPIO particles to image cardiac inflammation including cardiac graft rejection.
Methods. We searched the scientific biomedical databases Medline/PubMed, BioMedCentral, Google Scholar, Ovid and, ProQuest from to 2000 to 2013 for publications relevant to the topic.
Conclusions. SPIO nanoparticles due to their unique properties could become a useful tool in imaging cardiac inflammation. However, the task is to find a suitable particle size and coating with corresponding pharmacokinetics, establish the right dose and MRI scan timing for individual applications.

Key words: magnetic resonance imaging, inflammation, superparamagnetic iron oxide

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CHARACTERISTICS OF SPIO

Advances in nanotechnologies in the last decades have enabled vast progress in molecular and cellular imaging. It allows the non-invasive visualization of the cells and even molecules inside living organisms. One of the substances capable of imaging cells in Magnetic Resonance Imaging (MRI) is the superparamagnetic iron oxide nanoparticle (SPIO). SPIO particles for intravenous use consist of an iron oxide (maghemite or magnetite; γ-Fe2O3 or Fe3O4) core coated with dextran or carboxydextran. The coating isolates iron core from plasma components thus prolonging plasma circulation time. It also prevents particles from aggregation and makes them biocompatible, soluble and stable[1].

Mechanism of action

The main principle behind SPIO nanoparticles is their large magnetic moment in the presence of an external magnetic field, but no magnetic moment when the field is zero[2]. This is referred to as superparamagnetism.

In the MRI, the presence of SPIO particles leads to shortening of the T2/T2* relaxation time. In other words, the SPIO particles are visible in MRI as hypointensities in the T2 weighted image. Under certain circumstances, the SPIO particles can also have a T1 relaxation effect.

There are a variety of core sizes and types of coating corresponding to different pharmacokinetics, blood half- life, biodistribution and magnetic properties of each particle[3]. The nanoparticle coating allows the attachment of various ligands[4].

After intravenous administration, the SPIO particles are eliminated from blood by being phagocytosed by circulating immune cells, mostly macrophages. In case of greater permeability of the vessel walls, such as occurs in inflammation, the SPIO particles leak into the interstitium and become phagocytosed by tissue macrophages. Thus, macrophages become labeled and detectable in MRI in vivo. The iron core is released from the coating inside of a macrophage. Iron then either enters the intracellular storage iron pool as ferritin or is transferred to plasma as transferrin. The latter is transported to erythroid precursor cells in bone marrow to be incorporated into haemoglobin[5].

The viability and function of human mononuclear peripheral blood cells labelled with SPIO particles remains unaffected. After in vitro labeling, these cells were injected into the venous system and were tracked to the site of inflammation – a tuberculin skin test in healthy volunteers[6].

Types of SPIO

SPIO nanoparticles are classified by size as very small (4-8 nm), ultrasmall (10-40 nm), small (60-200 nm) and large (300 nm–3.5 μm). See Table 1.

The size of the particle determines its biodistribution and plasma circulation time[1]. Generally, the larger particles, the faster the uptake into the reticuloendothelial system cells, and the better the contrast on MRI. Smaller

Table 1. Overview of clinically tested types of SPIO.

International non-proprietary name	Particle size	Indications
Ferumoxid	120-180 nm	liver imaging, cell labeling
Ferumoxtran	15-30 nm	metastatic lymph node and macrophage imaging, blood pool agents, cell labeling
Ferumoxytol	30 nm	iron deficiency anemia treatment in patients with chronic kidney disease, macrophage imaging, blood pool agent, cell labeling
Ferumoxsil	300 nm	orally administered for gastrointestinal system imaging
Ferucarbotran	21 nm	blood pool agent, cell labeling, liver imaging

Modified from[1,2,6]

particles have a longer blood half-life and larger fraction may end up in the lymphatic system. The smaller particle, the deeper it can travel into a tissue. There is a variety of types of coating corresponding to different pharmacokinetics[3]. Nanoparticle coating allows attachment of various ligands, such as macrophage receptors, monoclonal antibodies or cell adhesion molecules[4,7].

Comparison to gadolinium

SPIO particles as MRI contrast agents, offer several advantages over gadolinium contrast agents. They are safe to use in patients with or at risk of nephrogenic systemic fibrosis. Compared to gadolinium, the superparamagnetic contrast media do not leak into interstitium, have a long blood half-life and higher relaxivity. This together with better safety profile and accumulation in macrophages, could make SPIO particles compete with gadolinium contrast agents in the future.

Vascular contrast media

The long blood circulating half-life and no leak into the interstitium makes SPIO particles a perfect vascular contrast medium. It has been shown in human studies, that SPIO enhanced MRI was suitable for imaging of large vascular structures such as cardiac chambers, aorta and pulmonary arteries[8]. It was better than non-enhanced MRI in depicting deep vein thrombosis[9] and hemodialysis fistulas[10]. SPIO-enhanced MRI was tested for imaging myocardial perfusion[11] and for MRI coronary angiography, where SPIO particles were moderately accurate in the detection of significant coronary artery stenosis[12].

Imaging of inflammation

SPIO particles showed not only the ability to image inflammatory processes in vivo[13,14], but also demonstrated the potential to monitor the effect of anti-inflammatory drugs in a number of studies, both animal[15,16] and human[17]. There are two ways how SPIO particles display the inflammation. One actually visualizes increased vessel wall permeability. SPIO particles are strictly intravascular pool agents, meaning they only leak into interstitium in case of higher permeability of vessel wall, as observed in inflammation. Inflammation is then seen as a perivascular leak of SPIO. This effect is achieved early after intravenous administration of SPIO. The latter comes when the particles are phagocytosed by the macrophages. It happens both in the blood stream and in the area of inflammation. The SPIO labeled macrophages are visible on MRI T2 weighted image as dark speckles or hypointensities in the tissue. These two effects overlap in time, with the former prevailing hours after drug administration, the later approximately one to two days after the administration. In a study in mice with experimental stroke, it has been shown that most of the SPIO enhancement 24-hours post ischemic brain injury was caused by non-specific mechanisms such as brain-blood barrier leakage, rather than peripheral phagocyte infiltration[15,18]. After 48 h post ischemic brain injury, most iron related signal changes on MRI were indisputably associated with macrophages, as detected on histology[19].

Atherosclerosis is now understood as a multi-factorial chronic inflammatory disease, characterized by intense immunological activity with macrophages and T-lymphocytes being the major players. The high macrophage content in the atherosclerosis plaque in SPIO-enhanced MRI is considered a sign of a plaque vulnerable to rupture due to ongoing inflammation[20]. Similarly, in cerebral aneurysms, the uptake of SPIO particles in MRI is a sign of instability with a higher probability of rupture[21]. SPIO enhanced MRI in human carotid atheroma identified macrophages in vivo, which was validated with histology in patients scheduled for carotid endarterectomy[22]. The SPIO enhanced MRI was also used for testing the effect of aggressive lipid-lowering therapy in both animal[16] and human carotid plaque[17].

Myocardial infarction is associated with inflammation, as an influx of macrophages can be seen in post mortem histology. The effect of anti-inflammatory drugs after acute myocardial infarction has been tested with the prospect of better myocardial repair and regeneration. In recently published studies, SPIO particles were used to visualize the inflammation accompanying acute myocardial infarction in humans[23-25].

Acute cellular graft rejection of the heart is characterized by immune cell infiltration, edema and myocyte damage, which results in impaired mechanical left ven-

tricle function. Most non-invasive approaches to detect rejection, display only the result - the disturbance in ventricle mechanics. In contrast, the SPIO particles have a potential to display the primary process and thus detect graft rejection in very early stages.

In animal studies, SPIO particles showed the ability to detect rejection in renal, lung and heart transplants in rats[26]. Macrophages labeled with SPIO particles induced a significant decrease in MR signal intensity in the allograft, and the degree of signal attenuation had an excellent correlation with the pathological rejection grade[27,28]. Another study in rats showed acute cardiac transplant rejection using SPIO blood pool contrast agent. MRI was performed 43 min after SPIO infusion and featured increased vessel permeability for iron oxide in rat hearts undergoing rejection. The degree of rejection confirmed by histology correlated with increase in endothelial permeability for iron oxide particles[29].

To the best of our knowledge, there has been no human study applying SPIO enhanced MRI to detect heart transplant rejection as human applications have many pitfalls. Moderate and severe graft rejection demands immediate treatment which results in immediate immune response. From this point of view, a time period of 24 to 48 h from administering contrast agent to MRI may seem too long and perhaps a blood pool contrast agent would be more suitable in clinical settings.

A human study using SPIO enhanced MRI in the field of transplantology was the one by Hauger et al. and involved the kidneys. This team published a study where SPIO-enhanced MRI was applied for imaging macrophage infiltration in kidneys in patients scheduled for kidney biopsy. Two patients with transplant kidneys were included. In these two patients, MRI revealed a clear visible signal loss in all renal compartments, more pronounced in the medulla. Histological examination revealed numerous macrophages, resulting in diagnosis of acute kidney rejection[14].

In experimental autoimmune myocarditis in rats, the iron oxide superparamagnetic and fluorescent nanoparticles provided better image contrast and detectability of focal myocardial inflammation compared to conventional MRI (ref.[30]). To our knowledge, there has been no human study published using SPIO enhanced MRI in myocarditis or sarcoidosis yet.

CONCLUSION

SPIO–enhanced MRI has shown clinical potential in various medical fields and several advantages over gadolinium, such as better safety profile and macrophage accumulation. SPIO nanoparticles have proven ability to feature myocardial inflammation in various animal studies and lately also in patients after myocardial infarction, yet further clinical use of SPIO nanoparticles in imaging cardiac inflammation remains to be a challenge.

ABBREVIATIONS

SPIO, Superparamagnetic iron oxide; MRI, Magnetic resonance imaging.

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