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Enhancement Effect of Superparamagnetic Iron Oxide Nanoparticle-Based MRI Contrast Agent at Different Concentrations and Magnetic Field Strengths

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***Abstract*—**Magnetic Resonance Imaging Contrast Agents (MRI-CM) are significant in the clinical and biological imaging as they have the ability to alter the normal tissue contrast, thereby affecting the signal intensity to enhance the visibility and detectability of images. Superparamagnetic Iron Oxide (SPIO) nanoparticles, coated with dextran or carboxydextran are currently available for clinical MR imaging of the liver. Most SPIO contrast agents are T2 shortening agents and Resovist (Ferucarbotran) is one of a clinically tested, organ-specific, SPIO agent which has a low molecular carboxydextran coating. The enhancement effect of Resovist depends on its relaxivity which in turn depends on factors like magnetic field strength, concentrations, nanoparticle properties, pH and temperature. Therefore, this study was conducted to investigate the impact of field strength and different contrast concentrations on enhancement effects of Resovist. The study explored the MRI signal intensity of Resovist in the physiological range of plasma from T2-weighted spin echo sequence at three magnetic field strengths: 0.47 T (r1=15, r2=101), 1.5 T (r1=7.4, r2=95), and 3 T (r1=3.3, r2=160) and the range of contrast concentrations by a mathematical simulation. Relaxivities of r1 and r2 (L mmol^{-1} Sec^{-1}) were obtained from a previous study and the selected concentrations were 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, and 3.0 mmol/L. T2-weighted images were simulated using TR/TE ratio as 2000 ms /100 ms. According to the reference literature, with increasing magnetic field strengths, the r1 relaxivity tends to decrease while the r2 did not show any systematic relationship with the selected field strengths. In parallel, this study results revealed that the signal intensity of Resovist at lower concentrations tends to increase than the higher concentrations. The highest reported signal intensity was observed in the low field strength of 0.47 T. The maximum signal intensities for 0.47 T, 1.5 T and 3 T were found at the concentration levels of 0.05, 0.06 and 0.05 mmol/L, respectively. Furthermore, it was revealed that, the concentrations higher than the above, the signal intensity was decreased exponentially. An inverse relationship can be found between the field strength and T2 relaxation time, whereas, the field strength was increased, T2 relaxation time was decreased accordingly. However, resulted T2 relaxation time was not significantly different between 0.47 T and 1.5 T in this study. Moreover, a linear correlation of transverse relaxation rates (1/T2, s–1) with the concentrations of Resovist can be observed. According to these results, it can conclude that the concentration of SPIO nanoparticle contrast agents and the field strengths of MRI are two important parameters which can affect the signal intensity of T2-weighted SE sequence. Therefore, when MR imaging those two parameters should be considered prudently.

***Keywords*—**Concentration, Resovist, Field strength, Relaxivity, Signal intensity.

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I. Introduction

MAGNETIC Resonance Imaging (MRI) has been extensively explored as a versatile platform for routine medical and biological imaging with a high degree of spatial resolution, excellent soft tissue contrast and absence of radiation risk. Generally, the MRI contrast originates due to the signal intensity of the imaging sample, produce from magnetization of the protons. The degree of magnetization is determined by the properties of the imaging sample with the applied pulse sequence and applied magnetic field strength [1]. However, the nature of insufficient inherent sensitivity at the small clinical diagnostic targets in complex tissue environments requires the application of MRI contrast agents for better pathological delineation and precise diagnosis [2]-[4].

MRI contrast agents are substances which can alter the tissue relaxation thereby affecting the contrast enhancement [1]. A number of contrast agents have been currently available in the clinical and biological settings. Their efficacy is determined based on the magnetic properties, pharmacokinetics properties (bio-distribution) and the dominant effects of the agent at the image enhancement [2], [4]-[6].

A. Magnetic Properties of MRI Contrast Agents

Paramagnetism- Paramagnetic substances are metals with un-paired electrons in the outer orbital shells. Currently, most MRI contrast agents in the clinical setting are based on the paramagnetic metal ions [6]

Superparamagnetism- Superparamagnetic agents are composed of magnetite (Fe3O4) or maghemite (γ- Fe2O3), water in-soluble iron oxide crystals which often referred to as nanoparticles. Each of this nanoparticle contains several thousand paramagnetic Fe ions (Fe2+ and Fe3+). When these Fe ions are magnetically arranged in the crystals, they can create a large net magnetic moment (with the presence of external magnetic field) which is greatly exceeded that of typical paramagnetic ions [6].

B. Bio-Distribution

Three types of contrast agents can be determined based on how they distribute in-vivo after intravenous administration.

Small molecular weight contrast agents which are able to diffuse through the vascular membrane, distribute in extra-vascular fluid (ECF). These agents are referred as ECF agents. Some contrast agents with large molecular weight, are unable to transfer through the vascular membrane. Therefore, they are remaining inside the blood stream. These types of contrast agents are referred as intravascular agents and most of the iron oxide particles included into this category. Some contrast agents are specifically accumulated in a given organ or tissue type. These agents are referred as tissue specific contrast agents.

[6].

C. Image Enhancement

Based on the relaxivities (r2 = transverse relaxivity or r1= longitudinal relaxivity measures from L mmol^{-1} s^{-1}) and image enhancement of MRI contrast agents, T2 and T1, two types of contrast agents can be identified. Higher relaxivities of these contrast agents with optimizing the value of the r1/r2 ratio in each case leads to a more effective contrast enhancement [3], [4], [7].

The relaxivity (r_{1or2}) for a MRI contrast agent can be calculated according to (1):

$$r_{1or2} = \left[\frac{1}{T_{1or2}} - \frac{1}{T_0} \right] / C_{CA} \quad (1)$$

where 1/T 1 or 2 denotes the T1 (longitudinal) or T2 (transverse) relaxation rate of the contrast solution, T_0 is the relaxation time of the solvent without contrast agent, C_{CA} is the concentration of ions, responsible for the contrast. This relaxivity of the contrast agent is generally dependent on the strength of the applied magnetic field, the temperature and the concentration as expressed in (1). Therefore, it is essential to consider those parameters when measuring the relaxivities [4], [5].

TABLE I
RELAXIVITIES OF RESOVIST AT THREE DIFFERENT FIELD STRENGTHS OBTAINED FROM A PREVIOUS STUDY

Trade name	**0.47 T**		**1.5 T**		**0.47 T**	
	r1	r2	r1	r2	r1	r2
Resovist	15	101	7.4	95	3.3	160

All values were reported in l mmol-1 sec-1 [4]

D. Iron Oxide Nanoparticles as Contrast Agents of MRI

Although there are many paramagnetic metal ions available, Gadolinium based paramagnetic compounds (mainly Gadolinium-diethylenetriamine pentaacetic acid chelate (Gd-DTPA) and other derivatives) are the most readily applicable conventional MRI contrast agents which produce positive contrast enhancement on T1-weighted images [8]. As mentioned before, paramagnetic materials are metals with unpaired electrons in the outer orbital shells (transition and lanthanide metals), giving rise to magnetic dipoles when exposed to a magnetic field [6]. As a result of the composition of seven unpaired f-electrons, the Gadolinium-based compounds can induce a large magnetic fluctuation or magnetic momentum experienced by surrounding protons [6]-[9]. If the induced frequency due to this fluctuation becomes closer to the Larmor frequency of the system, it creates a significant enhancement of proton relaxation [6]. However, because of the limitations of non-specific target-tissue distribution, side effects and fast elimination from the tissues, created a path to identify, improve and develop the other types of MRI contrast agents [8], [10].

Iron oxide nanoparticles are one of a common type of substances which utilize for producing the tissue-specific contrast agents used in contrast-enhanced MRI without the base of Gadolinium [11], [12]. Different sizes of iron oxide particles are available in the clinical settings. So from those, usually the iron oxide particles which have more than 50 nm (>50 nm) in diameter are referred as Superparamagnetic Iron Oxide (SPIO) agents while others that have less than 50 nm (<50 nm) in diameter is referred as ultra-small superparamagnetic iron oxides (USPIO) agents [13]. Two iron oxide-based agents have been developed and clinically approved for MR imaging in the world: ferumoxides (Endorem, distributed in the USA as Feridex) and ferucarbotran (SH U 555 A, Resovist) [13].

In addition to the MRI contrast enhancement, these SPIO agents have demonstrated great potential applications in many medical and biological fields, including tissue repair, bio-separation and cancer treatment through hyperthermia [8]. These SPIO agents which composed of nano-sized iron oxide crystals usually coated with dextran or carboxydextran. As mentioned before, the optimization of r2, r1 values together with the r1/r2 ratio by the facile tuning of the nanoparticle magnetic properties allows to serve these SPIO agents as effective T2 or T1 MRI contrast agents (by generation a hyper or hypo-intense signals). As a consequence of the local magnetic field perturbations induced by these magnetized iron oxide cores in the presence of an external magnetic field, the alternation of the tissue signal occurs by means of precession frequency difference of the water protons [3], [14]. The effect of this process more pronounced in T2 and T2 * relaxation property of the tissue. Therefore, MR imaging is generally performed using T2 or T2*-weighted sequences with SPIO agents providing a negative, hypo-intense signal on the acquired images [8], [15].

Gadolinium-based MR contrast agents have liver-specific properties which can target hepatocytes. Unlike them, Kupffer cells in the reticuloendothelial system (RES), primarily in the liver, have the ability to selectively taken the SPIO agents and exert their effects on the alternation of both T2- and T1-relaxation times [6].

E. The Resovist as the MRI Contrast Agent

As mentioned before, Resovist (ferucarbotran) is one of a clinically approved SPIO MRI contrast agent coated with low molecular weight carboxydextran. This contrast agent exhibits an approximate hydrodynamic diameter of 60 nm and it composed of Fe_3O_4 core material [4], [15]. Furthermore, as because of a SPIO agent, Resovist is considered to be an organ-specific contrast agent which can be implemented to detect the pathological conditions in the Liver. However, due to the smaller core diameter, it enables the enhancement effect on T1-weighted images in addition to the T2 contrast enhancement (same like ultrasmall superparamagnetic iron oxides (USPIO)

agents). Moreover, administration of Resovist can be done as a rapid bolus which allows the application in both dynamic and delayed imaging techniques [15].

When considering safety profiles of the Resovist, overall reported incidence of adverse events was 7.1% (75/1053 subjects). Among them, the most common adverse reactions reported were vasodilatation and paraesthesia (< 2%). Resovist is first approved in Sweden in the year 2001 and it is currently available in Europe and major Asian countries. Comparable to Feridex/Endorem, the safety profile appears more favorable for Resovist [13].

The enhancement effect of Resovist also depends on various intrinsic, extrinsic parameters and the relaxivity is the main influential factor which affects for this enhancement process. However, the concentration and the magnetic field strength have the ability to manipulate the relaxivity of MRI contrast agents. Therefore, understanding the relationships between these parameters and the relaxivities that contribute to MRI contrast can provide an essential guidance that may direct towards a precise diagnosis with increased lesion conspicuousness. The optimization of contrast enhancement utilizing different parameters also important in economic implications [16]. Therefore, this article intends to find out the impact of different contrast concentrations on the enhancement effect of Resovist at different magnetic field strengths

II. Materials and Method

This study was mathematically simulated the MRI signal intensity for different concentrations of Resovist at three magnetic field strengths by assuming the T2-weighted spin echo sequence. The selected field strengths were 0.47 T, 1.5 T and 3 T and concentrations were 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, and 3.0 mmol/L. According to the assumption, T2-weighted images were simulated using TR/TE ratio as 2000 ms /100 ms. Relaxivities of r1 (L mmol-1 Sec-1) and r2 (L mmol-1 Sec-1) were obtained in the physiological range of plasma at the temperature of 37-40 ^{0}C from a previous study (Table I) [5].

The spin echo sequences (SE) utilize the SE signal (S) to produce the SE images can be expressed as:

$$S = \rho\left(1-\exp^{\left(\frac{-TR}{T1}\right)}\right)e^{\frac{-TE}{T2}} \quad (2)$$

where ρ, TR and TE are proton density, Time of Repetition and Time of Echo, respectively [17]. This expression demonstrates that proton density spin echo images are modified by the ratios of TR/T1 and TE/T2. To simulate the signal intensities at different concentrations of Resovist, this expression has utilized with the combination of (1).

III. Results and Discussion

The contrast agents are typically used in plasma at the body temperature of 37°C. Therefore, in this study the available r1 and r2 relaxivities of Resovist in plasma at 37-40^{0}C were extracted from the literature [5].

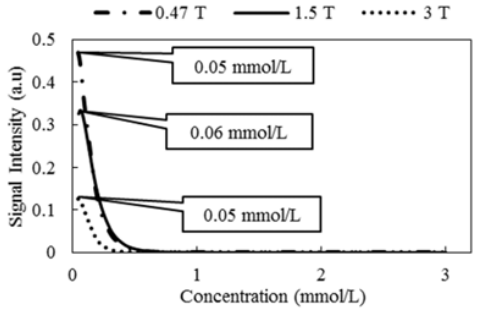

Fig. 1 A plot of signal intensity with different concentration of Resovist at different field strengths obtained from T2-weighted SE sequence

Simulated signal intensity values using relaxivities in plasma (37– 40^{0}C) at three magnetic field strengths are summarized in Fig. 1. These results confirm that the exact relationship between the obtained MRI signal intensity in T2-weighted spin echo sequence and Resovist concentration is nonlinear and it depends on the magnetic field strengths. A significant signal intensity changes can be identified only up to 0.5 mmol/L concentration and beyond this limit the produced signal intensity is unable to discriminate. Moreover, the field strength dependence of the obtained signal intensity was also found to be more pronounced at low concentrations (< 0.06 mmol/L) and the highest signal intensity can be observed at the field strength of 0.47 T. The maximum signal intensities for 0.47 T, 1.5 T and 3 T were observed at the concentration levels of 0.05, 0.06 and 0.05 mmol/L, respectively and theses signal intensities are exponentially decaying with the increase of Resovist concentration [18]. These results are in agreement with the previous study results conducted by [19] which demonstrated a gradual concentration dependent signal-drop of Resovist.

As demonstrated in Fig. 2, a higher T2 relaxation time can be observed at low field strength with low concentration levels. With increasing concentration of Resovist, the T2 time of the protons is shorter, indicated by the steeper exponential decay of the T2 relaxation time. This process confirms that the decay rate is dependent on iron oxide concentration [20]. As mentioned before, the T2 relaxation time is decreasing with the increasing of the field strength. This T2 relaxation pattern with the concentration corroborates with the literature which was done using hydrated $MnCl_2$. $GdCl_3$ and Optimark under the earth magnetic field [21]. Moreover, as demonstrated in Fig. 2, a significant difference of the T2 relaxation time was unable found between 0.47 T and 1.5 T in this study.

Fig. 3 depicts the linear correlations of transverse relaxation rates (1/T2, s–1) of Resovist against the concentrations. According to the literature [5], the highest transverse relaxation rates of 1/ *T*2 is yielded at the highest selected magnetic field strength of 3 T and the difference of the transverse relaxation rates between 0.47 T and 1.5 T is minimum. Fig. 3 also demonstrates that the difference between the transverse relaxation rates in each magnetic field at low concentrations is comparatively minimum than the higher concentration levels.

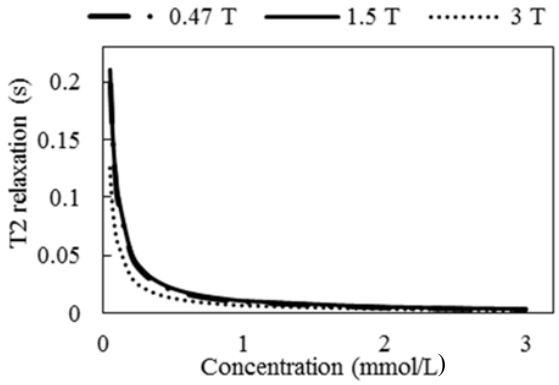

Fig. 2 T2 relaxation time as a function of different concentrations of Resovist at different field strengths

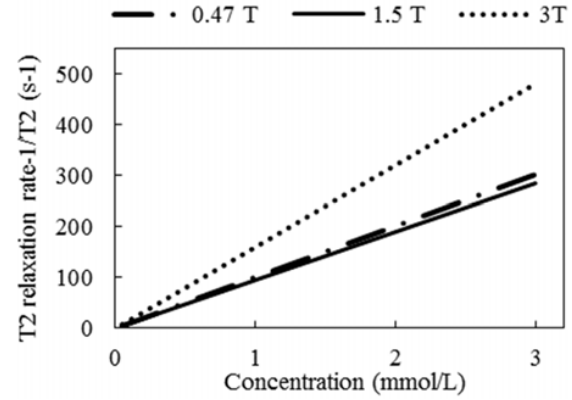

Fig. 3 Transverse relaxivity r2 (1/ T2) as a function of different concentrations of Resovist

IV. Conclusions

This study has investigated the impact of field strength and different contrast concentrations on enhancement effects of Resovist. According to the obtained results, it clearly demonstrates that the magnetic field strength and the contrast agent concentrations are important parameters which affect for generating the signal intensity. Furthermore, the results indicated that those two parameters have altered the signal intensity of Resovist in T2-weighted SE imaging sequence. A comparatively higher signal intensity was achieved in the low magnetic field strengths with the application of low contrast concentration in T2-weighted SE imaging sequence. Moreover, in each selected magnetic field strengths, the signal intensity of Resovist was exponentially decreased with the increase of the concentrations. However, in this study Resovist demonstrated a comparatively similar effect on transverse relaxation rates (1/T2, s–1) with the concentration in both 0.47 T and 1.5 T magnetic fields.

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