

Effect of iron oxide nanoparticles coating type on the relationship between nanoparticles concentration and signal intensity in inversion recovery T1-weighted MRI

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Abstract

Background: Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles are used as blood pool contrast agent for magnetic resonance angiography and perfusion imaging. Our aim in this study was to investigate the effect of the two coating types of iron oxide nanoparticles on the relationship between nanoparticles concentration and signal intensity (SI) in T1-weighted MR images.

Methods: Different concentrations of the polyethylene glycol (PEG), and carboxydextran-coated iron oxide nanoparticles were imaged using inversion recovery Turbo-FLASH (Turbo fast low-angle shot) pulse sequence with inversion times (TIs) of 300-900 ms (interval of 100 ms). The maximum non-linear and linear relationship between the corrected SI (after non-uniformity correction) and the concentration of the two coated nanoparticles were calculated in T1-weighted images.

Results: The maximum non-linear relationship between the corrected SI and the concentration of the PEG, and carboxydextran-coated nanoparticles were obtained at concentrations of 400 and 200 $\mu\text{mol Fe/L}$ at a TI of 900 ms, respectively. In addition, the maximum linear relationship between the corrected SI and the concentration of the PEG, and carboxydextran-coated nanoparticles ($R^2=0.99$) appeared at 228.184 and 205.654 $\mu\text{mol Fe/L}$ with a TI of 300 ms, respectively.

Conclusion: The maximum non-linear corrected SI of the carboxydextran-coated nanoparticles was slightly higher than that of the PEG-coated nanoparticles at similar TIs. However, the PEG-coated nanoparticles were better than the carboxydextran-coated nanoparticles as a T1 contrast agent for perfusion measurements.

Keywords: MRI, T1-weighted image, Iron oxide nanoparticles, Coating, Inversion recovery.

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Introduction

Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles are used as blood pool contrast agent (BPCA) for magnetic resonance angiography (MRA) and perfusion imaging. Their large magnetic moment and the intravascular distribution of the nanoparticles make them contrast agents for MR perfusion studies (1). The high r_1 relaxivity of the nanoparticles leads to a reduction of the blood T1 for a long period and

produces high blood signal (2). The T1 effect of contrast agents is enhanced by the use of T1-weighted images. Moreover, among various types of MR sequences, the inversion recovery (IR) sequence is useful for MRA and perfusion imaging because of the excellent blood suppression and visualization of small amounts of contrast agent (3). Selecting an appropriate inversion time (TI) for the IR pulse sequence is important for providing significant diagnostic infor-

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mation. The TI itself is affected by the dose of the contrast agent (4, 5).

The coating material surrounding the iron oxide core of the nanoparticles affects the relaxivity, chemical stability, biocompatibility, biodistribution, and blood half-life of the nanoparticles (1, 6, 7). So far, different types of coating materials, including dextran (1), carboxydextran (8), carbohydrate-polyethylene glycol (PEG) (1), and citrate (9, 10), have been used for MRA and perfusion studies. Comparisons of citrate-coated iron oxide nanoparticles with gadopentetate dimeglumine for first-pass MRA of the aorta and renal arteries (9) and with gadofosveset trisodium for cardiac MRA in pigs (10) were performed and demonstrated the advantages of nanoparticles for the studies. Since the SI of MR images is affected by the concentration of the nanoparticles, some researchers have evaluated the relationship between iron oxide nanoparticles concentrations and SI using dextran (11, 12) and carboxydextran-coated (8, 13) particles. They reported the nanoparticles' concentration which led to maximum linearity between concentration and SI, or maximum signal enhancement. One study evaluated the effect of the coating material on the accumulation of iron oxide nanoparticles in the axillary lymph nodes for MR lymphography (14). However, it is not clear which coating type of USPIO nanoparticles is useful for MR perfusion measurement and which nanoparticles' concentration leads to the maximum SI.

The present study was focused on comparing the relationship between SI and different concentrations of the two types of coated (carboxydextran and PEG) USPIO nanoparticles in T1-weighted images by use of the IR Turbo-FLASH sequence with different TIs. Therefore, by determining which coated nanoparticles produce a higher SI with a lower concentration, it is possible to use a lower dose of contrast agent for MR studies.

Methods

Contrast Agents

Nanomag-D-spio nanoparticles (Micro-mod Partikeltechnologie GmbH, Rostock, Germany) with a mean diameter of 20 nm, a core size of 7 nm and two different coating materials including carboxydextran (COOH) and PEG were used as contrast agents. The concentration of Fe in ferrofluids was measured with an atomic absorption spectrometer (analytik jena, novAA® 400, Jena, Germany). The nanoparticles were diluted with distilled water, and different concentrations of both types of the coated particles were prepared. The concentrations were 0 to 100 µmol Fe/L (5 µmol Fe/L intervals) and 100 to 500 µmol Fe/L (100 µmol Fe/L intervals).

To obtain the real SI, the uniformity of the coil should be considered (15). The preparation of a constant concentration (50 µmol Fe/L) of the PEG-coated nanoparticles was also performed for measurement of the non-uniformity of the coil.

The glass vials were filled with different concentrations of each type of the nanoparticles and separately put into a perspex phantom with the dimensions of 13×13×13 cm³.

Theory

Standard IR sequence was used for SI calculation (16):

$$S(t) = S_0 \left[\frac{1 - 2 \exp\left(-TI \left(\frac{C(t)}{K} + \frac{1}{T1_{Pre}}\right)\right)}{\exp\left(-TR \left(\frac{C(t)}{K} + \frac{1}{T1_{Pre}}\right)\right)} + 1 \right], \quad (1)$$

Where S(t) and C(t) are the SI after administration of the contrast agent and the concentration of the contrast agent at time t, respectively. S₀ is the observed SI in the absence of contrast agent, TI is inversion time, T1_{Pre} is the longitudinal relaxation time before contrast application, and TR is the repetition time. K is a constant that depends on the contrast agent. The T2-shortening effect is negligible at low concentrations of the contrast agent while at

high concentrations of the nanoparticles; Eq. 1 should be multiplied by $\exp(-\frac{TE}{T2})$

where TE is echo time (16).

Image Acquisition

MR imaging was performed with a 1.5 T MRI system (Siemens MAGNETOM Avanto, Germany). A standard clinical head coil was used for MR imaging. The phantom containing vials filled with different concentrations of each contrast agent was carefully placed in the center of the coil.

An IR Turbo-FLASH pulse sequence was performed for T1-weighted MR imaging in a coronal orientation. The MR imaging parameters were: 920 ms/ 2.5 ms/ 15° (TR/ TE/ flip angle); 10 mm slice thickness; 128×128 matrix size, and 2 signal averaging. The imaging parameters were applied for the phantom consists of different concentrations and then for the phantom containing constant concentration which was exactly placed at the same position of the vials with different concentrations.

Since for TIs less than 300 ms, the T1 recovery curve did not cross the horizontal axis, TI values were chosen between 300 and 900 ms (with 100 ms intervals) for this study.

Image Analysis

The image data in DICOM format was analyzed using the Interactive Data Language (IDL, Research Systems, Inc. <http://www.rsinc.com>) software. SI of each vial was determined in a region of interest (ROI) consists of 9 pixels in the center of the vial. Then calculation of the correction factors for the coil non-uniformity was performed by in-house IDL programs and the corrected SI was calculated with multiplying these factors by the SI of the vials with different concentrations. Plotting the curves and estimating the maximum linear relationship between SI and TI with squared correlation coefficient (R^2) of 0.99 were also performed by use of in-house IDL programs.

It should be mentioned that both linear (for perfusion study) and non-linear relationships between the maximum corrected SI and the concentration of the two nanoparticles were considered in this study.

Results

The Fe concentrations measured by atomic absorption spectrometer were 1.29 and 1.94 mg/ml for the carboxydextran- and PEG-coated nanoparticles, respectively; which was used for preparation of the different values of concentrations.

Figure 1 demonstrates the coronal image of the phantom containing different concentrations of the nanoparticles.

The mean non-uniformity coil correction factors for the carboxydextran- coated nanoparticles were calculated as 1.05, 1.07, 1.10, 1.03, 1.03, 1.02, 0.99, 1.00, 1.00, 1.06, 0.98, 0.98, 1.00, 0.97, 1.04, 1.03, 1.01, 1.01, 0.99, 1.02, 1.02, 1.01, 0.99, 0.99 and 0.99 for the vials with the concentrations of 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, and 500 $\mu\text{molFe/L}$, respectively.

In addition, the value of non-uniformity coil correction factors for the PEG-coated nanoparticles were calculated as 1.08, 1.10, 1.10, 1.03, 1.03, 1.02, 0.99, 0.98, 1.00, 1.05, 0.98, 0.98, 1.00, 0.97, 1.05, 1.03,

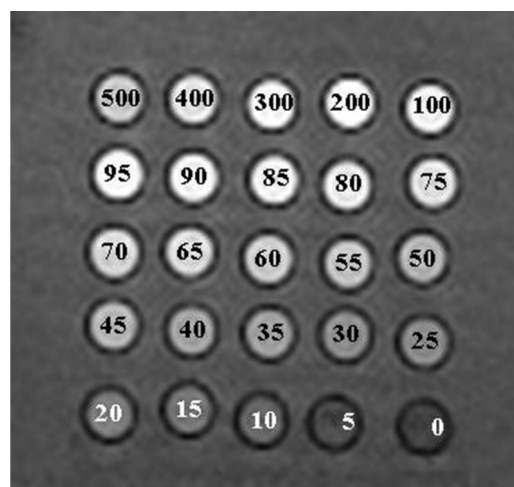


Fig. 1. Coronal image of the phantom. The position of different concentrations ($\mu\text{mol Fe/L}$) of the nanoparticles inside the vials is seen in this figure.

0.98, 1.01, 0.98, 1.02, 1.02, 1.01, 0.99, 1.02, and 1.02 for the vials with the concentrations of 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90,

95, 100, 200, 300, 400, and 500 $\mu\text{molFe/L}$, respectively.

Figure 2 shows the mean corrected SI (for non-uniformity of the coil) from the 9 pix-

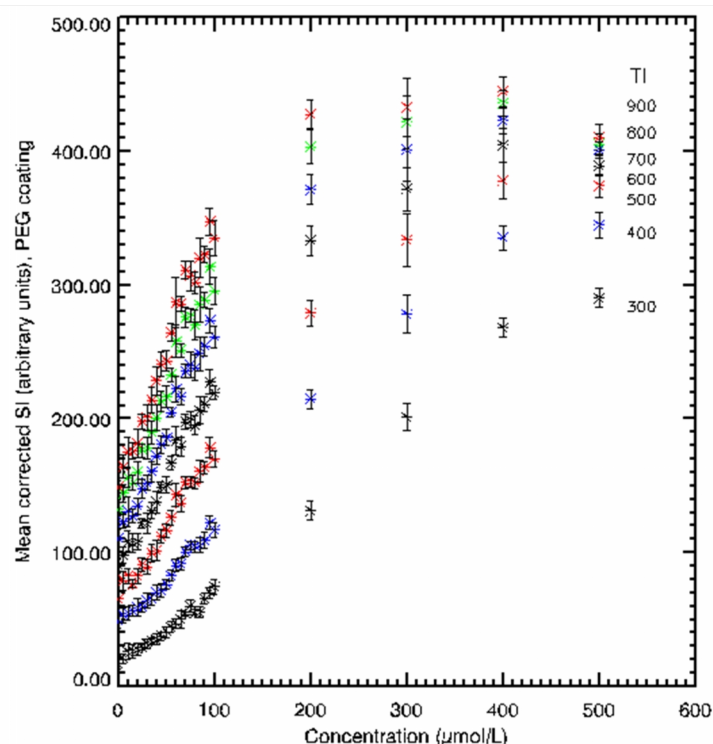


Fig. 2. Mean corrected SI (for non-uniformity of the coil) versus concentration of the PEG-coated nanoparticles at different TIs. The error bars show the standard deviation of the SI from 9 pixels in each vial.

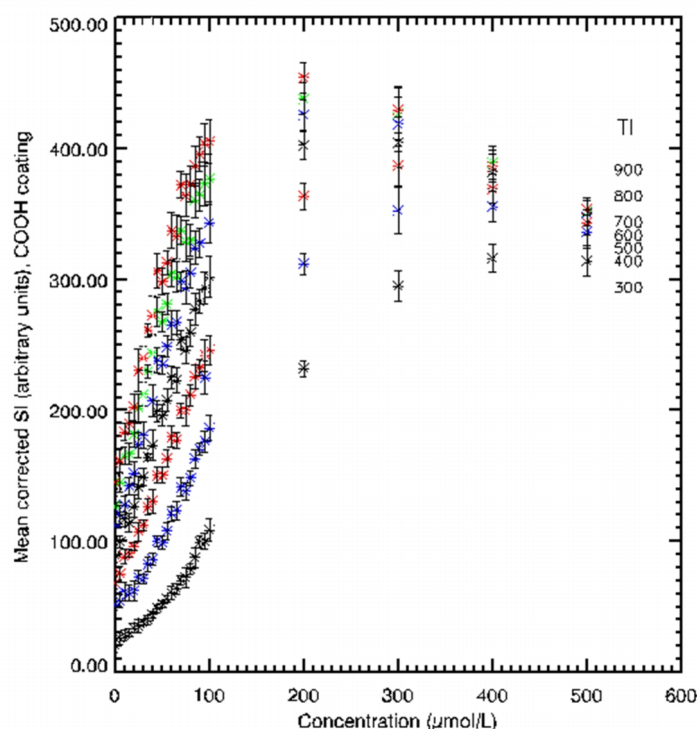


Fig.3. Mean corrected SI (for non-uniformity of the coil) versus concentration of the carboxydextran-coated nanoparticles at different TIs. The error bars show the standard deviation of the SI from 9 pixels in each vial.

els in each vial versus the concentration of the PEG-coated nanoparticles at TIs of 300-900 ms. The maximum non-linear corrected SIs of 290.44 ± 6.90 and 335 ± 8.80 (mean \pm SD) were obtained at a concentration of $500 \mu\text{mol Fe/L}$ for low TIs of 300 and 400 ms, respectively. In addition, the maximum non-linear corrected SIs of 377.9 ± 13.3 , 404.60 ± 12.60 , 442.59 ± 9.80 , 435.94 ± 9.40 , and 148.93 ± 4.60 appeared at a concentration of $400 \mu\text{mol Fe/L}$ for TIs of 500, 600, 700, 800, and 900 ms, respectively.

As Shown in Fig. 2, T1 and T2-shortening effects are dependent on TI and the concentration of the nanoparticles. These effects were seen for all corrected SI versus concentration curves at different TIs. T1-shortening effect appeared at lower TIs (300 and 400 ms) and a concentration of $500 \mu\text{mol Fe/L}$ and led to an increase in the SI. Also a T2-shortening effect at high concentrations (more than $400 \mu\text{mol Fe/L}$) appeared for TIs of 500-900 ms.

Figure 3 indicates the mean corrected SI

(for non-uniformity of the coil) versus the concentration of the carboxydextran-coated nanoparticles at TIs of 300-900 ms. The concentration of $400 \mu\text{mol Fe/L}$ gave the maximum non-linear corrected SIs of 316.21 ± 10.5 and 355.40 ± 11.7 (mean \pm SD) for TIs of 300 and 400 ms, respectively. The maximum non-linear corrected SIs of 402.39 ± 10.60 , 425.75 ± 11.5 , 437.88 ± 12.06 , and 453.95 ± 11.9 appeared at a concentration of $200 \mu\text{mol Fe/L}$ for TIs of 600, 700, 800, and 900 ms, respectively. In addition, the maximum non-linear corrected SI of 386 ± 15.02 was seen at a concentration of $300 \mu\text{mol Fe/L}$ for a TI of 500 ms. The figure also shows T1 and T2-shortening effects for all TIs. These effects will be dependent on the TI and the concentration of the nanoparticles. A T1-shortening effect dominated at lower concentrations and led to an increase in the SI. The T1-shortening effect appeared at lower TIs (300 and 400 ms) and concentration of $400 \mu\text{mol Fe/L}$. Also a T2-shortening effect

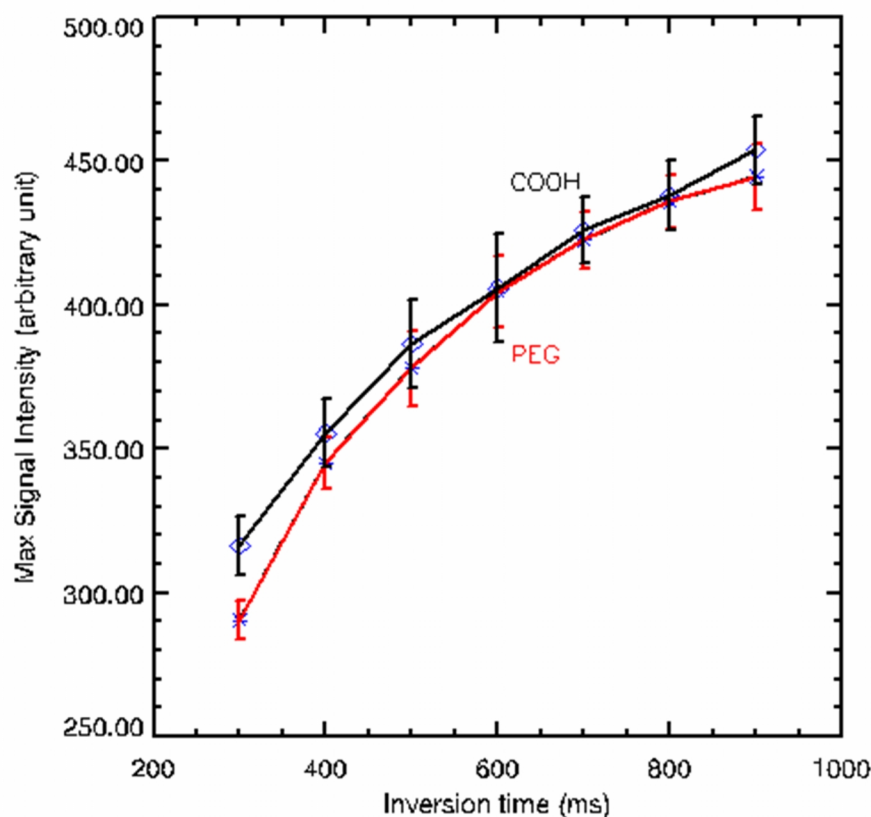


Fig.4. The maximum non-linear SI versus TI for the PEG- and carboxydextran-coated nanoparticles. The figure shows that the maximum non-linear SI of the carboxydextran-coated particles is slightly higher than the PEG-coated particles at the similar TI. The error bars show the standard deviation of the SI from 9 innermost pixels from center of each vial.

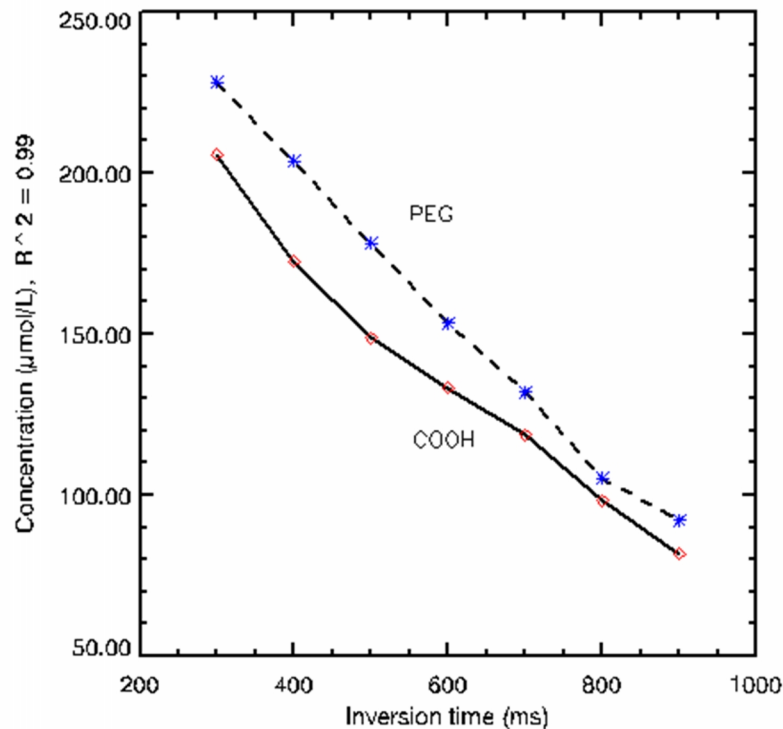


Fig.5. The maximum concentration of contrast agent that gives $R^2 = 0.99$ versus TI for the PEG- and carboxydextran-coated nanoparticles. The figure shows that an increase in TI led to a decrease in the range of the linearity.

at high concentrations (higher than 200 $\mu\text{mol Fe/L}$) appeared for TIs of 600-900 ms and led to a decrease in the SI.

Figure 4 indicates the maximum non-linear SI versus TI for the PEG- and carboxydextran-coated nanoparticles. The figure shows that the maximum non-linear SI of the carboxydextran-coated particles was higher than that for the PEG-coated particles at a similar TI.

Figure 5 shows the maximum concentration of contrast agents that gave $R^2 = 0.99$ versus TI for the PEG- and carboxydextran-coated nanoparticles. The maximum linear relationship between concentrations and the corrected SI that gave an R^2 equal to 0.99 was 228.18 and 205.65 $\mu\text{mol Fe/L}$ at low TI (300 ms), respectively, for the PEG- and carboxydextran-coated nanoparticles. In addition, these values were reduced to 92.15 and 81.83 $\mu\text{mol Fe/L}$ at the highest TI (900 ms) for the two coated nanoparticles. The figure also shows that an increase in TI led to a decrease in the range of the linearity between SI and concentration.

Discussion

The strength of the SI will be changed by many factors such as the magnetic field strength, the pulse sequences parameters, imaging protocols, the dose, injection rate, bolus volume of the contrast agent, and the tissue topology (17-25). The relationship between the SI and the concentration of the contrast agent has been defined as Eq. 1 for IR sequences (16).

PEG is a polymeric surfactant which is used as the iron oxide nanoparticles coating material because of its high solubility, stability in aqueous solutions, biocompatibility, and prolonged blood circulation time. PEG can minimize or prevent opsonization of the nanoparticles. Thus, it is an appropriate material for MR angiography and perfusion imaging (26). On the other hand, carboxydextran is a biocompatible organic polymer which decreases the occurrence of allergic reactions and has a long circulation time in blood. The long blood half-life of both coated nanoparticles provides enough time for acquisition of imaging data.

The T1 and T2 shortening effects will ap-

pear on images. The T1-shortening effect is dominant at low concentrations of contrast agent and both T1 and T2 can be affected at high concentrations (see Figs. 2 and 3). Therefore, the relationship between the SI and concentration is linear at low concentrations and non-linear at high concentrations.

Figs. 2 and 3 show the concentration which led to the maximum non-linear SI at different TIs for the two coated nanoparticles. As can be seen from the figures, the T2-shortening effect was started from concentrations of 400 and 500 $\mu\text{mol Fe/L}$ for the carboxydextran- and PEG-coated nanoparticles, respectively, at $\text{TI} = 300$ ms. That effect appeared from concentration of 200 and 400 $\mu\text{mol Fe/L}$ for the carboxydextran- and PEG-coated nanoparticles, respectively, at high TI (600-900 ms). The T1-shortening effect is seen at lower concentrations.

According to Fig. 4, the maximum non-linear SI of the carboxydextran-coated nanoparticles is slightly higher than that of the PEG-coated nanoparticles at similar TIs because of the difference in coating types.

Analysis of the concentration-time curve reveals some information about perfusion and hemodynamic parameters of a tissue. Since MRI cannot measure concentration of contrast agent, if the relationship between SI and concentration of contrast agent to be linear, the concentration will be measured indirectly from SI. Therefore SI-time curve can be used as concentration-time curve (27). This possibility is provided by considering the R^2 concept, which gives the linear relationship between SI and concentration. Fig. 5 shows that the maximum linearity of the carboxydextran-coated nanoparticles was lower than that of the PEG-coated nanoparticles for similar TIs. Therefore, the PEG-coated nanoparticles are better than the carboxydextran-coated nanoparticles as T1 contrast agents for perfusion measurement because of the high SI. According to the similar core size of the iron oxide nanoparticles in both contrast agents, the difference in linearity is due to differences in the two coating types of the nano-

particles.

Although the R^2 of the PEG-coated nanoparticles is higher than that of the carboxydextran-coated nanoparticles, the maximum non-linear SI of the carboxydextran-coated nanoparticles was slightly higher than for the PEG-coated nanoparticles at similar TIs.

This study indicates that the TI and the coating type of the nanoparticles are important parameters for measuring SI. They have an effect on the value of both the linear and the non-linear relationship between SI and the concentration of contrast agent (see Figs. 2-5). An increase in TI leads to a decrease in the range of the linearity.

The linear relationship between the concentration of the 20 nm carboxydextran-coated nanoparticles and SI using TIs of 100-400 ms was investigated by Saharkhiz et al. (13). They found the maximum linearity at the concentrations of 139.98 and 76.83 $\mu\text{mol Fe/L}$ for TIs of 300 and 400 ms, respectively; while the concentration values for the maximum linearity in our study with similar TIs were 205.65 and 172.70 $\mu\text{mol Fe/L}$ for the carboxydextran-coated nanoparticles, respectively (Fig. 5). This finding shows that even with similar coating and TIs, the resulted linearity is different due to using different imaging parameters (TR, TE, and matrix size) in the two study. Our previous studies show that the imaging parameters (such as TR and TE) can have an effect on the strength of SI and the relationship between SI and contrast agent concentration (28, 29). Therefore, the results of the two studies are completely different.

Canet et al. reported a linear relationship between the concentrations of AMI-25 (dextran-coated) nanoparticles and SI when they used only a TI of 300 ms (11). They showed a linear relationship between the nanoparticles' concentration and SI for concentrations up to 200 $\mu\text{mol Fe/L}$, while it was 228.18 and 205.65 $\mu\text{mol Fe/L}$ for the PEG- and carboxydextran-coated nanoparticles, respectively, at a TI similar to that in our study (see Fig. 5). In spite of the dif-

ference in nanoparticles size and imaging parameters in the two studies, the linearity difference obtained with the dextran-coated nanoparticles in the study of Canet et al. and the carboxydextran-coated particles in the current study was very small. The reason is that carboxydextran is one of the dextran derivatives. In another study, the maximum enhancement of the dextran-coated USPIO nanoparticles was found at 200 $\mu\text{mol Fe/L}$ when a spin-echo pulse sequence with a $\text{TR}=500$ ms and $\text{TE}=22$ ms was applied (12). This finding is in agreement with our results obtained with TIs of 600-900 ms for the carboxydextran-coated nanoparticles, while there was no TI providing similar results with the PEG-coated particles (see Figs. 2 and 3). Chambon et al. (12) also reported maximum enhancement of the nanoparticles at a concentration of 400 $\mu\text{mol Fe/L}$ at a $\text{TR}=160$ ms and $\text{TE}=20$ ms. This is in agreement with our findings for TIs of 300 and 400 ms for the carboxydextran-coated nanoparticles and TIs of 500-900 ms for the PEG-coated particles (see Figs. 2 and 3). The findings indicate the important role of the pulse sequences and imaging parameters in maximum enhancement. On the other hand, regarding the similar core size of both coated nanoparticles in the present study, an influence of the coating material on the maximum SI was seen.

Conclusion

The relationships between the SI and the concentrations of the two coated types (carboxydextran and PEG) of iron oxide nanoparticles were evaluated on T1-weighted MR images.

This study shows that the different coating types of the nanoparticles and different TIs have an effect on both the linear and the non-linear correlation between the SI and the nanoparticles concentration.

The maximum non-linear SI of the carboxydextran-coated nanoparticles is slightly higher than that of the PEG-coated particles. However, the PEG-coated nanoparticles are better than the carboxydextran-

coated nanoparticles as a T1 contrast agent for perfusion measurement because they produce a higher maximum linear relationship between the SI and the concentration of the contrast agent at similar TIs ($R^2 = 0.99$). Our study shows that an increasing in TI produces a decrease in the range of the linearity.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Corot C, Robert P, Idee JM, Port M. Recent advances in iron oxide nanocrystal technology for medical imaging. *Adv Drug Deliv Rev* 2006 Dec; 58:1471-1504.
2. Bjørnerud A, Johansson L. The utility of superparamagnetic contrast agents in MRI: theoretical consideration and applications in the cardiovascular system. *NMR Biomed* 2004 Nov; 17:465-77.
3. Botnar R. Cardiovascular molecular imaging. *Proc Intl Soc Mag Reson Med*. 2011 May; 19:1-7.
4. Bogaert J, Taylor AM, Kerkhove FV, Dymarkowski S. Use of inversion recovery contrast-enhanced MRI for cardiac imaging: spectrum of applications. *AJR* 2004 Mar;182:609-15.
5. Nazarpour M. Effect of inversion times on minimum signal intensity of the contrast agent concentration by use of inversion recovery T1-weighted fast imaging sequence MJIRI 2014 Nov; 28: 128.
6. Bautista MC, Bomati-Miguel O, Zhao X, Morales MP, Gonzalez-Carreno T, Perez de Alejo R, et al. Comparative study of ferrofluids based on dextran-coated iron oxide and metal nanoparticles for contrast agents in magnetic resonance imaging. *Nanotechnology* 2004 Jan;15:S154-9.
7. Oghabian MA, Guiti M, Haddad P, Gharehaghaji N, Saber R, Alam NR, et al. Detection sensitivity of MRI using ultra-small super paramagnetic iron oxide nano-particles (USPIO) in biological tissues. *EMBS* 2006 Jun, 28th Annual International Conference of the IEEE 5625-6.
8. Reimer P, Bremer C, Allkemper T, Engelhardt M, Mahler M, Ebert W, et al. Myocardial perfusion and MR angiography of chest with SH U 555 C: results of placebocontrolled clinical phase I study. *Radiology* 2004 May;231:474-81.
9. Schnorr J, Wagner S, Abramjuk C, Wojner I, Schink T, Kroencke TJ, et al. Comparison of the iron oxide-based blood-pool contrast medium VSOP-C184 with gadopentetate dimeglumine for first-pass magnetic resonance angiography of the aorta and renal arteries in pigs. *Invest Radiol* 2004

Sep;39:546–53.

10. Schnorr J, Taupitz M, Schellenberger EA, Warmuth C, Fahlenkamp UL, Wagner S, et al. Cardiac magnetic resonance angiography using blood-pool contrast agents: comparison of citrate-coated very small superparamagnetic iron oxide particles with gadofosveset trisodium in pigs. *Rofo* 2012 Feb;184(2):105–12.

11. Canet E, Revel D, Forrat R, Baldy-Porcher C, de Lorgier M, Sebbag L, et al. Superparamagnetic iron oxide particles and positive enhancement for myocardial perfusion studies assessed by sub-second T₁-weighted MRI. *J Magn Reson Imaging* 1993 May;11:1139-45.

12. Chambon C, Clement O, Blanche AL, Shchouman-claeys E, Frija G. Superparamagnetic iron oxides as positive MR contrast agents: in vitro and in vivo evidence. *Magn Reson Imaging* 1993 Nov;11(4):509-19.

13. Saharkhiz H, Gharehaghaji N, Nazarpour M, Mesbahi A, Pourissa M. The Effect of Inversion Time on the Relationship between Iron Oxide Nanoparticles concentration and Signal Intensity in T₁-weighted MR Images. *Iran J Radiol* 2014 May;11(2): e12667.

14. Oghabian MA, Gharehaghaji N, Masoudi A, Shanehsazzadeh S, Ahmadi R, Faridi Majidi R, et al. Effect of coating materials on lymph nodes detection using magnetite nanoparticles. *Adv Sci Eng Med* 2013 Jan;5:37–45.

15. Nazarpour M. Non uniformity of different clinical coils in MRI. *IJMP* 2014;11(4): 270-5

16. Nazarpour M. Effect of concentration of contrast agent on the inflow effect for measuring absolute perfusion by use of inversion recovery T₁-weighted Turbo FLASH images. *Radiol Phys Technol*. 2012 Nov;5:86-91.

17. Nazarpour M, Mayabi Z, Shfaie A, Pesanian E, Aghaverdizadeh D. Maximum relationship between signal intensity and concentration of contrast agent in 0.3 T and 1.5 T using T₁-weighted spin echo sequence. *Medical Journal of Tabriz University of Medical Sciences & Health Services* 2011 Feb/Mar;32(6): 72-6 (Persian).

18. Gharehaghaji N, Oghabian MA, Sarkar S, Amirmohseni S, Ghanaati H. Optimization of pulse sequences in magnetic resonance lymphography of axillary lymph nodes using magnetic nanoparticles. *J Nanosci Nanotechnol* 2009 Jul;9: 4448-52.

19. Gharehaghaji N, Oghabian MA, Sarkar S, Darki F, Beitollahi A. How size evaluation of lymph node is protocol dependent in MRI when

using ultrasmall superparamagnetic iron oxide nanoparticles. *J Magn Magn Mater* 2009 May; 321(10): 1563–5.

20. Nazarpour M, Poureisa M, Daghighi MH. Comparison of maximum signal intensity of contrast agent on T₁ weighted images using spin echo, fast spin echo and inversion recovery sequences. *Iran J Radiol* 2013 Oct;10(1): 27-32.

21. Nazarpour M, Poureisa M, Daghighi MH. Investigations of optimal dose of contrast agent concentration from routine dose using spin echo and inversion recovery T₁-weighted sequences in MRI. *Medical Journal of Tabriz University of Medical Sciences & Health services* 2013 Dec/Jan;34(5): 74-8 (Persian).

22. Nazarpour M. Effects of inversion and saturation times on relationships between contrast agent concentrations and signal intensities of T₁-weighted magnetic resonance images. *Radiol Phys Technol* 2010 Feb;3:120-6.

23. Nazarpour M. Effect of phase-encoding scheme on the relationship between contrast agent concentration and signal intensity on inversion recovery Turbo Fast Low-Angle Shot T₁-weighted images. *Radiol Phys Technol* 2014 Jun;7:262-70.

24. Bernstein MA, King KF, Zhou XJ. *Handbook of MRI Pulse Sequences*. London: Elsevier Academic Press; 2004.

25. Rohrer M, Bauer H, Mintonovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solution at different magnetic field strengths. *Invest Radiol* 2005 Nov;40:715–24.

26. Peng XH, Qian X, Mao H, Wang AY, Chen ZG, Nie S, et al. Targeted magnetic iron oxide nanoparticles for tumor imaging and therapy. *Int J Nanomedicine* 2008 Sep; 3(3):311–21.

27. Nazarpour M. Organ blood flow measurement with T₁ and T₂*-weighted MRI techniques (book). Saarbrücken: LAP LAMBERT Academic Publishing GmbH & Co. KG; 2012 Mar. ISBN 978-3-8484- 3648-4.

28. Nazarpour M. The effect of repetition time on the maximum linear relationship between contrast agent concentration and signal intensity on T₁ weighted image using inversion recovery (IR) sequence. *Iran J Radiol* 2009 July;6(4): 247-252.

29. Nazarpour M, Poureisa M, Daghighi MH. Effect of Echo Time on the Maximum Relationship between Contrast Agent Concentration and Signal Intensity Using FLAIR Sequence. *IJMP* 2013 Winter & Spring;10(1-2):59-67.