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Measurement and correction of stimulated echo contamination in T₂-based iron quantification

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Abstract

The purpose of this study was to characterize the effects of stimulated echo contamination on MR-based iron measurement derived from quantitative T₂ images and develop a method for retrospective correction. Two multiple spin echo (MSE) pulse sequences were implemented with different amounts of stimulated echo contamination. Agarose-based phantoms were constructed that simulate the relaxation and susceptibility properties of tissue with different concentrations of dispersed (ferritin-like) and aggregated (hemosiderin-like) iron. Additionally, myocardial iron was assessed in nine human subjects with transfusion iron overload. These data were used to determine the influence of stimulated echoes on iron measurements made by an MR-based iron quantification model that can separately measure dispersed and aggregated iron. The study found that stimulated echo contamination caused an underestimation of dispersed (ferritin-like) iron and an overestimation of aggregated (hemosiderin-like) iron when applying this model. The relationship between the measurements made with and without stimulated echo appears to be linear. The findings suggest that while it is important to use MSE sequences with minimal stimulated echo in T₂-based iron quantification, it appears that data acquired with sub-optimal sequences can be retrospectively corrected using the methodology described here.

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Keywords

Iron quantification; T_2 ; ferritin; hemosiderin; myocardial iron

1. Introduction

Non-invasive measurement of tissue concentrations of hemosiderin and ferritin *in vivo* is an urgent clinical need for the management of a variety of transfusion-dependent disorders, including thalassemia, sickle-cell disease, aplastic anemia, and myelodysplasia. These conditions require frequent blood transfusions that introduce larger than normal levels of iron into the body. Because the body lacks any physiological mechanism for the excretion of excess iron, the iron is progressively deposited in the liver, heart, endocrine and other organs. With carefully monitored iron-chelation therapy, treatment can often prevent or delay the consequences of iron toxicity. For this reason, new, non-invasive quantitative techniques are sought to evaluate iron levels throughout the body¹. Though conventional methods exist to determine total hepatic iron levels, such as biopsy and biomagnetic susceptibility, there are few reliable quantitative methods to investigate the life-threatening complication of cardiac iron overload. MR imaging has proven promising in assessing myocardial iron deposition, due to its unique sensitivity to paramagnetic materials²⁻⁴.

The body stores iron in two molecular forms, hemosiderin, a particulate and insoluble fraction, and ferritin, a dispersed and soluble fraction. The dependence of toxic iron species on the physiological levels of these two non-toxic storage forms is an area of intensive investigation at the moment, not least because chelation treatment may affect the concentration of these storage forms differently. Conveniently, differences in the solubility and distribution of ferritin and hemosiderin produce distinguishable effects on the T_2 and T_2^* weighted MR images.

An iron quantification model has been developed by Jensen that compares T_2 decay curves obtained with different inter-echo times to separately measure dispersed and aggregated iron, taking advantage of differences in their effects on spin relaxation. This method has been successfully employed in several clinical studies. Quantifying dispersed (ferritin-like) and aggregated (hemosiderin-like) iron using this model requires multiple quantitative measurements of T_2 at varying inter-echo times ranging from a few to tens of milliseconds. Acquiring several single spin-echo sequences with different echo times is clinically impractical due to long scan duration. An alternative approach is a multi-echo spin-echo (MSE) pulse sequence¹¹. However, the T_2 relaxation in MSE can be contaminated by stimulated echoes, confounding results of the analysis.

Stimulated echoes can occur for any sequence of three or more pulses. Radio frequency pulse imperfections leave part of the magnetization with a longitudinal component, and a series of pulses can return this magnetization at a later time to the transverse plane creating stimulated echoes. The magnetization spending time as a longitudinal component should be removed from the signal, as it does not have a pure T_2 relaxation history¹¹. The stimulated echo contribution to the signal can be reduced by the application of longitudinal magnetization spoiler gradients and the use of optimized composite RF pulses. However, these pulses require several milliseconds to complete, and there is additional time needed for the spoiler gradient after the pulse, thus increasing the shortest achievable echo time. In tissue with very short T_2 relaxation times, such as tissues with excess iron deposition, the minimum echo time available by this pulse sequence is insufficient. In addition, composite pulses cannot be used to perform multi-slice imaging because the pulse shape is not slice-selective. However, slice-selective pulses introduce another source of stimulated echoes

because they typically do not deposit the same power across the slice profile, often delivering substantially less than 180° refocusing at the slice edges¹³. For these reasons, the fast, slice-selective MSE sequences that are routinely used for T_2 cardiac imaging still have substantial stimulated echo contamination.

This experiment explores the effects of stimulated echo on T_2 -based quantitative iron measurement by the method of Jensen⁶. We specifically pursued this investigation to correct our own previously acquired clinical imaging data, but we expect that this method can be generalized for use in other clinical cohorts where retrospective analysis using this iron quantification model is desired. We constructed agarose-based phantoms that simulate the susceptibility and relaxation properties of hemosiderin and ferritin in tissue. We examined these and a preliminary group of human subjects to determine the effects of stimulated echo contamination on the estimate of T_2 and the subsequent iron quantification. A strategy is proposed to retrospectively calibrate *in vivo* measurements which have been inadvertently modulated by stimulated echo.

2. Materials and methods

2.1 Theory

Ferritin is a nano-sized, often diffusely distributed, soluble molecule that can be rapidly mobilized for use in physiological processes. Hemosiderin is a micron-sized, aggregated, insoluble molecule used for long-term iron storage. To distinguish between these two types of dispersed and aggregated iron molecules, Jensen and coworkers developed a theoretical model which separates their effects in spin echo MRI sequences. Given an MSE sequence where the echo time is extended after the first echo so that the 180° RF pulses occur at times:

$$t=(\tau, 2\tau+\Delta t, 2\tau+3\Delta t, 2\tau+5\Delta t, \dots) \quad (1)$$

then the T_2 decay curve of tissue containing both forms of storage iron is predicted by this theory to have the approximate analytic form:

$$S(t)=S_0 e^{-RR_2 t} \exp(-A^{3/4} \Delta t^{3/4} (t-t_s)^{3/8}) \quad (2)$$

where the time shift, t_s , is defined to be:

$$t_s=2\tau \left[1-\left(\frac{\tau}{\Delta t}\right)^2 \right] \quad (3)$$

and S_0 is the initial signal intensity, 2τ is the first spin echo time, and $2\Delta t$ is the inter-echo time. To reduce the effect of background noise, the functional expression fit to the data has the form:

$$S_{fit}=\sqrt{S_{ideal}^2+\sigma^2} \quad (4)$$

where S_{ideal} is the ideal signal in the absence of noise and σ is the background signal⁶. Thus, we perform a four-parameter fit of S_0 , RR_2 , A , and σ . A series of MSE sequences with different inter-echo times can thus be used to determine both RR_2 , the reduced relaxation rate, and A , the aggregation index. According to the model, the hemosiderin concentration, C_A , is proportional to the aggregation index A , such that $C_A = \alpha_3 A$. The ferritin iron concentration, C_D is linearly related to the reduced relaxation rate such that $C_D = \alpha_1 + \alpha_2 RR_2$. The expression for the total iron concentration is then given by:

$$C_T = C_A + C_D = \alpha_1 + \alpha_2 RR_2 + \alpha_3 A \quad (5)$$

where the calibration parameters α_1 , α_2 , and α_3 are determined empirically.

2.2 Phantom Preparation

Several previously validated phantoms were utilized to mimic clinically relevant concentrations of dispersed and aggregated iron forms⁶. MnCl_2 was used to simulate the iron bound in ferritin because the ratio of relaxation rates ($R_2/R_1 = 10.3$ at 1.5T) is similar to that of ferritin solutions as well as biological tissue. Iron oxide filled microspheres with a 2.9 μm radius were used to simulate the micro-sized hemosiderin protein complex. The microsphere is constructed of magnetite (Fe_3O_4) nanoparticles embedded in a polymer matrix (product code UM3CN/5737, Bangs Laboratories, Fishers, Indiana). The mass of iron per microsphere is 4.4×10^{-9} mg Fe/particle, which is approximately two orders of magnitude smaller than the mass of iron bound to a hemosiderin protein. This was necessary since the susceptibility of the iron microspheres is about 100 times greater than the average hemosiderin molecule at 1.5 T. With the above substitutions for ferritin and hemosiderin, we define the phantoms total concentration of iron, C_T in Eq. (5) to be the sum of the dispersed MnCl_2 concentration, C_D , and the particulate microsphere iron concentration, C_A .

Different mixtures of microspheres and MnCl_2 were prepared to make six phantoms containing six sample tubes each (1.5 cm diameter and 15 cm^3 volume) arranged with 2 cm spacing in a hexagonal pattern. Each tube contained variable amounts of iron oxide microspheres with a constant MnCl_2 concentration suspended in 2% agarose gel. The MnCl_2 concentrations in the 6 different phantom arrangements varied from 0 mM to 0.675 mM in increments of 0.135 mM. In each phantom, the iron concentrations varied from 0 to 0.1 mg Fe/ cm^3 in increments of 0.02 mg Fe/ cm^3 . All phantoms were immersed in an aqueous solution bath in a 19 cm diameter cylindrical container to reduce magnetic field inhomogeneities. The bath signal was suppressed by doping the water with 50 mM of MnCl_2 .

2.3 Pulse Sequence

All MR measurements were performed at room temperature on a 1.5T MR scanner (Philips Medical Systems, Best, The Netherlands) equipped with a five-element cardiac coil array. The scanner had a maximum gradient strength of 33 mT/m and a slew rate of 150 T/m/s. The phantom experiments used a coronal orientation so that the single (slice-selective) 10 mm slice was a cross-section of the tubes. A square field of view of $250 \times 250 \text{ mm}^2$ included all of the tubes and the bath. The acquisition matrix was 128×128 , resulting in an in-plane resolution of $1.95 \times 1.95 \text{ mm}^2$.

We implemented two different MSE sequences. First, we acquired data using a sequence we call “Clinical MSE” which represents the standard manufacturer’s preset sequence available on our scanner for MSE T_2 imaging. In order to achieve a very short echo time, we selected the Turbo Spin Echo sequence with the turbo factor equal to the number of echoes in the echo train. This sequence has the first pulse in the echo train set to 180° and subsequent pulses set to 160° , and the refocusing and excitation slice thickness are the same. This sequence is expected to have significant stimulate echo contamination. Second, we acquired a data set using a sequence we call “Optimized MSE” which has all refocusing pulses set to 180° and the slice profile is improved by forcing the thickness of the refocusing pulse to be three times that of the excitation pulse¹³. This sequence is expected to have very little stimulated echo contamination. The second sequence is an adaptation of an improvement to MSE imaging implemented by Pell and collaborators¹³. A major source of stimulated

echoes in MSE imaging is the poor slice profile of the refocusing pulse. Spins located physically further away from the slice center receive a smaller amount of RF power producing inaccurate flip angles. For this reason, there is an advantage if the 180° refocusing slice edges are outside of the excitation volume. Pell and coworkers have determined empirically that the optimal slice ratio occurs when the refocusing slice thickness is three times larger than the excitation slice thickness¹³. We determined empirically through measurement of MnCl_2 relaxation rates that the Pell modification is essential to acquire accurate quantitative T_2 maps in multi-slice MSE imaging (data not shown). In our experiment, the increase in refocusing slice thickness is achieved by reducing the slice gradient.

We implemented three echo times for the MSE sequences described above. The first echo occurs at 4 ms and the acquisition duration is 100 ms per heart beat for all sequences. The inter-echo times (after the first 4 ms echo) were 4 ms (25 echoes), 8 ms (13 echoes), and 16 ms (7 echoes), for a total of 45 samples. Thus, the latter two sequences have a “shift” after the first echo that increases the inter-echo spacing for the remaining echoes. The purpose of this shift is to have all three sequences with the first echo occurring at 4 ms so the intensity of the sequences can be identically scaled. Each MSE sequence had a repetition time (TR) of 2 s, parallel imaging acceleration factor of 1.5, total imaging time of 182 s, and a flip angle (FA) of 90° .

2.4 Human Imaging

Human subjects with iron-overload were recruited for the validation of these sequences in a manner consistent with the Institutional Review Board policies of our university. All subjects were willing participants who gave informed and signed consent. A total of 9 volunteers with thalassemia major and iron-overload (5 males, 4 females, 29 ± 6 years) were scanned. One subject repeated the exam, and another performed it three times for a total of 12 examinations. To limit the scanning session to one hour, we chose to perform only single slice (slice-selective) sequences in human subjects. The cardiac examinations used short-axis orientation, slice thickness = 10 mm, resolution 128×128 , and field of view = $37 \text{ cm} \times 37 \text{ cm}$. SENSE parallel imaging was used to reduce the scan time in the MSE sequences with an effective acceleration factor of 1.5. Electrocardiographic (ECG) triggering was used to acquire the data at end systole to have maximal septal wall thickness in the images, and navigator respiratory gating was used to acquire the data under free-breathing conditions.

2.5 Image Analysis

For the phantoms, a region of interest (ROI) centered on each of the bottles in the phantom is propagated over all the images in the echo train using Image Processing and Analysis in Java (ImageJ, National Institutes of Health, Public Domain). Since the MSE sequences all have the first echo occurring at 4 ms, the intensity of the first echo in each sequence is rescaled for the three MSE sequences so that the first echoes have the same signal intensity. RR_2 and A are determined by simultaneously fitting the model of Eqs. (1–4) to data from all three of the MSE sequences by using the standard Levenberg-Marquardt method of least squares minimization¹⁶ in Matlab (The Mathworks, Natick, MA).

For human imaging, ROIs were drawn in ImageJ by a physician trained in cardiac MRI. ROIs were placed in the endocardium of the septal wall avoiding the insertion of the right ventricle (Figure 1). For each sequence, the ROI was first drawn on the 4ms echo and propagated to subsequent echoes. The physician then visually inspected all subsequent echoes adjusting the ROI placement if cardiac motion during the acquisition period rendered the ROI non-optimal in any of the echoes. Thus, a single ROI size and placement was found

that satisfactory sampled the septum in all echoes. The human data is fit with the same method as the phantoms.

3. Results

Results for one of the phantoms with varying concentrations of microspheres are displayed in Figures 2 and 3. Since this phantom has no additional relaxation agent (MnCl_2), the R_2 is dominated by the effect of the agarose and the fluid supplied with the microspheres. Figure 2 shows that for all concentrations of iron oxide microspheres that RR_2 is significantly ($p < 0.005$) underestimated by the “Clinical MSE” sequence as determined by two-sample paired student’s t-tests. This sequence also erroneously measured the aggregation index A for all iron concentrations by overestimating, albeit less significantly ($p < 0.08$), as shown in Figure 3.

An example of the cardiac T_2 decay curve from a Thalassemia subject is presented in Figure 4 for the 25 echo “Clinical” and “Optimized” MSE sequences. The effects of the stimulated echo can be qualitatively appreciated in this example.

Computation of the “Clinical MSE” and “Optimized MSE” sequences on the entire set of phantoms is shown in Figures 5 and 6. We found that taking into consideration all phantoms that the “Clinical MSE” sequence significantly ($p < 0.001$) underestimated the RR_2 and significantly ($p < 0.001$) overestimated the A value. Specifically, linear regression analysis ($r^2 = 0.99$) of these data results in the relationships

$$RR_2 = 1.18 RR_2' \quad [6]$$

$$A = 0.78 A' \quad [7]$$

Where RR_2 and A refer to the reduced relaxation rate and aggregation index of the “Clinical MSE” sequence and RR_2' and A' refer to the “Optimized MSE” sequence.

Data from the human subjects is also presented in Figure 5 and Figure 6. Results for human subjects were similar to the phantoms. The sequence “Clinical MSE” with stimulated echo contamination significantly ($p = 0.001$) underestimated RR_2 . Differences in A were not significantly correlated in the human subjects, likely because the dynamic range of A values was very small since these well-chelated subjects had little particulate myocardial iron according to the results of the iron quantification model.

4. Discussion

The human body has two principal iron storage molecules, ferritin, a nano-sized soluble form, and hemosiderin, a micro-sized particulate form. A new, non-invasive imaging method proposed by Jensen that separately quantifies these two molecular forms of storage iron improves our ability to assess and monitor patients with iron overload and test the efficacy of iron-chelating therapies^{6–10}. Non-invasive MR-based iron quantification methods are particularly desirable for cardiac tissue where the clinical consequences of iron-overload are severe, and the diagnostic methods to measure it are few. The MR iron quantification method discussed here requires the acquisition of very accurate T_2 maps. Multi-spin echo (MSE) T_2 pulse sequences with short echo times and rapid sampling are necessary to acquire T_2 maps in the heart. However, rapid MSE imaging is often subject to stimulated echo contamination.

Through a comprehensive evaluation of phantoms, we conclude that special attention must be paid to eliminate the effects of stimulated echo in this type of iron quantification. Stimulated echo contamination can occur when the refocusing flip angle is inaccurate and/or the refocusing slice profile is poor, and results in the transverse magnetization decaying partially by T_1 relaxation mechanisms. When this component is returned to the transverse signal, the undesirable coherence pathway mixes T_1 relaxation character into the signal and has the effect of making the T_2 appear longer. Thus the effect is most substantial in the case of $T_1/T_2 \gg 1$. While stimulated echo contamination is undesirable in most quantitative T_2 techniques, it is particularly detrimental to our ability to distinguish hemosiderin and ferritin iron effects. In particular, the larger perceived T_2 values significantly (~20%) underestimate the reduced relaxation rate, RR_2 , and therefore, underestimate the ferritin iron fraction by an amount dependent on the ratio of T_1 to T_2 in the tissue. Similarly, our results show that the presence of stimulated echoes consistently overestimates the parameter A , and therefore results in an erroneously high hemosiderin fraction. This result is consistent with Eq. (5) above which defines the total iron of a sample to be proportional to a linear combination of A and RR_2 .

In order to be able to retrospectively correct our own previously acquired clinical data that was contaminated with stimulated echo, we performed a comparison between our clinical sequence and an optimized sequence in a large series of phantoms and a group of nine iron overload human subjects. This showed over a wide range of particulate iron and solution relaxation rates that it was possible to relate the theoretical parameters, RR_2 and A , measured by the two sequences with a simple proportionality constant Eqs. (6 and 7). This establishes a defining factor which can be used to correct our data, and the phantom correction methodology could be applied to other sequence types.

In conclusion, we found from our investigation that it is essential to the accurate determination of RR_2 and A , and subsequent iron quantification, to use an MSE sequence with minimal stimulated echo, however, it appears that data acquired with a sub-optimal sequence can be corrected by using the methodology described here provided appropriate calibration measurements can be acquired.

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Figure 1.

ROIs were placed in the endocardium of the septal wall avoiding the insertion of the right ventricle by a trained physician. For each sequence, the ROI was first drawn on the first echo and propagated to the subsequent echoes. All echoes were then inspected and the ROI was adjusted if motion during the acquisition period compromised the ROI placement. In this way, a single ROI was prescribed that satisfactory sampled the septum in all echoes.

Figure 2.

Reduced relaxation rates measured by the MSE sequences in an agarose based phantom with varying concentration of iron oxide microspheres. For all concentrations, the "Clinical MSE" significantly ($p < 0.005$) underestimated the RR_2 when compared to the "Optimized MSE".

Figure 3.

Aggregation index, A , measured by the MSE sequences in an agarose based phantom with varying concentration of iron oxide microspheres. For all concentrations, the “Clinical MSE” significantly overestimated A with trend level significance ($p < 0.08$) when compared to the “Optimized MSE”.

Figure 4.

An example of the cardiac T_2 decay curve from a Thalassemia subject for the 25 echo (4 ms inter-echo) “Clinical” and “Optimized” MSE sequences that qualitatively demonstrates the effects of stimulated echo on the T_2 signal.

Figure 5.

Reduced relaxation rate (RR_2) measured in the 6 phantoms and human subjects. RR_2 calculated from the "Optimized MSE" sequence is compared to the RR_2 value from the "Clinical MSE" sequence. The "Optimized MSE" sequence significantly ($p < 0.001$) underestimates the RR_2 in all phantoms. This sequence also significantly ($p = 0.001$) underestimated RR_2 in our cohort of volunteers with iron overload. Linear regression analysis ($r^2 = 0.99$) of the phantom data defines a scaling factor of 1.18 between RR_2 values measured with these two sequences.

Figure 6.

Aggregation index (A) measured in the 6 phantoms and the human subjects. The value for A calculated from the "Optimized MSE" sequence is compared to the value of A from the "Clinical MSE" sequence. The "Optimized MSE" sequence significantly ($p < 0.001$) overestimates A in all phantoms. The linear regression analysis ($r^2 = 0.99$) of the phantom data defines a scaling factor of 0.78 between A values measured with these two sequences. The human subject data has little correlation since the dynamic range for A in this group was very limited.