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Simultaneous Quantitative Susceptibility Mapping (QSM) and R2* for High Iron Concentration Quantification with Three-Dimensional Ultrashort Echo Time (UTE) Sequences – an Echo Dependence Study

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Abstract

Purpose—To evaluate the echo dependence of three-dimensional ultrashort echo time quantitative susceptibility mapping (3D UTE-QSM) and R2* measurement in the setting of high concentrations of iron oxide nanoparticles (IONPs).

Methods—A phantom study with iron concentrations ranging from 2 to 22 mM was performed using a 3D UTE Cones sequence. Simultaneous QSM processing with Morphology Enabled Dipole Inversion (MEDI) and R2* single exponential fitting were conducted offline with the acquired 3D UTE data. The dependence of UTE-QSM and R2* on echo spacing (ΔTE) and the first echo time (TE1) was investigated.

Results—A linear relationship was observed between UTE-QSM measurement and iron concentration up to 22 mM only with the minimal TE1 of 0.032 ms and ΔTE of less than 0.1 ms. A linear relationship was observed between R2* and iron concentration up to 22 mM only when TE1 was less than 0.132 ms and ΔTE was less than 1.2 ms. UTE-QSM with MEDI processing showed strong dependence on ΔTE and TE1, especially at high iron concentrations.

Conclusion—UTE-QSM is more sensitive than R2* measurement to echo time selection. Both an ultrashort TE1 and a small ΔTE are needed in order to achieve accurate QSM for high iron concentrations.

Keywords

ultrashort echo time; cones; QSM; R2*; high iron concentration

Introduction

Iron oxide nanoparticles (IONPs) have been increasingly used to generate magnetic resonance imaging (MRI) contrast for molecular imaging applications (1,2). The ability to accurately and non-invasively quantify IONPs is desirable for many emerging applications, including drug delivery (3–6), cell labeling and tracking (7–9), and magnetic fluid hyperthermia (10–12). In addition, endogenous iron, an essential cofactor for proteins with functions including oxygen delivery, mitochondrial respiration and the inactivation of harmful oxygen radicals, can accumulate under pathological conditions (13–16). When systemic or local iron concentrations exceed the binding capacity of iron storage and transport proteins, the free iron will deposit into tissues. These iron deposits accelerate the production of free radicals, resulting in membrane lipid peroxidation, cellular injury, and ultimately organ dysfunction (17–20). For example, patients receiving frequent blood transfusions such as those with sickle cell anemia or thalassemia major can develop secondary hemochromatosis with resultant liver cirrhosis and heart failure (21,22), and patients with hemophilia can have repeated joint hemorrhage leading to focal iron deposition and subsequent joint deterioration (23). Noninvasively measuring endogenous iron deposits would be clinically useful in medical conditions associated with very high iron content, for instance to monitor response to chelation therapy so that iron burden can be reduced while minimizing the risk of over chelation. Consequently, there is a growing interest in quantitative in vivo estimation of both endogenous and exogenous iron accumulation.

Iron is a paramagnetic transition metal that causes shortened T1, T2, and T2* relaxation times as well as phase changes of nearby water protons by its magnetic susceptibility effect (24–26). Since there is a linear increase in susceptibility with iron concentration, quantitative susceptibility mapping (QSM) MRI methods have been developed to estimate iron accumulation in vivo (27–32). There are two widely used QSM processing algorithms: the Morphology Enabled Dipole Inversion (MEDI) (33,34) and iLSQR (subtracting the susceptibility artifacts from the initial susceptibility by the sparse linear equation and least-squares algorithm) methods (35,36). These two methods and their extensions have shown success in quantifying tissue susceptibility with applications in brain (37,38), cartilage (with STAR-QSM) and cortical bone (with Chemical Shift QSM) (39,40).

Most QSM methods calculate the tissue frequency shift using phase information at different echo times (TEs), and therefore are highly dependent on the accuracy of phase measurement. High iron concentrations can be particularly problematic because the high degree of T2* shortening leads to rapid signal decay with a low or no signal when using conventional clinical multi-echo gradient recalled echo (GRE) sequences. High iron concentrations also greatly increase the resonance frequency shift, which can cause severe phase wrapping beyond the capability of traditional phase unwrapping methods. As a result, QSM based on GRE sequences with longer TEs (e.g., TE > 2 ms) may fail when evaluating high iron concentrations.

Ultrashort echo time (UTE) sequences greatly reduce TE from the several milliseconds typically used in conventional clinical sequences down to tens of microseconds or less, allowing the direct detection of signals from short T2 tissues such as cortical bone (41). UTE

sequences have been used to measure $R2^*$ ($1/T2^*$) of high IONP concentrations, and may be used to detect the associated fast phase evolution. The improvement in signal detection and phase measurement with UTE suggests that its combination with QSM (UTE-QSM) may allow for more accurate estimation of susceptibility when the $T2^*$ is greatly reduced by high iron concentrations. However, although originally believed to be TE-independent, recent literature has shown that QSM measurements can be highly TE-dependent (42). Therefore, it is of critical importance to understand the TE-dependence of UTE-QSM type sequences at high iron concentrations.

In this study, we aimed to investigate the capability and limitations of the UTE-QSM technique in evaluating high iron concentrations. A phantom study using different iron concentrations was carried out with a three-dimensional (3D) UTE sequence combined with the MEDI method. The dependence of UTE-QSM and $R2^*$ measurement on echo time was also investigated by using different combinations of echo spacing (ΔTE) and the first echo time ($TE1$).

Methods

Phantom Preparation

Two sets of phantoms were prepared for this study. The first set was a gadolinium (Gd) phantom, with diluted gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, NJ, USA) in six 3 mL syringes in a cylindrical container (10 cm in diameter; height 30 cm) filled with agarose gel (0.9% by weight). The syringes contained six different concentrations of Magnevist: 1.5, 3, 4.5, 6, 7.5 and 9 mg/mL. The second set was an iron phantom which was composed of 3 mL syringes (1 cm diameter) filled with 2 mL of Feridex I.V. solution (ferumoxides injectable solution, Berlex Laboratories, Wayne, New Jersey, USA) at six different concentrations: 2, 6, 10, 14, 18 and 22 mM. The syringes were put in a cylindrical container (10 cm in diameter; height 30 cm) filled with agarose gel (0.9% by weight). During MRI, the longitudinal direction of the syringes was parallel to the B_0 field to minimize susceptibility effects.

Pulse Sequences

MR imaging of the phantoms was performed on a 3T Signa HDxt scanner (GE Healthcare Technologies, Milwaukee, Wisconsin, USA) using a previously reported three-dimensional UTE Cones (3D UTE Cones) sequence (43–45). The basic 3D Cones sequence employed a short rectangular excitation pulse followed by 3D spiral trajectory k-space sampling with a conical view ordering. A transmit/receive quadrature coil (BC-10, Medspira, Minneapolis, Minnesota, USA) with a diameter of 22 cm was used for signal excitation and reception.

For the gadolinium (Gd) phantom study, imaging parameters included: matrix = $128 \times 128 \times 100$, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, TR/TE = 30/3/4/5 ms, flip angle = 12° , bandwidth = 83.3 kHz, scan time = 5 minutes per scan.

For the iron phantom study, imaging parameters included: acquisition matrix = $200 \times 200 \times 60$, voxel size = $0.4 \times 0.4 \times 0.5 \text{ mm}^3$, repetition time (TR) = 11.8 ms, flip angle = 18° , bandwidth = 62.5 kHz, scan time = 4 minutes per scan. Initially, the linearity between $R2^*$ and iron

concentration was examined using 12 TEs: 0.032, 0.132, 0.232, 0.332, 0.432, 0.632, 0.932, 1.232, 1.832, 2.432, 3.632, and 4.832 ms. Five sets of UTE acquisitions at evenly spaced TEs starting at TE₁ were used for UTE-QSM and R2* analyses of the echo combination datasets. To study the effect of TE on UTE-QSM analysis, five different echo spacings (TE = 0.06, 0.1, 0.3, 0.6, 1.2 ms) were investigated with TE₁ kept at a fixed value of 0.032 ms, leading to a total of 25 scans. To study the effect of TE₁, six different TE₁s (TE₁ = 0.032, 0.132, 0.232, 0.332, 0.632, 0.932 ms) were investigated with TE kept at 0.1 ms, leading to a total of 30 scans.

Quantitative Susceptibility Mapping

Each 3D UTE Cones acquisition was reconstructed into both magnitude and phase images using a re-gridding algorithm, which interpolates the measured signal from Cones spokes onto a Cartesian grid. Nominal TEs were used for QSM calculation. Because of the non-uniform sampling density of our spiral trajectory, density compensation was applied to the measured signal prior to re-gridding. To form an echo combination dataset with specified TE and TE₁, 5 single echo acquisitions with increasing TE were combined to form a 4D complex matrix.

The MEDI QSM reconstruction algorithm (33) was applied offline with the same complex matrix for measuring the susceptibilities from each of the different iron concentrations. The cylindrical phantom was masked and the B₀ direction calculated from localization information. The first three echoes of each dataset were used for estimating frequency shift in an iterative fashion. A region growing based phase unwrapping algorithm (46) was implemented to obtain the global frequency shift. The Projection onto Dipole Fields (PDF) algorithm was used to obtain the background removed frequency shift and phase map. Dipole inversion of the local susceptibility distribution was achieved using an iterative Bayesian regulation method. For all datasets, the regularization parameter λ and radius for the spherical mean value operator were kept as 1000 and 5, respectively, for calculating magnetic susceptibility χ .

ROI Data Analysis and R2* Fitting

The relationship between QSM and R2* for different iron concentrations and different echo combinations was derived from user-defined regions of interest (ROIs). ROIs with fixed diameters of 1 cm were used to cover each tube. χ for each ROI was calculated using the MEDI algorithm. To study the stability of the QSM results for the different iron concentrations, averaged χ for each ROI of the different echo combinations were plotted. To study the linear relationship between the QSM results and different iron concentration, normalized QSM results (divided by χ for the 6 mM phantom, which was chosen arbitrarily) were plotted for each echo combination.

R2* values for each ROI were obtained using a Levenberg-Marquardt fitting algorithm developed in-house, based on Eq. 1. A constant term C was introduced to account for background noise and artifacts associated with UTE data acquisition and image reconstruction.

$$S(TE)=s_0 \times e^{-R2^* \times TE} + C \quad [1]$$

R2* and UTE-QSM analysis algorithms were written in Matlab (MathWorks, Natick, MA) and were executed offline on axial UTE images obtained with the protocols described above. The program allowed placement of ROIs on the first image of the series, which were then copied to the corresponding position on each of the subsequent images. The mean intensity within each of the ROIs was used for R2* curve fitting.

Results

The gadolinium phantom study demonstrated an excellent linear relationship between UTE-QSM measurements and Gd concentrations (Supporting Fig. S1). Linear regression shows a R^2 of 0.9984, suggesting that the UTE-QSM sequence together with MEDI processing can reliably estimate susceptibility.

Figure 1 shows the R2* fitting results for the iron phantom study using UTE-QSM. The magnitude image of the phantom at the minimum echo time is shown in Fig 1(a), where the syringe with the lowest iron concentration demonstrates the highest signal intensity. Using 12 TEs ranging from 0.032 ms to 4.832 ms, a linear relationship was observed between R2* and iron concentration as shown in Fig 1(b), with a R^2 of 0.9983 and a slope of 0.194 ms⁻¹/mM. Fig 1(c) shows that iron concentrations below 18 mM are relatively linear over a range of TE. However, the longest TE at 1.2 ms overestimated the R2* at the highest iron concentrations of 18 and 22 mM. Interestingly, the R2*s of the lowest two iron concentrations were slightly overestimated with the shortest two TEs of 0.06 and 0.1 ms. Fig 1(d) shows that R2* fitting is relatively linear for iron concentrations lower than 16 mM for all TE1, but at iron concentrations above 16 mM the linear relationship becomes worse as TE1 increases.

Figure 2 demonstrates how the QSM results depend on both iron concentration and echo spacing. Detailed results on UTE-QSM measurements for different IONP concentrations using different TE and TE1 are shown in Supporting Table S1. Fig 2(a) and (b) are the calculated phases after background removal and QSM results from MEDI using the PDF algorithm. QSM results were successfully obtained from the phase information. An obvious signal decay, as well as phase wrapping, can be observed at higher iron concentrations. Additional phase images are available in Supporting Figure S2. Figure 3 demonstrates that the QSM of iron concentrations below 6 mM remain stable for all the echo combinations with MEDI processing. A linear relationship exists between QSM value and iron concentration for TE = 0.06 ms. However, the calculated QSM value of higher iron concentrations is increasingly underestimated as echo spacing increases.

Figure 4 shows the QSM results for echo combinations with different TE1s. An obvious signal decay, as well as phase wrapping, can also be observed at higher iron concentrations in Fig 4(a) and (b). Additional phase images are available in Supporting Figure S3. Figure 5 demonstrates that the QSM of iron concentrations below 10 mM are approximately linear

for all tested TE1s, however the QSM values appeared to plateau at higher iron concentrations in a manner dependent on TE1. Only the QSM values from the shortest TE1 at 0.032 ms were approximately linear over all tested iron concentrations.

Discussion

It is of great clinical significance to quantify endogenous and exogenous iron deposition in the human body. Clinical MRI sequences with conventional TE combinations are not able to accurately quantify iron overload (31). Sequences with much reduced TEs, such as UTE, zero echo time (ZTE) or sweep imaging with Fourier transformation (SWIFT) type sequences make it possible to accurately quantify iron overload (47–49). Nevertheless, these methods have limitations for accurate quantification in vivo, as paramagnetic and diamagnetic substances are unable to be separated due to the positive-real nature of $R2^*$ or $R1$ (32). By shortening the first echo time with 3D radial UTE, QSM has been successfully applied for the study of ultra-short $T2^*$ tissues such as cortical bone (50). In this study, simultaneous QSM and $R2^*$ measurements were carried out to systematically investigate the capability of UTE-QSM sequences to quantify iron over a large dynamic range. Our results demonstrated that high iron concentrations will significantly reduce the signal decay time and induce dramatic phase wrapping within conventional echo times, leading to inaccurate $R2^*$ and MEDI-based QSM measurements. We found that QSM measurements were only accurate over a large dynamic range of iron concentrations when the first echo time was greatly reduced and echo spacing was narrowed.

This study systematically investigated the dependency of MEDI-based QSM as well as $R2^*$ relaxometry on echo time by compiling single echo 3D UTE Cones acquisitions of a phantom containing six different IONP concentrations into echo combination datasets. The echo combination datasets varied either by the first echo time or by echo spacing interval. By comparing Fig 3(b) and Fig 5(b), it can be concluded that a linear relationship between QSM and iron concentration only exists when TE1 is reduced to 0.032 ms and TE is less than 0.1 ms. The linear relationship gradually worsens for higher iron concentrations when TE1 or TE are increased. As might be expected, the $R2^*$ analysis was more dependent on the first echo time than the echo spacing at high iron concentrations, reflecting the more severe reduction in initial signal magnitude. Our results are consistent with a recent study that showed that QSM of bone could only be successfully obtained with reduced TE1 and TE (50). In contrast, another study using a TE1 of 3 ms and TE of 2 ms was unable to calculate bone susceptibility because bone signal was not detected (39). For clinical studies on iron overload, UTE with minimal nominal TEs and short echo spacing will be necessary for accurate QSM measurement, particularly in zones with highly concentrated iron.

Comparisons of MEDI- and iLSQR-based QSM, as well as other QSM methods, were not carried out in this study (53). The iLSQR algorithm may show different dependence on TE1 and TE than the MEDI algorithm, especially for higher iron concentrations. Sood et al. first reported that iLSQR-based QSM is dependent on echo time selection, especially for different tissue properties (42). After a more systemic study, Cronin et al. concluded that phase wrapping algorithms as well as tissue properties might be the main reasons for the TE dependence in iLSQR (51). In future studies, we will investigate the TE dependence in

UTE-QSM with iLSQR processing, together with Laplacian unwrapping and other phase unwrapping algorithms.

A birdcage coil was used in this study for signal reception to avoid QSM reconstruction errors caused by phase combination. In practice, both the magnitude and phase images can be combined with an improved adaptive combined method when using multichannel coils (52).

This study has several limitations. First, IONPs of different concentrations were suspended homogeneously in our phantom, however IONPs would be expected to accumulate or aggregate within biologic tissues, causing nonhomogeneous susceptibility values in vivo. Second, the chemical shift effect was not considered in this study. UTE-QSM together with IDEAL techniques may help resolve potential issues. This study focuses on the measurable dynamic range changes with current QSM methods when combined with UTE sequences. The chemical shift effect is unlikely to affect the UTE-QSM results in this study. Third, the highest concentration of IONPs in this study was 22 mM, which is much lower when compared with 37.5 mM in a study of UTE T2* or T1 measurement (47), and 57.5 mM in a study using SWIFT (48,49). As one of the main findings in this study, the QSM dynamic range is highly dependent on both the first echo time and echo spacing. By further reducing echo spacing, even higher iron concentrations are expected to be accurately quantified at the cost of longer scan time. Parallel imaging or compressed sensing can be applied to reduce the scan time (54, 55). Fourth, multiple single echo 3D UTE Cones acquisitions were used for QSM study of high iron concentrations, which is more accurate but very time consuming and inappropriate for clinical applications. Interleaved multi-echo or echo-shifted 3D UTE Cones data acquisitions could be used for accurate QSM of both low and high iron concentrations while greatly reducing the total scan time (56). Fifth, UTE-QSM with iLSQR processing was not conducted in this study. Since iLSQR and iLSQR-based susceptibility tensor imaging have shown greater robustness for long T2 tissues, the TE1 and TE dependence of iLSQR using UTE-QSM at high iron concentrations would be interesting and will be investigated in the future.

Conclusion

Simultaneous QSM and R2* measurements of high iron concentration up to 22 mM was carried out based on 3D UTE Cones sequences. The effects of the first echo time and echo spacing on the accuracy in QSM and R2* measurements were investigated on iron phantoms. QSM shows greater dependence on the first echo time and echo spacing than R2*. UTE-QSM with MEDI processing shows a strong dependence on both echo spacing and the first echo time, especially for high iron concentrations. Reasonable selection of echo spacing and the first echo time is important for future QSM study of iron overload diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Phantoms with iron concentrations ranging from 2 to 22 mM are detected with high signal with the 3D UTE sequence using a TE of 0.032 ms. (b) A linear relation was observed between R2* and iron concentration using 12 TEs (0.032 to 4.832 ms). (c) Dependency of the apparent R2* of various iron concentrations on echo spacing (ΔTE) with TE1 fixed at 0.032. (d) Dependency of the apparent R2* of various iron concentrations on the first echo time (TE1) with ΔTE fixed at 0.1 ms.

Figure 2.

QSM results of the iron phantom for different TE with TE1 fixed at 0.032 ms. The (a) calculated phase (with background removed) and (b) QSM reconstructed with the MEDI algorithm are shown.

UTE-QSM with different Echo Spacing (ΔTE)

Figure 3.

QSM ROI analysis depends on both iron concentration and echo spacing (ΔTE). (a) MEDI derived QSM values change with ΔTE dependent on the iron concentration (CC). (b) MEDI derived QSM values at higher iron concentrations are more linear with short ΔTE . QSM values for each dataset were normalized by the QSM value at 6 mM iron.

Figure 4.

QSM results of the iron phantom for different TE1 with TE fixed at 0.1 ms. The (a) calculated phase (with background removed) and (b) QSM reconstructed with the MEDI algorithm are shown.

UTE-QSM of different First Echo Times (TE1)

Figure 5.

QSM ROI analysis depends on both iron concentration and first echo time (TE1). (a) MEDI-derived QSM values change with TE1 dependent on the iron concentration (CC). (b) QSM values are consistently underestimated by longer TE1 as the iron concentration increases. QSM values for each dataset were normalized by the QSM value at 6 mM iron.