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Evaluation of Iron Content in Human Cerebral Cavernous Malformation using Quantitative Susceptibility Mapping

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Abstract

Objectives—To investigate and validate quantitative susceptibility mapping (QSM) for lesional iron quantification in cerebral cavernous malformations (CCM).

Materials and Methods—Magnetic resonance imaging (MRI) studies were performed in phantoms and 16 patients on a 3T scanner. QSM, susceptibility weighted imaging (SWI), and R2* maps were reconstructed from *in vivo* data acquired with a three-dimensional, multi-echo, and T2*-weighted gradient echo sequence. Magnetic susceptibility measurements were correlated to SWI and R2* results. In addition, iron concentrations from surgically excised CCM lesion specimens were determined using inductively coupled plasma mass spectrometry and correlated with QSM measurements.

Results—The QSM images demonstrated excellent image quality for depicting CCM lesions in both sporadic and familial cases. Susceptibility measurements revealed a positive linear correlation with R2* values ($R^2 = 0.99$ for total, $R^2 = 0.69$ for mean; $p < 0.01$). QSM values of known iron-rich brain regions matched closely with previous studies and in interobserver consistency. A strong correlation was found between QSM and the concentration of iron phantoms (0.925 , $p < 0.01$), as well as between QSM and mass spectroscopy estimation of iron deposition

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(0.999 for total iron, 0.86 for iron concentration; $p < 0.01$) in 18 fragments of 4 excised human CCM lesion specimens.

Conclusions—The ability of QSM to evaluate iron deposition in CCM lesions was illustrated via phantom, *in vivo* and *ex vivo* validation studies. QSM may be a potential biomarker for monitoring CCM disease activity and response to treatments.

Introduction

Cerebral cavernous malformation (CCM) is a common hemorrhagic vascular anomaly of the human brain, presenting in sporadic and familial autosomal dominant forms. CCM affects more than 0.5% of the population, predisposing them to a lifetime risk of stroke and epilepsy related to repetitive lesional hemorrhages [1-5]. There is currently no therapy to prevent the repetitive bleeds in CCM lesions. Previous studies [6] have recapitulated CCM disease in animal models based on genetically induced hits, and identified potential molecular targets for therapeutic intervention. Recent studies [6, 7] in mice have suggested a promising role of novel therapies aimed at decreasing lesion genesis and iron deposition within lesions. However, progress toward clinical trials in man has been hindered by a lack of knowledge on how best to monitor disease burden and assess changes in iron deposition within lesions, including response to therapeutic interventions in the clinical setting.

CCM lesions contain deoxyhemoglobin and hemosiderin, from which the susceptibility effects cause signal decay resulting in hypointense signal on T2*-weighted magnetic resonance images (MRI). Susceptibility weighted imaging (SWI) was shown to have a higher sensitivity for detecting CCM lesions than the conventional T2*-weighted MRI [8]. However, SWI is a *qualitative* technique [9, 10], which can only be used to assess changes in lesion counts over time, and does not provide a means to evaluate temporal changes in iron deposition within individual lesions.

A new MRI technique, quantitative susceptibility mapping (QSM), has shown potential to estimate brain iron deposition by quantifying local tissue magnetic susceptibility [11-14]. Using the phase data that captures magnetic field changes by local susceptibility sources (such as iron), QSM quantifies susceptibility by solving the local field to source inverse problem [15]. Recent advances have made great strides such that quantitative susceptibility maps can be obtained with a single acquisition [11, 13, 16-18], significantly improving its feasibility in the clinical environment. It was shown that QSM provided excellent depiction of brain lesions with iron deposition in a number of neurologic disorders including microbleeds [19], multiple sclerosis [20], brain tumors [21], intracranial calcifications and hemorrhages [22], and neurodegenerative diseases [23, 24]. In addition, QSM has been correlated with iron measurements using X-ray fluorescence imaging and inductively coupled plasma mass spectrometry (ICPMS) in post-mortem brains [25, 26].

CCM presents a unique challenge due to the variations in lesion size, different hemorrhagic products, and non-uniform iron distribution within individual lesions. The goal of this study is to evaluate the feasibility of QSM, and its preliminary validation as a biomarker of iron content in CCM lesions.

Materials and Methods

Iron Phantoms Preparation

Five phantoms with various iron compounds and iron containing molecules were constructed for validating QSM acquisition and reconstruction. Each phantom contained seven vials with linearly increasing concentrations of the iron-containing material. Phantom #1 contained Ferumoxytol (carboxymethyl-dextran coated ultra small super paramagnetic iron oxide, Advanced Magnetix, Cambridge, MA) with concentrations of (0, 10, 20, 30, 40, 50, 60) $\mu\text{g Fe/mL}$. Phantom #2 contained ferric iron (Iron(III) chloride, Sigma-Aldrich) with concentrations of (0, 100, 300, 500, 700, 900, 1200) $\mu\text{g Fe/mL}$. Phantom #3 contained ferrous iron (Iron(II) sulfate, Sigma-Aldrich) with concentrations of (0, 100, 300, 500, 700, 900, 1200) $\mu\text{g Fe/mL}$. Phantom #4 contained extracted human hemoglobin (Sigma-Aldrich) with concentrations of (0, 10, 20, 30, 40, 50, 60) $\mu\text{g Fe/mL}$. Phantom #5 contained ferritin from equine spleen (Sigma-Aldrich) with approximate concentrations of (0, 29, 145, 290, 435, 580, 725) $\mu\text{g Fe/mL}$, assuming 29% w/w (iron/ferritin). Vials in each phantom were all immersed in a water container.

Patient Imaging

A total of sixteen patients with CCMs (6 men, 10 women, mean age 50 ± 16 years; 20 - 72 years of age) were recruited with the approval from our local Institutional Review Board. Written informed consent was obtained from each subject prior to the study. Two patients received a second scan 6 months after their initial baseline scans.

All imaging was performed on a 3T MRI system (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) equipped with high performance gradient coils (45 mT/m maximum gradient strength, 200 mT/m/ms slew rate). A standard 12-channel phased array head coil was used as the receiver. A three-dimensional, T2*-weighted, multi-echo, spoiled gradient echo sequence was used for data collection. The imaging parameters were: axial oblique imaging plane with full brain coverage; 8 echo times (TE) with uniform spacing; TE [min, max] = [3.6, 45] ms; TR = 55 ms; flip angle = 15° ; bandwidth = 240 Hz/Pixel; field of view = 240 mm; acquisition matrix = 256×256 ; slice thickness = 1.5 mm; number of slab encodings = 80. Parallel imaging using Generalized Autocalibrating Partially Parallel Acquisition [27] was used with an acceleration factor of 2. The imaging time was 7 minutes and 40 seconds.

Ex vivo Imaging and Chemical Analysis

Four human CCM lesions were extracted during surgery. The lesion specimens were stored in 10% formalin. Lesions with a diameter/height greater than 10 mm were cut into 4 - 6 smaller fragments and each fragment was imaged separately. Imaging of the specimens took place on the same 3T MRI system with a custom 1.5 cm single loop coil (Stark Contrast, Erlangen, Germany). The lesion specimen was immersed in formalin in a vial, bottom of which was filled with Agar gel. The following imaging parameters were used: TE [min, max] = [4, 52] ms; TR = 58 ms; flip angle = 15° ; field of view = 25×50 mm; acquisition matrix = 64×128 ; slice thickness = 0.4 mm. The imaging time was 2 minutes and 29 seconds. All lesion specimens were imaged on two different dates to test for reproducibility.

The iron content and concentration in each lesion fragment were determined via chemical analysis. The CCM specimen was first digested with nitric acid in a microwave digester (Milestone EthosEZ microwave digestion system, Sorisole, BG, Italy) prior to ICPMS, which detects all iron ions in the plasma despite the chemical environment. The iron concentration was measured using an Inductively Coupled Plasma Mass Spectrometer (ThermoFisher X Series II ICP-MS, Thermo Fisher Scientific, MA, USA).

Data Reconstruction and Processing

The algorithm used for QSM reconstruction has been previously described [13, 16]. In short, the raw phase images from the multiple-echo MRI data were fitted to estimate the magnetic field map after corrected for the phase wrap artifacts. The background field, caused by the large susceptibility sources such as air/tissue interface, was removed with a projection onto dipole field approach [16] to estimate the local magnetic field that reveals the local susceptibility sources. The susceptibility distribution map was then computed by solving the field-to-source inversion problem using the morphology enabled dipole inversion technique [11, 13, 17].

For each patient, QSM images were calculated using the first n echo times where $4 \leq n \leq 8$. Data from the longest echo time ($TE = 45$ ms) was used for SWI reconstruction [9]. $R2^*$ maps were calculated with a pixel-wise monoexponential fit of magnitude data from all echo times.

Region-of-interests (ROI) was used to estimate the susceptibility measurements. For the phantom study, the mean susceptibility value of the water vial ($0 \mu\text{g Fe}/\mu\text{L}$) was subtracted from other vials to correct for the diamagnetic effects of the plastic vial.

Data Analysis

In the phantom study, susceptibility measurements were correlated to the actual iron concentrations in all phantoms.

In the patient study, 5 known iron-rich regions of the brain including red nucleus, putamen, caudate nucleus, substantia nigra, and globus pallidus were manually segmented for each patient. The mean susceptibility value was calculated and compared to previous studies in healthy volunteers [13, 28]. Patients with CCM lesions nearby those regions were excluded due to susceptibility overestimation as a result of the iron-leakage from the lesions. One physician (more than one year experience in CCM) performed a blinded count for the number of lesions on both SWI and QSM for each patient. Lesions with axial diameters greater than 5 mm were manually segmented using ROIs across multiple slices by two independent observers to evaluate interobserver consistency. Normal brain parenchyma (susceptibility < 0.05 ppm [13, 19]) within the ROI was excluded from the lesion

susceptibility calculation. Mean ($\sum_{ROI} \chi_n / N$) and total susceptibility ($\sum_{ROI} \chi_n \cdot v$, v is the voxel size) were calculated for each lesion and correlated to the corresponding $R2^*$ measurements.

In the *ex vivo* validation study, the mean and the total susceptibility were calculated for each lesion fragment using ROI, and correlated to the iron concentrations and total iron contents determined using ICPMS.

Statistical Analysis

Linear regression analyses were performed between susceptibility and lesion volume, and susceptibility and $R2^*$ measurements. The F-test was performed to evaluate significance. Reproducibility was assessed using coefficients of variation (CV). Pearson's correlation coefficient was used to evaluate paired correlation among measurements. Bland-Altman method was used to evaluate interobserver consistency. Kruskal-Wallis test was used to assess differences in results obtained with different echo times. The QSM and SWI lesion count results were compared using a nonparametric Wilcoxon signed-rank test. All statistical evaluations were performed using MATLAB and $p < 0.05$ was considered statistically significant.

Results

Iron Phantom Validation

The mean susceptibility values measured by QSM of each iron phantom are plotted against the corresponding iron concentrations, shown in Figure 1. A representative slice of the iron phantom using Ferumoxytol is also shown. Absolute iron quantification from the QSM measurement was demonstrated with the Ferumoxytol phantom. Different iron levels were clearly delineated by QSM for all phantoms. A good fit using a linear model was obtained ($R^2 > 0.97$), indicating QSM can accurately identify paramagnetic materials and distinguish different susceptibility levels.

In vivo Validation

Sample magnitude and QSM images are illustrated in Figure 2 a-b without any CCM lesions present. Five known naturally iron-rich regions of the brain were outlined in Figure 2a, and the mean susceptibility values of those regions were compared to previous literature reported values as a way of validating our QSM estimates *in vivo* (Figure 2c). The iron-rich regions appeared hyperintense compared to the nearby parenchyma since iron is paramagnetic. The mean susceptibility values in those regions were similar to previous studies in healthy volunteers [13, 28].

Representative slices illustrating solitary and familial CCM lesions are shown in Figure 3. The lesions appeared hypointense on SWI. 21 CCM lesions with diameter greater than 5 mm were extracted for ROI analysis. The total (summation over voxels) susceptibility values are plotted against lesion ROI volumes in Figure 4 (top row). A strong positive linear correlation was found between the total susceptibility and lesion ROI volume ($R^2 = 0.86$, $p < 0.01$, slope = 0.38). The same was not observed between mean (average over voxels) susceptibility and lesion ROI volume ($R^2 = 0.13$, $p > 0.05$, slope = $3e-5$). The linear regression between $R2^*$ and susceptibility showed a slope of 154.5 ($R^2 = 0.99$, $p < 0.01$) for the total and 77.9 ($R^2 = 0.69$, $p < 0.01$) for the mean measurement (Figure 4, bottom row).

High interobserver consistency was obtained in this study (bias for total susceptibility = -2.3, 95% CI=[-73.1, 68.5], and bias for mean susceptibility = 0.01, 95% CI=[-0.08, 0.11]).

There was no significant difference in total and mean susceptibility of the lesions among QSM images reconstructed with 4 – 8 echoes ($p = 0.9993$ and 0.9078 , respectively) for both CCM lesions and the five iron-rich brain regions (Figure 2c).

Thirteen sporadic and three familial cases were identified in this study. Eleven sporadic cases contained a single (solitary) lesion and two sporadic cases contained two lesions each. All lesions were well depicted on both SWI and QSM. The blinded lesion count results showed a high correlation (0.9034) between SWI and QSM findings without significant difference ($p = 0.88$).

No new lesions were identified in the patients with repeated scans. No significant changes in the total and the mean susceptibility values in the same lesions were found for the two repeated cases. This observation was consistent with the stable clinical status for both patients.

Ex vivo Validation

A total of 18 lesion fragments from 4 CCM lesions were analyzed with ICPMS. Chemical analysis of all lesion fragments revealed the total iron content ranged from 0.0033 to 0.2158 mg and concentrations from 0.057 to 2.57 mg/g wet tissue. The total susceptibility was correlated to the total iron content by ICPMS (Figure 5a) with a correlation coefficient of 0.999 ($p < 0.01$). The mean susceptibility values and iron concentrations were plotted in Figure 5b with a correlation coefficient of 0.86 (0.96 excluding the first sample point as an outlier). The high lesional iron concentration from the first sample might be the consequence of instrumentation errors. Excluding this single outlier point, the empirical conversion factor from mean susceptibility to iron concentration was 0.8 (ppm · gram of wet tissue/mg of Fe). The *ex vivo* QSM result was highly reproducible, yielding a CV of 5.38% and 6.53% for the mean and total susceptibility measurements, respectively. The cross-correlation with mass spectroscopy confirmed that QSM could accurately reflect the relative difference in iron content in different CCM lesions.

Discussion

In this study, we applied QSM in CCM patients for the first time. The aim of the study was to investigate the feasibility of QSM, with the ultimate goal of monitoring CCM disease progression and/or response to treatment. Specifically, we hypothesize that QSM is sensitive to CCM lesions and is feasible for the clinical environment; and QSM values are in the expected range for brain iron and reflect the appropriate concentrations of heme and nonheme iron. Three studies were performed to systematically test those hypotheses: iron phantom validation, *in vivo* human validation and *ex vivo* lesion validation.

In the phantom study, QSM clearly delineated various concentrations in iron phantoms ranging from highly paramagnetic (e.g. Ferromoxytol, 0.03 ppm · mL/ μ g Fe) to weakly paramagnetic (e.g. Ferritin, 0.0007 ppm · mL/ μ g Fe). The iron concentration in each vial can

be converted from the QSM measurements, provided the magnetization of the iron compound is known [29]. In this study, the absolute iron concentration for the Ferumoxytol phantom was converted from susceptibility measurements based on the conversion equation

$$\chi_{\text{Ferumoxytol}} = \frac{\mu_0 M_{Fe}(B_0)}{B_0} \rho = 29.6 \text{ ppm } \mu\text{L}/\mu\text{g},$$
 where μ_0 is the vacuum permeability and $M_{Fe}(B_0)$ is the magnetization of the compound at B_0 (23.6 electromagnetic unit (emu) per gram [30]). The iron concentrations estimated from QSM closely matched the actual iron concentrations with a good linear fit ($R^2 = 0.998$, $p < 0.01$). The purpose of this study was to demonstrate the sensitivity of QSM to different iron forms of a wide range of susceptibility levels, including those commonly found in human brain. However, the clinical applicability and feasibility of QSM to CCM cannot be known without human investigation.

In the patient study, QSM was performed in 16 CCM patients. We compared our findings in five known iron-rich structures of the brain to previous studies and obtained similar results [13, 28]. Variations in susceptibility level distribution among lesions were observed across all patients. It should be noted that CCMs could contain a variety of hemorrhagic products in the acute / subacute (oxyhemoglobin, deoxyhemoglobin, intracellular / extracellular methemoglobin) or chronic (hemosiderin / ferritin) stages [31-33]. QSM measures the net volume susceptibility, that is, the averaged susceptibility of all contributing sources (e.g. various hemorrhagic products, calcium, myelin, etc.) in a single voxel. It is impossible for a single QSM measurement to distinguish all susceptibility sources. However, in the context of CCM, it is reasonable to assume iron is the dominant source of the paramagnetic signal. Under this assumption, we measured the total susceptibility (proportional to the total iron content) and mean susceptibility (proportional to the iron concentration) in each lesion with excellent interobserver consistency. Our results indicated a strong positive linear correlation between the total susceptibility and the lesion volume, but not between the mean susceptibility and lesion volume. This suggests the lesional iron concentration is independent of lesion size and the total iron deposition, which may be a unique characteristic when evaluating the severity of the disease or likelihood to cause hemorrhage. The optimal metric to assess the disease status will require further investigation. No significant clinical activity was reported in the two repeated cases between the two scans. No new lesions were observed and existing lesions remained stable, reflected by the minimal chronological changes in susceptibility measurements.

It has been shown that $R2^*$ mapping was sensitive to iron accumulation in the brain [34]. A strong correlation between QSM and $R2^*$ was observed in this study, providing additional evidence that QSM is sensitive to changes in brain iron. Although both QSM and $R2^*$ are derived from the same dataset, there are several key differences between the two techniques. $R2^*$ is a measure of the signal decay of the transverse magnetization. Both paramagnetic and diamagnetic materials result in indistinguishable appearances on the $R2^*$ map, similar to SWI. QSM produces a signal that is directly proportional to the intrinsic biophysical property of tissue. This enables QSM to distinguish between para- and diamagnetic materials (e.g. calcium) [14, 21]. In addition, $R2^*$ value may depend on imaging voxel volume and field strength, and has a non-linear relationship with iron deposition. QSM has better sensitivity to detect brain iron and more robust against acquisition parameter variation than $R2^*$ [19, 20]. In practice, since both QSM and $R2^*$ can be obtained simultaneously via

a single acquisition; they may complement each other to provide further insights of the underlying pathology.

The number of echoes (4 – 8) used for QSM reconstruction did not yield a significant difference in the quantitative analysis. Although a smaller number of echo times would reduce signal-to-noise ratio (SNR) [19], our results suggest the SNR reduction is tolerable even with just 4 echo times, which implies the scan time can potentially be shortened by half. This is an important factor to consider when implementing QSM for routine clinical use.

As a direct assessment of lesional iron quantification with QSM, we compared the susceptibility values with iron content determined by mass spectroscopy in human lesion specimens. A strong correlation was observed between the two methods. The *ex vivo* study clearly demonstrated the accuracy of QSM in terms of iron quantification. It also validated that mean susceptibility was proportional to iron concentration and the total susceptibility was proportional to the total iron content. Future studies are necessary to compare QSM results of the same lesion obtained both *in vivo* and *ex vivo*.

Some limitations of this study must be noted. The QSM data was acquired without flow compensation. The susceptibility estimation in areas with high flow (e.g. arteries) may be inaccurate due to unreliable phase data. Since slow flow is reported in dilated cavernous channels in CCM [35], we anticipate this had minimal impact to our data. QSM values are influenced by myelin content in the brain [18] which was not accounted for in this study. This may imply slight underestimations of the susceptibility since myelin is diamagnetic [28, 36]. However, we note that myelin is not an important component of CCM, which lack intervening brain tissue [37]. The effects of myelin within CCM lesion might thus be minimal. A Field-dependent Relaxation Rate Increase (FDRI) method can be used to indicate iron content with reduced myelin effects [28, 38]. However, FDRI requires two acquisitions at different field strength, significantly limiting its applicability. Furthermore, brain iron accumulation has been shown as a part of normal aging process [39]. Age related difference in iron deposition in the brain is region specific [28]. In this preliminary study, we did not account for this difference and some susceptibility measurements may be biased depending on lesion location and the patient age. The correction for aging-related effects will be a part of the future investigation, especially addressing inter-patient comparisons.

In summary, we have shown that QSM, a non-invasive MRI technique, can provide novel information on CCM related to lesional iron deposition. As a preliminary trial, QSM had demonstrated strong clinical feasibility for CCM evaluations. Iron was assumed the dominant susceptibility source in CCM lesions and was reflected in the results obtained by QSM and mass spectroscopy. As a part of an ongoing study and future investigations, we aim to assess longitudinal susceptibility changes during natural disease progression in the same patients, and determine the correlation between susceptibility and the clinical activity of respective CCM lesions. The clinical correlation of QSM will be addressed in a detailed study, including retrospective correlation of QSM with lesion and patient features, and prospective correlation with clinical changes. Animal models of CCM disease in mice [6, 7]

will be used evaluate susceptibility distribution within lesions, and its relation to local heme and nonheme iron on correlative histology.

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Figure 1.

Iron phantom results. A representative slice of the QSM results for the Ferumoxytol phantom is shown. A positive linear correlation is observed for all phantoms between the iron concentration and the mean susceptibility values measured by QSM, demonstrating QSM's ability to identify and distinguish paramagnetic materials with different susceptibility levels. The absolute iron concentrations estimated from the QSM measurements (see Discussion for conversion method) closely matched the actual iron concentration in the Ferumoxytol phantom (slope = 1.05, $R^2 = 0.99$). The iron quantification was not performed for the remaining sets of phantoms due to unknown conversion factors.

Figure 2.

Preventative slices of QSM and validation with previous studies. a) Iron-rich regions including red nucleus, putamen, caudate nucleus, substantia nigra, and globus pallidus are outlined in the magnitude images. b) Corresponding QSM images. c) Mean susceptibility measurements in those regions with various echo times. Comparisons were made to similar studies in the literature (Liu et al. (11) and Bilgic et al. (25)).

Note: Sample populations were divided into young and old groups in the Bilgic study. The numbers quoted here are the average for the whole sample population.

Figure 3.

Examples of sporadic and familial CCM cases. CCM lesions appear hypointense on SWI and hyperintense on QSM. The hypointensity on the SWI is only a qualitative measurement and cannot be used to assess lesional iron content. In contrast, QSM is a quantitative measurement and the total susceptibility is directly proportional to the lesional iron content. The susceptibility distribution within a single CCM lesion is displayed on the top right.

Figure 4.

Lesional susceptibility measurements comparison with lesion volume and R2* values. Top row: total and mean lesion susceptibility versus lesion ROI volume. Bottom row: total and mean lesion susceptibility versus total and mean lesion R2* value, respectively.

Figure 5.

Ex vivo lesion sample validation results. The total and the mean susceptibility values of the surgically excised lesion samples were plotted against the iron concentration (mg/g wet tissue) and the total iron content (mg) determined by mass spectroscopy. A sample QSM slice of the human lesion specimen is also shown. The cause for the high iron concentration in lesion sample 1 is unknown, likely a consequence of instrumentation errors.