Quantitative Susceptibility Mapping Is Superior to T1-weighted Imaging for Detecting and Measuring Gadolinium

Yi Wang, PhD • Martin R. Prince, MD, PhD

Dr Wang is the faculty distinguished professor of radiology and professor of biomedical engineering at Cornell University. His research interests focus on developing MRI technology to enable precision disease diagnosis and treatment guidance using physics modeling, computation tools, and biomedical knowledge. Dr Wang is a fellow of the American Institute for Medical and Biological Engineering, Institute of Electrical and Electronics Engineers, and International Society for Magnetic Resonance in Medicine (ISMRM), serves on National Institutes of Health (NIH) study sections, and is a principal investigator for five NIH grants.

Dr Prince is a professor of radiology at Cornell University and Columbia University and specializes in body MRI. His research interests focus on optimizing body MRI and MR angiography techniques and on the safety of gadolinium-based contrast agents. Dr. Prince received the ISMRM gold medal for developing contrast-enhanced MR angiography.

It has long been suspected that trace amounts of gadolinium are retained in the body after gadolinium-based contrast agent (GBCA) administration. The visualization of hyperintensities on T1-weighted images after six or more GBCA administrations indicates gadolinium accumulation in the dentate nucleus and globus pallidus (GP) and has generated substantial concerns about toxicity and interest in deposition mechanisms (1,2). Additional T1 hyperintense sites in the brain became evident in patients after more than 35 administrations of linear GBCAs (3). This T1 hyperintensity is seen with administration of linear but not macrocyclic GBCAs (4). However, macrocyclic GBCAs can accumulate in the brain, albeit at lower concentrations, as shown in an autopsy study (5). How can we detect small quantities of macrocyclic GBCAs in brain tissue?

In their breakthrough study in this issue of *Radiology*, Choi et al (6) report brain tissue changes associated with repeated injection of macrocyclic GBCAs at quantitative susceptibility mapping (QSM), but not at standard T1-weighted MRI. QSM measures tissue magnetic

susceptibility in parts per billion. Choi et al used generalized estimating equations to determine the associations between MRI measures and number of GBCA doses in 90 patients with brain tumor. Gadobutrol was the only GBCA used for follow-up MRI (mean of eight administrations). Choi et al found that the magnetic susceptibility of the GP increased by 1.4 parts per billion per gadobutrol administration. Interestingly, generalized estimating equations showed a trend of increased susceptibility at the dentate nucleus, about half the GP accumulation. This macrocyclic GBCA finding differs from the linear GBCA finding that the dentate nucleus accumulation was more than twice the GP accumulation according to T1-weighted measurements (3) and may reflect a difference in deposition mechanism.

This spectacular improvement in the ability to noninvasively detect trace amounts of gadolinium in the brain by using QSM verifies that macrocyclic GBCA accumulates in the brain. However, it raises many more questions. Why is QSM more sensitive than conventional T1-weighted MRI in detecting gadolinium accumulation in brain tissues? Can we extrapolate this advantage to detect gadolinium enhancement at routine clinical imaging? Can we lower the gadolinium doses in our routine clinical MRI examinations?

To answer these questions, we need to appreciate the advantages and limitations of QSM postprocessing of gradient-echo (GRE) data (7). First, we consider the physics underlying the sensitivities to magnetic susceptibility sources for T1-weighted and GRE MRI. After the signal-excitation radiofrequency pulse, there is an evolution of the water proton precession phase driven by the magnetic field of local static magnetic susceptibility sources, the magnetic field of surrounding magnetic susceptibility sources, and the small local fluctuating sources (mostly exchanging protons). For T1-weighted imaging, a short echo time (TE) at GRE imaging (or 180° refocusing pulse in spin-echo imaging) minimizes the susceptibility effects. A TE of 3 msec was used in the study by Choi et al. For GRE data acquired with long TEs, substantial susceptibility effects on proton precession are captured in the GRE phase signal in addition to T1-weighted information in the GRE magnitude signal. For measuring small susceptibility sources, Choi et al obtained GRE images with a long TE of 20 msec. For measuring a range

From the Department of Radiology, Weill Cornell Medicine, Cornell University, 515 E 71st St, New York NY 10021. Received June 29, 2020; revision requested June 29; revision received June 29; accepted July 2. **Address correspondence to** Y.W. (e-mail: yi.wang@med.cornell.edu).

Conflicts of interest are listed at the end of this article.

See also the article by Choi et al in this issue.

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of strengths of susceptibility sources, multiple echoes can be acquired with additional shorter TEs to sensitize strong susceptibility sources without increasing scanning time (7). Gadolinium, with its large paramagnetic moment from seven unpaired electrons, is a strong susceptibility source, dwarfing brain tissue noniron susceptibility sources such as water, proteins, and membranes by a factor of 1000. This explains the amazing sensitivity for detecting gadolinium on GRE images.

Second, QSM postprocessing of GRE images is needed to separate small local susceptibility sources from surrounding sources. Both GRE magnitude and phase images contain effects of susceptibility contrasts from local and surrounding sources. The surrounding source effects on GRE images are known as blooming artifacts. The effect of a local susceptibility source is buried in the blooming artifacts. Therefore, deconvolution of the blooming artifacts is needed to reveal local tissue susceptibility sources. QSM deconvolves the GRE phase images by using magnetism physics modeling and constraining the QSM image to resemble the magnitude image (7). The susceptibility information extracted from this QSM postprocessing of GRE images is over and above the information derived from T1-weighted magnitude images. Accordingly, QSM inherently has greater information content compared with routine T1-weighted imaging for depicting and helping to measure gadolinium.

The results of the retrospective study by Choi et al suggest that we can enhance the utility of GRE at routine MRI by saving and analyzing the acquired GRE phase data. GRE sequences are widely available on every MRI system, and every GRE acquisition in an MRI protocol is an opportunity to perform QSM if phase data are saved. However, changing practice is a big hurdle given the added computational burdens and the challenge of establishing QSM interpretation. Ideally, QSM postprocessing is automated and incorporated into the standard scanner image processing chain with support from MRI manufacturers. Although any GRE sequence can be improved by analyzing the susceptibility effects in the phase component of the data, most QSM studies used multiecho three-dimensional GRE sequences with long scanning times of about 6 minutes (8). Strong susceptibility at air-tissue interfaces render signal decay too rapid to collect reliable phase data close to the nasal cavity and ear canals with use of routine TEs. However, these technical limitations are overcome with improved radiofrequency and gradient coils, quality-preserving fast imaging strategies, and innovative postprocessing methods. A trend toward higher field strengths also helps QSM because, in addition to the signal-to-noise ratio benefit, the susceptibility signal scales linearly with field strength.

The advantage of QSM over T1-weighted imaging in detecting small quantities of gadolinium demonstrated by Choi et al implies that we can improve on GBCA-enhanced T1-weighted imaging used in clinical practice. The higher QSM detection sensitivity to gadolinium may be explored to reduce the dosage of GBCA administration, which has been established according to the lower T1-weighted detection

sensitivity. The quantitative feature of QSM may be explored for longitudinal, cross-scanner, and multicenter studies, overcoming the challenges of T1-weighted quantification. Tracking gadolinium deposition in the brain, now possible for both linear and macrocyclic GBCAs by using QSM, may help elucidate deposition pathways and clarify any clinical ramifications. Measuring gadolinium in the brain is similar to measuring brain iron, where QSM has already been established as the superior method for depicting iron-rich deep gray nuclei (9). The brain research community studying iron accumulation-related biology and pathology has migrated to GRE acquisition with QSM postprocessing (8). In this perspective, investigating QSM for detecting and measuring gadolinium in GBCA-enhanced MRI represents an exciting translational imaging research direction.

A limitation of the study by Choi et al was the retrospective nature, which restricted QSM reconstruction to the available phase data of the acquired three-dimensional GRE sequence at a single TE of 20 msec. The GRE sequence parameters could be optimized to acquire more echoes with shorter TEs within the same acquisition time for a greater dynamic range of phase to precisely measure a full spectrum of gadolinium concentrations. With a repetition time of 28 msec used by Choi et al, five echoes could be easily acquired, including an even longer TE of approximately 24 msec for better gadolinium sensitivity. There were also large variations in the measurements at different points over years of follow-up in this study. The use of cerebrospinal fluid in lateral ventricles as a zero reference during QSM reconstruction helps reduce these longitudinal variations (10).

In summary, Choi et al demonstrated that QSM is highly sensitive in the detection of small quantities of gadolinium deposition in the brain after macrocyclic GBCA administration. QSM measurements agreed with autopsy and potential deposition pathways and overcame the undetectable difficulty of traditional T1-weighted MRI. This is a wake-up call regarding the limitations of routine T1-weighted imaging in detecting gadolinium enhancement and/or retention and the opportunity for much higher sensitivity by using QSM.

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References

1. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology* 2014;270(3):834–841.
2. McDonald RJ, Levine D, Weinreb J, et al. Gadolinium Retention: A Research Roadmap from the 2018 NIH/ACR/RSNA Workshop on Gadolinium Chelates. *Radiology* 2018;289(2):517–534.
3. Zhang Y, Cao Y, Shih GL, Hecht EM, Prince MR. Extent of Signal Hyperintensity on Unenhanced T1-weighted Brain MR Images after More than 35 Administrations of Linear Gadolinium-based Contrast Agents. *Radiology* 2017;282(2):516–525.
4. Kanda T, Osawa M, Oba H, et al. High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macrocyclic Gadolinium Chelate Administration. *Radiology* 2015;275(3):803–809.

5. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and Other Non-Group 1 Gadolinium Contrast Agents Deposit Low Levels of Gadolinium in Brain and Bone Tissue: Preliminary Results From 9 Patients With Normal Renal Function. *Invest Radiol* 2016;51(7):447–453.
6. Choi Y, Jang J, Kim J, et al. MRI and quantitative magnetic susceptibility maps of the brain after serial administration of gadobutrol: a longitudinal follow-up study. *Radiology* 2020;297:143–150.
7. de Rochefort L, Liu T, Kressler B, et al. Quantitative susceptibility map reconstruction from MR phase data using bayesian regularization: validation and application to brain imaging. *Magn Reson Med* 2010;63(1):194–206.
8. Wang Y, Spincemaille P, Liu Z, et al. Clinical quantitative susceptibility mapping (QSM): Biometal imaging and its emerging roles in patient care. *J Magn Reson Imaging* 2017;46(4):951–971.
9. Liu T, Eskreis-Winkler S, Schweitzer AD, et al. Improved subthalamic nucleus depiction with quantitative susceptibility mapping. *Radiology* 2013;269(1):216–223.
10. Liu Z, Spincemaille P, Yao Y, Zhang Y, Wang Y. MEDI+0: Morphology enabled dipole inversion with automatic uniform cerebrospinal fluid zero reference for quantitative susceptibility mapping. *Magn Reson Med* 2018;79(5):2795–2803.