Clinical Note

Diminished Visibility of Cerebral Venous Vasculature in Multiple Sclerosis by Susceptibility-Weighted Imaging at 3.0 Tesla

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Multiple sclerosis (MS) is a disease of the central nervous system characterized by widespread demyelination, axonal loss and gliosis, and neurodegeneration; susceptibility-weighted imaging (SWI), through the use of phase information to enhance local susceptibility or T2* contrast, is a relatively new and simple MRI application that can directly image cerebral veins by exploiting venous blood oxygenation. Here, we use high-field SWI at 3.0 Tesla to image 15 patients with clinically definite relapsing-remitting MS and to assess cerebral venous oxygen level changes. We demonstrate significantly reduced visibility of periventricular white matter venous vasculature in patients as compared to control subjects, supporting the concept of a widespread hypometabolic MS disease process. SWI may afford a noninvasive and relatively simple method to assess venous oxygen saturation so as to closely monitor disease severity, progression, and response to therapy.

Key Words: multiple sclerosis; magnetic resonance; susceptibility-weighted imaging; oxygenation; venography
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ALTHOUGH THE CLASSICAL teaching has been one of a chronic inflammatory demyelinating disease marked by multifocal white matter lesions, multiple sclerosis (MS) is being increasingly recognized as a disease of the central nervous system (CNS) characterized by widespread demyelination, axonal loss and gliosis, and neurodegeneration (1). In line with the diffuse histopathological changes observed in MS, prior study, such as through positron emission tomography (PET) examination, has revealed decreased oxygen utilization and extraction, with extensive reduction in cerebral glucose metabolism in MS patients (2). As tissue damage in MS has been shown to invariably extend beyond the focal plaque, modern MRI techniques are being developed to allow for the qualitative and quantitative demonstration of the global, diffuse nature of neuropathological changes to closely monitor disease severity, progression, and response to therapy.

Susceptibility-weighted imaging (SWI) (3), through the unique use of phase information to enhance local susceptibility or T2* contrast, is a relatively new and simple MRI application that can image cerebral veins by exploiting the magnetic susceptibility effects from paramagnetic deoxygenated hemoglobin. Using deoxyhemoglobin as an intrinsic contrast agent, SWI venography affords a direct and noninvasive assessment of venous blood oxygenation, which can be related to the overall metabolic picture in MS. Here, we visualize oxygen level changes in cerebral veins indicated by venous blood signal changes on SWI venography of patients with MS, and, furthermore, evaluate the relationship between the vascular visibility and lesion load in these patients.

MATERIALS AND METHODS

Subjects

Fifteen patients with clinically definite relapsing-remitting MS (4) (11 women, 4 men; mean age, 38.5 years; range, 26 to 52 years), with a mean duration of disease of 5.6 years (range, 1.3–11.9 years), were examined. None of these patients had any evidence or prior diagnosis of cardiovascular morbidity, cerebrovascular disease, or other neurological disease. All patients displayed a characteristic phenotype that included but was not limited to visual disturbances (i.e., diplopia), paresthesias, ataxia, dysphagia, and fatigue. Expanded Disability Status Scale (EDSS) scores averaged 2.5 among the 15 patients; none had used steroids within

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the previous 3 months; and 5 had received immunomodulating medication within 2 years of the current imaging study. The control population consisted of 14 healthy individuals whose ages were well-matched with individuals from the patient group (9 women, 5 men; mean age, 39.2 years; range, 23 to 50 years). According to the institutional guidelines, all subjects gave informed written consent approved by our Institutional Review Board before MRI.

MRI Acquisition

All imaging was conducted on a 3.0 Tesla (T) system (TIM Trio, Siemens, Erlangen, Germany) using an eight-channel array head coil. Standard protocol for MS study was performed, which included dual-echo fast spin-echo proton attenuation and T2-weighted imaging (repetition time [TR]/echo time [TE]1/TE2, 5500 ms/19 ms/101 ms; matrix, 256 × 256; pixel size, 0.86 × 0.86 mm^2), as well as contrast-enhanced T1-weighted imaging (TR/TE, 660 ms/14 ms). These routine sequences were acquired with 3-mm-thick contiguous axial sections for lesion identification. SWI was acquired with a three-dimensional (3D), radiofrequency spoiled, fast low-angle shot sequence and flow compensation in all three directions. This gradient moment nulling in all three orthogonal directions reduced signal loss in blood attributable to flow-dephasing (3). Thirty-two partitions (64-mm slab) were obtained with the following acquisition parameters: TR/TE/flip angle: 50 ms/20 ms/25°; matrix: 512 × 512; voxel size: 0.43 × 0.43 × 2 mm^3; and low bandwidth: 80 Hz per pixel. The total acquisition time of SWI was 5 min and 12 s, using parallel imaging (GRAPPA, iPAT factor of 2) to reduce the acquisition time. All SWI images were obtained before contrast agent injection and in an axial orientation parallel to the anterior commissure to posterior commissure (AC-PC) line. To maintain consistency between subjects, the center of the 3D slab was placed in the inferior border of body of corpus callosum to cover the periventricular region where most MS lesions occur.

Image Processing and Analysis

SWI is based on theoretical and experimental evidence developed for enhanced susceptibility effects using phase information. The raw magnitude and phase from each SWI scan was obtained and used to generate SWI venography. All phase images were reconstructed and corrected for field inhomogeneities by use of a high-pass filter of 64 using in-house image-processing software (SPIN). A phase mask was used to manipulate magnitude images and enhance venous visualization, with all positive phase values of 0 to +180° set to unity and negative phase values of 0 to $-\pi$ normalized to a gray scale of values ranging linearly from 0 to 1, such that 0 corresponded to −180° and 1 corresponded to 0°. The original magnitude image was multiplied by this phase mask four times to enhance the visibility of venous structures. Finally, SWI venograms were created by performing minimum intensity projection technique (mIP), with eight total projections of constant locations between the AC-PC line and centrum semiovale using contiguous sections. The 8-mm-thick (over four slices) periventricular slab was used for comparing patients and controls.

In comparing detected venous vasculatures in patients and controls, quantification of SWI venous blood voxels was done by segmentation of the venous structures of the brain based on SWI data. Venous segmentation was done using a statistical thresholding algorithm in several steps. First, 8-mm-thick SWI mIP images with enhanced venous vasculature were generated after image processing using both magnitude and phase images. Second, a statistical local thresholding algorithm, similar to algorithms that have been proposed for segmenting arteries (5), was applied to mark the veins based on their contrast in comparison to other brain tissue. Third, a thresholding was applied to the complex data (magnitude and phase) to remove the background noise and skull, as described elsewhere (6). Fourth, a novel shape filtering noise removal algorithm was used to remove false positives, and the venous vasculature map was generated for the computation of venous blood voxels. This vessel segmentation was run using the same thresholding parameters in both patients and controls at the fixed level of brain. After all voxels were examined, clusters of connected voxels were discarded if they were below a certain size to remove false positives. Clusters of connected voxels were further filtered through a shape analysis using the compactness (7) and relative anisotropy (RA) of each cluster to produce color-coded venous vasculature maps, with each color representing a single cluster. Finally, the number of voxels from each cluster was computed for quantification analysis. The results were then reviewed to verify that the segmentation was accurate. Given the current image resolution, the very small veins visualized on SWI mIP images may not have been detected on the segmentation map due to signal attenuation from partial volume effects when threshold was applied. The processes of constructing SWI venography, as well as segmentation result of venous vasculature from a normal volunteer, are demonstrated in Figure 1.

In MS patients, we also computed the T2 lesion load based on dual-echo fast spin-echo (proton attenuation and T2-weighted) images based on 3D VIEWNIX software system with the concept of "fuzzy connectedness" (8,9). The MS lesions, identified as "3D fuzzy objects," and the voxels belonging to the lesions, were created as 3D volume images, which provided the total number and volume of the lesions. The method of this segmentation of T2 lesions has been described and validated previously (10), and the reproducibility was shown to be >99% for T2 lesion segmentation.

The difference of segmentation results of venous blood on SWI venography between patients and controls were assessed using the upaired t-test, with $P < 0.05$ considered statistically significant. The correlation between the number of voxels of venous blood and lesion load in patients was analyzed using linear regression.

RESULTS

A dramatic loss of contrast between the venous vessels and the parenchyma is observed on SWI venograms of MS patients (Fig. 2), reflecting decreased venous blood

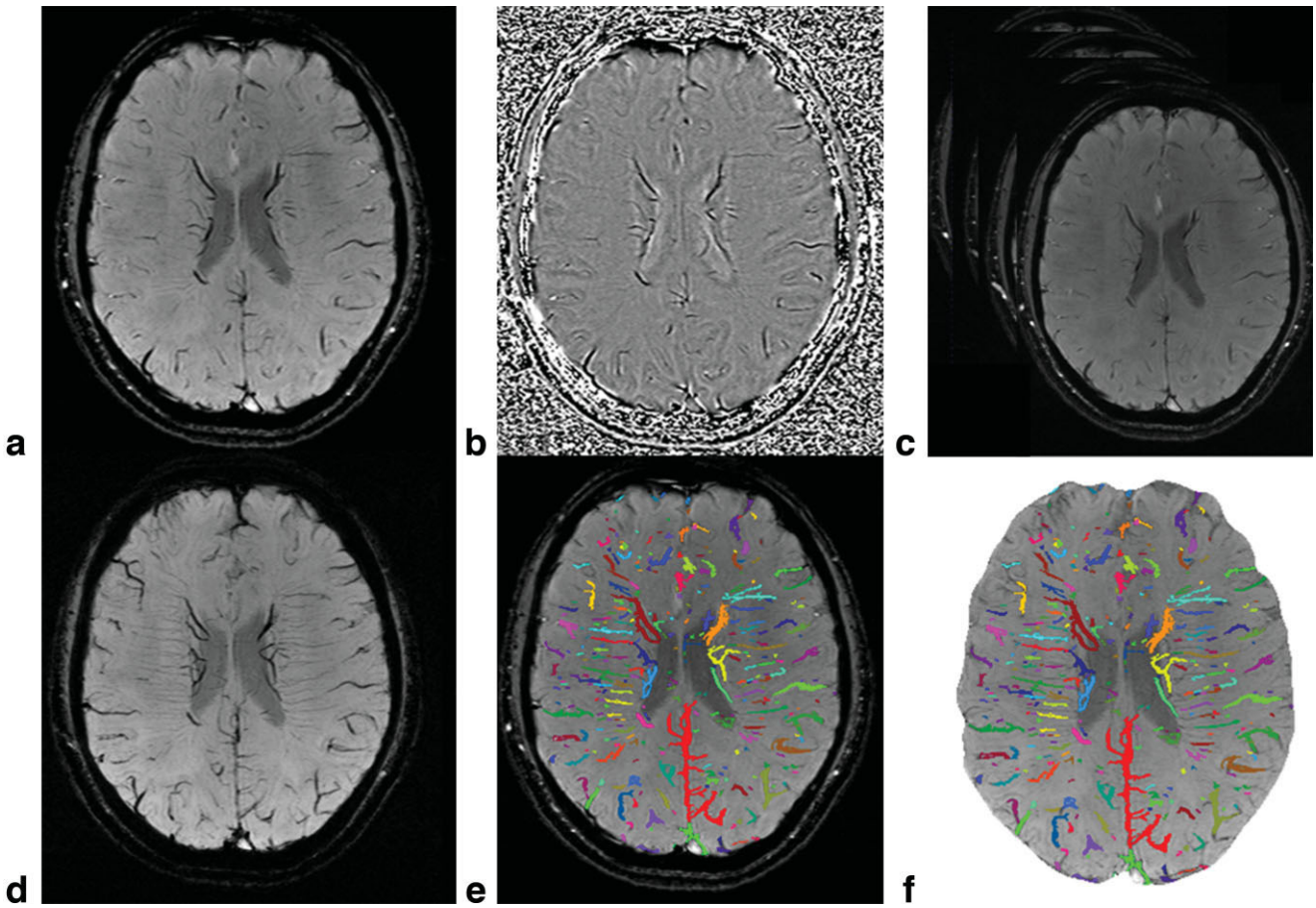

Figure 1. a,b: Image postprocessing and segmentation of venous structures were based on SWI magnitude (A) and filtered phase (B) images. **c,d:**Four magnitude images (C) were manipulated with filtered phase mask by multiplication factor of 4 to create minimum intensity projection (mIP) (D). Veins, which are augmented with phase on SWI mIP image, appear as dark linear structures in contrast to brain tissue background, and can be segmented using statistical thresholding algorithms. **e,f:** Processing steps involve vascular tracking on mIP images to generate color-coded venous vasculature maps (E), with each color representing a single collecting vein, and background removal (F) to calculate the number of voxels corresponding to each vein for quantification.

deoxyhemoglobin concentration. At the level of lateral ventricles, the longitudinal caudate vein of Schlesinger with its deep medullary tributaries is the primary collecting system for the cerebral deep white matter. As shown in Figure 2, at the level just below the centrum semiovale, collecting veins of both small and large diameter in the deep white matter are clearly delineated in healthy controls, as opposed to their decreased visibility on SWI venograms of MS patients. In addition, diminished visibility of veins is also found in the cortical and subcortical regions, suggesting that the process leading to the loss of contrast is widespread. The segmentation results and differences in mean number of venous blood voxels between patients (mean/SD: 9724.2/1001.9) and controls (mean/SD: 11024/708.7) is statistically significant ($P < 0.001$). Figure 3 demonstrates the distribution of segmented number of voxels of venous blood in each of the patients and controls. The relatively extensive range seen in patients as compared to controls is probably due to the variability of MS severity among patients.

Because most MS lesions occur in the periventricular white matter region, where the medullary venous system provides a rich drainage network for deep white matter, we also evaluated the relationship between venous visualization and MS lesion load. A moderate inverse correlation ($r = -0.60$; $P = 0.02$) is found between the number of venous blood voxels and lesion volume (cc) in patients with MS. As shown in Figure 4, the number of veins visualized on SWI venography is more apparently reduced in MS patients with a greater, as opposed to fewer, number of lesions seen on T2-weighted images.

DISCUSSION

SWI uses a fully flow-compensated, 3D high resolution, gradient echo sequence, with the application of filtered phase images to enhance contrast by means of susceptibility differences between tissues (3). SWI venography, by use of a magnetic susceptibility difference between oxygenated and deoxygenated hemoglobin, allows for the detailed visualization of cerebral veins without the use of an exogenous contrast agent. During normal metabolic gas exchange at the capillary level, oxygen is extracted from hemoglobin molecule, inducing a con-

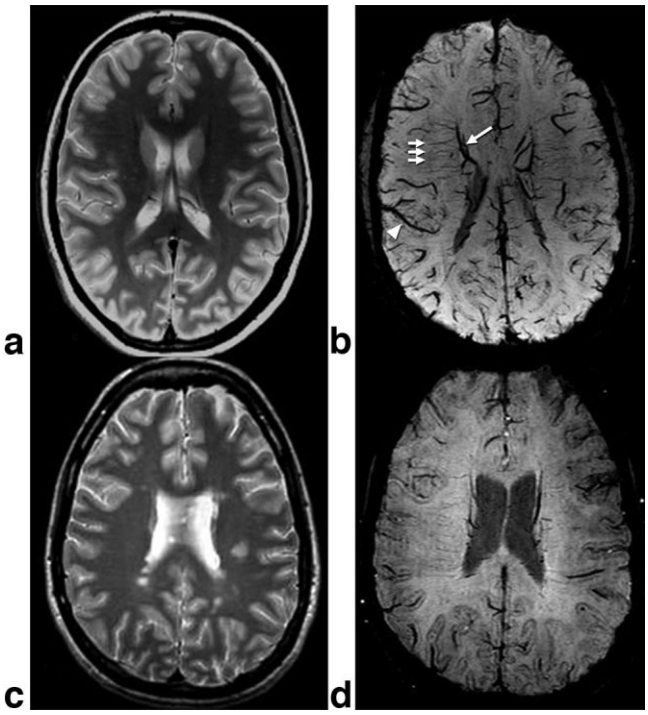

Figure 2. a–d: Conventional T2-weighted and SWI mIP images in a normal control (A,B) and in a patient with MS (C,D) demonstrate significantly reduced susceptibility contrast of venous blood on SWI processed mIP image in the patient as compared to the healthy control. Note that at the periventricular level, both small (e.g., medullary veins, indicated by small arrows) and large (e.g., longitudinal caudate vein of Schlesinger, indicated by long arrow) collecting veins, as well as cortical veins (arrowhead), are clearly delineated in the control participant, as opposed to their decreased visibility on SWI venograms in the patient with MS.

formational change and resulting in a deoxyhemoglobin molecule with four unpaired electrons. This paramagnetic deoxyhemoglobin molecule in the venous blood results in increased local magnetic field inhomogeneity against the external magnetic field, leading to spin

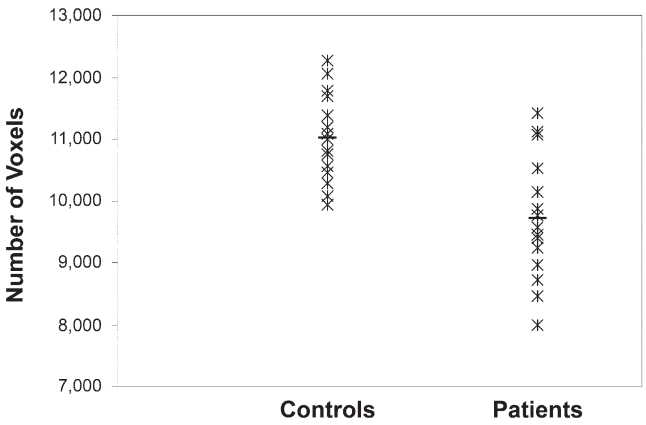

Figure 3. Segmented results of venous blood (number of voxels) in patients and control participants. A wider and downward shifted distribution is found in MS patients as compared to controls, with the dash (−) indicating mean values.

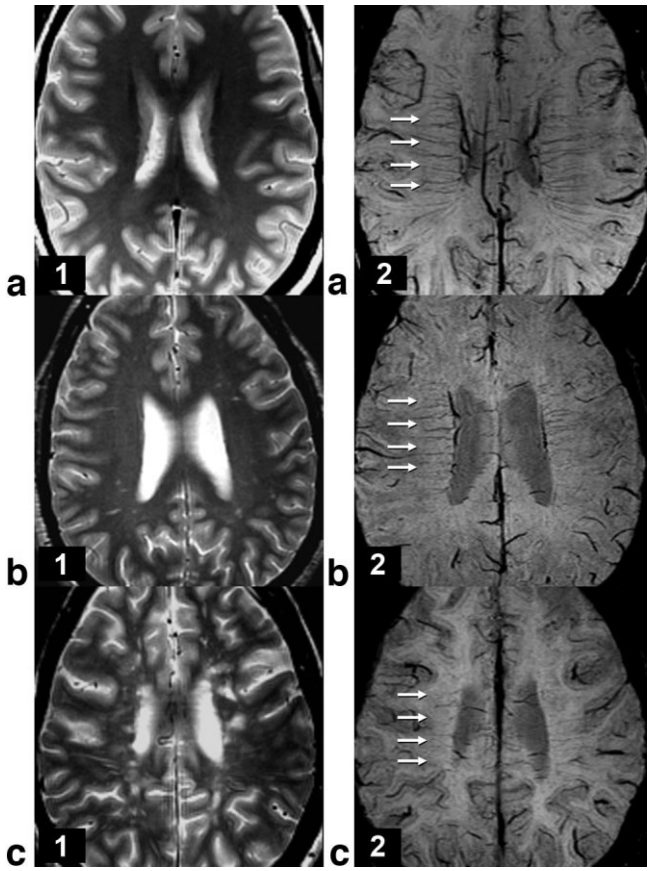

Figure 4. a1–c2: Conventional T2-weighted (A1,B1,C1) and SWI mIP images (A2,B2,C2) at the periventricular level (8 mm thick) in a normal control (A1,A2) and two MS patients (B1,B2,C1,C2) demonstrate a significantly reduced number of veins in patients as compared to controls. MS patients with more lesions (C2) have fewer venous architectures depicted on SWI mIP images (arrows) as opposed to patients with less lesions (B2).

dephasing and signal loss on SWI. Experiments of carbogen and caffeine ingestion (11,12) have revealed that SWI venography is quite sensitive in detecting blood oxygen level changes. At higher field strengths of MR magnets, SWI has potential to provide even higher image resolution and contrast due to increased signal-to-noise ratio and increased susceptibility effects. Using SWI venography at high-field 3.0T, we found significantly reduced visibility of periventricular white matter venous vasculature in patients with MS as compared to control subjects, and also noted that lesion load and venous visibility were negatively correlated.

Our finding of decreased visibility of veins in periventricular white matter in MS is thought to be a result of decreased oxygen utilization in the chronic and widespread diseased tissue state of MS that lends to decreased levels of oxygen extraction, or correspondingly, decreased levels of venous deoxyhemoglobin. In fact, prior PET investigation has shown that oxygen utilization, including regional cerebral oxygen utilization and oxygen extraction, is reduced significantly in both white matter and peripheral cortical gray matter in MS (2). Brain regional glucose metabolism in MS using fluoro-

deoxyglucose PET has revealed extensive hypometabolism throughout the cerebral cortex, subcortical nuclei, supratentorial white matter, and infratentorial structures (13), and it has even been demonstrated that decreases in the cortical cerebral metabolic rate of glucose correlate with total MS lesion area (14), corroborating our finding of a negative correlation between venous visualization and MS lesion load. This finding suggests that, with more lesions, oxygen underutilization becomes more prominent. Qualitative estimation of venous oxygenation levels on SWI by venous visibility, or quantitative measure of segmented number of voxels of venous blood, may thus serve as a marker for determining the global hypometabolic status of the brain in MS.

There exists the possibility, however, that diminished venous vasculature on SWI in MS represents altered venous hemodynamics or venous vascular occlusions (15). A previous study of ours in MS patients found significantly reduced cerebral blood flow in normal appearing white matter using perfusion MRI (16). Such reduced blood perfusion, either through vascular occlusion and/or stasis, however, would be expected to contribute to the enhancement of susceptibility effects, resulting in greater visibility of venous structures by SWI, due to increased oxygen extraction from vessels experiencing reduced blood flow, as well as secondary to increased iron content within thrombosed cerebral veins. Compared with other sophisticated quantitative MR measures (17,18) or invasive measurements of venous oxygenation, such as through SjO2 catheters (19), SWI offers a simple and noninvasive method that can be used as a routine clinical tool without the need for much image postprocessing. With markedly increased sensitivity in the detection of venous structures, SWI affords a noninvasive, albeit indirect, way to qualitatively assess venous blood oxygenation, and subsequently, disease burden.

In summary, our finding of diminished venous visibility as a function of blood oxygen saturation and its relationship to lesion load on SWI in MS lends credence to the increasingly recognized concept of MS as global brain pathology with sometimes subtle yet diffuse tissue damage. The quantitative measures of detected number of venous structures on SWI may allow the clinician to closely monitor disease severity, progression, and response to therapies.

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REFERENCES

1. Filippi M. Multiple sclerosis: a white matter disease with associated gray matter damage. J Neurol Sci 2001;185:3–4.
2. Brooks DJ, Leenders KL, Head G, Marshall J, Legg NJ, Jones T. Studies on regional cerebral oxygen utilisation and cognitive function in multiple sclerosis. J Neurol Neurosurg Psychiatry 1984;47: 1182–1191.
3. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). Magn Reson Med 2004;52:612–618.
4. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231.
5. Wilson DL, Noble JA. An adaptive segmentation algorithm for time-of-flight MRA data. IEEE Trans Med Imaging 1999;18:938–945.
6. Pandian DS, Ciulla C, Haacke EM, Jiang J, Ayaz M. Complex threshold method for identifying pixels that contain predominantly noise in magnetic resonance images. J Magn Reson Imaging 2008; 28:727–735.
7. Bribiesca E. A Measure of compactness for 3D shapes. Computers Math Appl 2000:1275–1284.
8. Udupa JK, Wei L, Samarasekera S, Miki Y, van Buchem MA, Grossman RI. Multiple sclerosis lesion quantification using fuzzy-connectedness principles. IEEE Trans Med Imaging 1997;16:598–609.
9. Nyul LG, Udupa JK. MR image analysis in multiple sclerosis. Neuroimaging Clin N Am 2000;10:799–816, x.
10. Udupa JK, Nyul LG, Ge Y, Grossman RI. Multiprotocol MR image segmentation in multiple sclerosis: experience with over 1,000 studies. Acad Radiol 2001;8:1116–1126.
11. Rauscher A, Sedlacik J, Barth M, Haacke EM, Reichenbach JR. Nonnvasive assessment of vascular architecture and function during modulated blood oxygenation using susceptibility weighted magnetic resonance imaging. Magn Reson Med 2005;54:87–95.
12. Ge Y, Haacke E, Grossman RI. Susceptibility weighted imaging (SWI) of cerebral blood oxygenation during voluntary hyperventilation and apnea. In: Proceedings of the 15th Annual Meeting of ISMRM, Berlin, Germany, 2007. (abstract 2300).
13. Bakshi R, Miletich RS, Kinkel PR, Emmet ML, Kinkel WR. High-resolution fluorodeoxyglucose positron emission tomography shows both global and regional cerebral hypometabolism in multiple sclerosis. J Neuroimaging 1998;8:228–234.
14. Blinkenberg M, Rune K, Jensen CV, et al. Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS. Neurology 2000;54:558–564.
15. Wakefield AJ, More LJ, Difford J, McLaughlin JE. Immunohistochemical study of vascular injury in acute multiple sclerosis. J Clin Pathol 1994;47:129–133.
16. Law M, Saindane AM, Ge Y, et al. Microvascular abnormality in relapsing-remitting multiple sclerosis: perfusion MR imaging findings in normal-appearing white matter. Radiology 2004;231:645–652.
17. Lu H, Ge Y. Quantitative evaluation of oxygenation in venous vessels using T2-relaxation-under-spin-tagging MRI. Magn Reson Med 2008;60:357–363.
18. Lu H, Zhao C, Ge Y, Lewis-Amezcua K. Baseline blood oxygenation modulates response amplitude: physiologic basis for intersubject variations in functional MRI signals. Magn Reson Med 2008;60: 364–372.
19. Clay HD. Validity and reliability of the SjO2 catheter in neurologically impaired patients: a critical review of the literature. J Neurosci Nurs 2000;32:194–203.