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Susceptibility-Based Analysis Of Dynamic Gadolinium Bolus Perfusion MRI

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Abstract

Purpose—An algorithm is developed for the reconstruction of dynamic, gadolinium (Gd) bolus MR perfusion images of the human brain, based on quantitative susceptibility mapping (QSM).

Methods—The method is evaluated in 5 perfusion scans obtained from 4 different patients scanned at 3T, and compared to the conventional analysis based on changes in the transverse relaxation rate ΔR_2^* and to theoretical predictions. QSM images were referenced to ventricular CSF for each dynamic of the perfusion sequence.

Results—Images of cerebral blood flow and blood volume were successfully reconstructed from the QSM-analysis, and were comparable to those reconstructed using ΔR_2^* . The magnitudes of the Gd-associated susceptibility effects in gray and white matter were consistent with theoretical predictions.

Conclusion—QSM-based analysis may have some theoretical advantages compared to ΔR_2^* , including a simpler relationship between signal change and Gd concentration. However, disadvantages are its much lower contrast-to-noise ratio, artifacts due to respiration and motion effects, and more complicated reconstruction methods. More work is required to optimize data acquisition protocols for QSM-based perfusion imaging.

Keywords

Quantitative susceptibility mapping; perfusion; dynamic susceptibility contrast MRI; cerebral blood flow

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Introduction

Perfusion-weighted imaging (PWI) performed using rapid MR imaging during bolus injection of a paramagnetic contrast agent (usually gadolinium (Gd)-based) is extensively used both in research and clinical practice, most notably for the evaluation of cerebrovascular disease and mass lesions of the brain. The analysis of PWI data is traditionally based on changes (Δ) in the blood and brain relaxation rates (usually R_2^* , but also R_2 and R_1 , where $k = 1/T_1$) as the bolus passes through the brain, in order to estimate quantities such as cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT). However, in addition to causing changes in relaxation rates, Gd also causes a shift in the resonance frequency of water in blood vessels and surrounding brain tissue because of its paramagnetism (1). This frequency shift can be estimated from the phase-change of the signal in a gradient echo MR scan, and has been previously proposed as an alternative method of quantifying the contrast agent concentration in PWI (1). However, the relationship between frequency and contrast agent concentration is complicated, and can only be assumed to be linear under certain geometric constraints, e.g. assuming that the contrast is localized to a cylindrical blood vessel oriented parallel to the main magnetic field, B_0 (2–7).

Recently, the technique of ‘quantitative susceptibility mapping’ (QSM) has been developed, which solves the inverse problem of relating the MR frequency changes in each pixel of the image to the underlying spatial distribution of the tissue susceptibility (8–12). High field, high resolution QSM MR imaging has been developed and applied to measuring quantities such as iron content of the deep gray matter nuclei (13), orientation of brain white matter bundles (based on the susceptibility anisotropy) (14–16), as well as detecting brain hemorrhage (17,18), venous structures (12) and their associated oxygenation (5). Since Gd is paramagnetic, it should also be possible to use QSM to provide a quantitative estimate of the time-dependent Gd concentration in the brain during bolus passage, and therefore be able to estimate perfusion. In this work, a practical algorithm is developed for the processing of dynamic QSM data, and the feasibility of performing QSM PWI in the human brain at 3.0T is investigated. Potential advantages for QSM-based PWI (over relaxation time based PWI) are that theoretically there should be a less complex relationship between the susceptibility change and Gd concentration and location (i.e. intra- or extra-vascular) and that the molar susceptibility χ_m measured should be independent of vessel orientation. In comparison, the theoretical relationship between changes in transverse relaxation rates and Gd concentration is complicated, and depends on many factors, including size and geometry of vessels (19). While previous approaches have exploited phase/frequency information for derivation of arterial input functions (AIF) (7,20), QSM has, to the best of our knowledge, not been used to estimate both the AIF and the response in the brain to bolus injection of Gd. Recent work by Xu et al. has examined the cerebral arterial and venous vascular dynamic susceptibility changes during contrast bolus passage; this manuscript focuses on the much smaller susceptibility changes in gray and white matter associated with the bolus passage, which have not previously been reported on (21). A QSM-based approach to measure both AIF and the tissue response may ultimately provide a more quantitative approach to PWI. Finally, since the term ‘dynamic susceptibility contrast’ (DSC) is actually commonly used in the

literature to describe DWI analyses based on ΔR_2^* , it is not used in this paper to avoid confusion with susceptibility based QSM analyses.

Methods

Relative Susceptibility Maps

All processing was performed using in-house software implemented in MATLAB R2011b (The Mathworks, Natick, MA). The algorithm used to process the MR perfusion data is schematically depicted in Figure 1; it uses both the magnitude and phase of the dynamic perfusion MR signal. Phase images were unwrapped using a Laplacian-based phase unwrapping method (9) and the frequency shift (Δf) calculated from ϕ/TE (assuming $\phi = 0$ when $TE = 0$). The relative magnetic field shift in ppm was then calculated by dividing Δf by the spectrometer frequency (128 MHz).

Frequency maps typically exhibit 'background' field gradients which vary both spatially and temporally. Sources of these background gradients include effects resulting from regions with different susceptibility, such as both intra- and extra-cerebral air spaces, as well as inflation and deflation of the lungs, leading to breathing-related frequency changes. Another (probably smaller) contributor is also inhomogeneity of the main magnetic field (B_0). Various methods have been proposed to remove these background gradients (10–12,22). In this study, the dipole fitting method (11) was applied to each dynamic of the perfusion sequence, using our implementation previously described in (15). Dipole fitting involves solving a minimization problem to estimate 'imaginary' susceptibility sources that are placed outside the brain to generate the measured background field in the brain:

$$\min_{\chi} \left(\left\| W \left(FT^{-1} \left\{ \left(\frac{1}{3} - \frac{(\vec{H}_0^{sb}) \cdot \vec{k}^{sb}}{\|\vec{k}^{sb}\|^2} \right) FT\{\chi\} \right\} - (\delta B_z^{sb}) \right\|_2^2 + \beta^2 \|\chi\|_2^2 \right) \quad [1]$$

where χ represents the fitted susceptibility sources, W is a weighting matrix (obtained from the magnitude images at each dynamic), M is the brain mask and β is a regularization parameter. δB_z^{sb} is the relative magnetic field shift distribution in space (in units of ppm), and the superscript *sb* denotes a quantity in the subject frame of reference. δf_z^{sb} is the relative frequency offset, and $\delta B_z^{sb} = \delta f_z^{sb} / (\gamma B_0)$ with γ being the gyromagnetic ratio. $\vec{H}_0^{sb}$ is the unit vector corresponding to the applied main magnetic field of magnitude μ_0^{sub} . FT and FT^{-1} denotes the Fourier and inverse Fourier transform respectively. $\vec{k}$ is the spatial frequency vector. The binary brain mask M was generated using the FSL BET tool (23) from the magnitude image of the first dynamic. A regularization parameter ρ of 1000 was used. Minimization was implemented using a custom iterative conjugate gradient based solver. The magnetic field shift distribution created by these fitted susceptibility sources was determined separately for each dynamic phase and then subtracted from its respective dynamic phase, to obtain the background corrected 3D frequency map at each dynamic, which was used for susceptibility calculation.

Susceptibility calculation (11,12) solves the ill-posed problem of deconvolution of the unit dipole perturber field from the local field shift distribution using regularized least squares optimization (11). Isotropic tissue susceptibility, represented by a scalar χ at each position in Euclidean space, was assumed. Using the spherical Lorentzian correction (24) and following the well-known convolution relationship, the relative magnetic field shift in the subject frame of reference δB_z^{sb} can be expressed using the underlying susceptibility distribution χ as (25):

$$\delta B_z^{sb} = FT^{-1} \left\{ \left(\frac{1}{3} - \frac{((H_0^{sb}) \cdot \mathbf{k}^{sb})^2}{\|\mathbf{k}^{sb}\|^2} \right) FT\{\chi\} \right\} \quad [2]$$

The quantitative susceptibility map was then estimated by solving a minimization problem in image space to satisfy the data fidelity condition using the 'LSQR' method (9):

$$\min_{\chi} \left\| W \left(FT^{-1} \left\{ \left(\frac{1}{3} - \frac{((H_0^{sb}) \cdot \mathbf{k}^{sb})^2}{\|\mathbf{k}^{sb}\|^2} \right) FT\{\chi\} \right\} - (\delta B_z^{sb}) \right) \right\|_2^2 + \alpha^2 \|M_{ot} \chi\|_2^2 \quad [3]$$

The regularization parameter α was set to 20. The brain mask M_{out} was the complement of the brain mask M used in the dipole fitting method described above. After this step, quantitative 3D maps χ of the relative tissue susceptibility are obtained, however the susceptibility values are not necessarily consistent from one dynamic to the next, so a referencing method is required.

CSF referencing

Commonly used reference regions of interest (ROI) in conventional (static) QSM are either the ventricular CSF, or deep white matter regions. In dynamic perfusion imaging, the contrast agent alters the susceptibility of white matter regions, and therefore, in the current study, ventricular CSF was used as a reference, with care taken to avoid regions proximal to the subependymal veins and choroid plexus. Since the slice thickness (4.4–5 mm) used in the perfusion images (see below) is quite large and appreciable partial volume effects are expected, the CSF reference ROI was selected from the central part of the ventricles. The initial CSF ROI was drawn manually on the first dynamic, and then the temporal variation in magnitude signal intensity over all the voxels in this initial ROI was calculated for all dynamics. Only voxels with variation ranges less than twice of the minimum range were selected as the final reference ROI. The average susceptibility value in the reference ROI in the QSM image at each dynamic was then used to yield the reference susceptibility maps $\chi_{ref}(t)$.

Calculation of Perfusion Images

An average pre-injection susceptibility map was calculated $\chi_{ref}(t_0)$ using all dynamics prior to the arrival of the Gd bolus in the brain, excluding the first six time points to assure that all images were in the steady state. Susceptibility difference maps, reflecting the change in susceptibility associated with the presence of the contrast agent, were then calculated at each

time point using $\Delta\chi_{rf}(t) = \chi_{rf}(t) - \chi_{rf}(t_0)$. The voxel-by-voxel concentration of Gd-DTPA can then be estimated from

$$C(t) = \frac{\Delta\chi_{rf}(t)}{\chi_m(Gd)} \quad [4]$$

where $\chi_m(Gd)$ is the molar susceptibility of Gd-DTPA contrast agent [reported to be $3.2 \times 10^{-4} \text{ L} \cdot \text{mol}^{-1}$ in SI units (26)].

For comparison, relative contrast agent concentration was also estimated using conventional ΔR_2^* -based processing of the magnitude images, assuming the linear relationship:

$$C(t) \propto \Delta R_2^*(t) = -\frac{1}{T_2^*} \ln\left(\frac{S(t)}{S(t_0)}\right) \quad [5]$$

where $S(t_0)$ was calculated from the same time points as were used to calculate $\chi_{rf}(t_0)$.

As a direct ROI measurement of the arterial input function (AIF, $C_a(t)$) was difficult (due to distortions - see below), it was determined semi-automatically using the average of between 4 to 16 voxels in the vicinity of the proximal middle cerebral artery (MCA) using the criteria given by Knutsson et al. (27). The AIF was calculated for both $\Delta R_2^*(t)$ and $\Delta\chi_{rf}(t)$ estimates of $C_a(t)$. A regularized singular value decomposition (SVD) method was used to generate images of regional cerebral blood flow (CBF_R and CBF_χ) and cerebral blood volume (CBV_R and CBV_χ). Briefly, based on indicator dilution theory (28), the ΔR_2^* -based perfusion theory (19) states that the plasma volume $v_p = CBV \cdot (1 - Hct)$ can be calculated from the tissue concentration C_t and the arterial concentration C_a according to

$$v_p = \frac{\int_0^\infty C_t(t) dt}{\int_0^\infty C_a(t) dt} = \int_0^\infty CBF \cdot R(t) dt \quad [6]$$

A Hematocrit (Hct) of 0.42 was assumed, within the physiological range of 0.34–0.47 (29). For CBF calculation, mathematical deconvolution (implemented in matrix form as SVD) is necessary to determine the tissue residue function $R(t)$ from the known AIF [$C_a(t)$] and tissue concentration, which are related as follows:

$$C_t(t) = CBF \int_0^t C_a(\tau) R(t - \tau) d\tau \quad [7]$$

As the SVD can be unstable in the presence of noise, the Tikhonov regularization method was used (30–33). Briefly, Equation 7 is formulated as a least squares problem, according to $\min_K \|AK - B\|_2^2 + \mu \|K\|_2^2$. The SVD of A is $A = U\Sigma V^T$. The matrix $\Sigma = \text{diag}(\sigma_0, \sigma_1, \dots, \sigma_{n-1})$ contains the singular values σ_i . A regularized matrix $\Sigma^\# = \text{diag}(f_0/\sigma_0, \dots, f_{n-1}/\sigma_{n-1})$ with $f_i = \sigma_i^2/(\sigma_i^2 + \mu^2)$ is formed such that the standard form Tikhonov regularization solution for K is $K = V\Sigma^\# U^T B$. The regularization parameter μ was fixed to a value of 0.3 for both ΔR_2^* and χ -related calculations. The CBF maps from both the OSM and the ΔR_2^* -based processing

approaches were normalized so that the average blood flow of white matter was 20 ml/100ml/min (34). Prior to deconvolution, both the AIF and tissue data were smoothed temporally using a 5-point moving average filter. No spatial filtering was applied.

Human Subject and *in-vivo* data acquisition

Five examinations of four subjects were included in this study. Details about the clinical history and findings on clinical imaging are given in Table 1. All subjects signed informed consent to be part of our institutional review board approved study of acute stroke imaging. Subject 3 was imaged twice with the same protocol, 11 days apart. In addition, one healthy volunteer (female, 52 years) was examined with the same protocol as the patients, however without the administration of an intravenous contrast bolus, for assessment of the temporal stability of the ΔR_2^* and χ reconstructions.

Imaging was performed on a 3.0 Tesla MR scanner (Philips Healthcare LLC, Best, The Netherlands) equipped with an 8-channel head coil. The perfusion sequence was a multi-slice 2D gradient echo EPI sequence (20–22 slices, 80 dynamics, FOV=240×240 (patient 1) or 212×212 (patient 2–4) mm², 256×256 (patient 1) or 112×112 (patient 2–4) matrix, 5 mm (patient 1) or 4.4 mm (patient 2–4) slice thickness, TR/TE 1500/40 msec, flip angle 70°, total duration 2 minutes). The image resolution was equal to that of standard clinical ΔR_2^* -based MR perfusion imaging performed at our institution, and is comparable to clinical ΔR_2^* -based MR perfusion sequences used at most institutions. Reconstruction of the full complex data (as opposed to magnitude calculation) was performed. Five seconds after the start of the perfusion sequence, bolus injection of 0.1 mmol/kg Gd-DTPA ('Magnevist', Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ) was administered in the antecubital vein by power injection at a rate of 5 mL/sec followed by a 20 mL saline flush performed at the same rate.

Results

Dynamic QSM reconstruction

Representative results during data processing are illustrated using data from subject 1. Comparison of the magnitude data to the phase data from an ROI centered on the mesial gray matter of the supraventricular region in the *in vivo* dataset is shown in Figure 2. The dashed curve represents the measured data, while the solid curve is a smoothed 6-point average. The periodic phase changes of a frequency approximating 1/3 Hz are attributed to extracranial bulk susceptibility changes related to breathing. The peak phase change is smaller compared to background than in the magnitude data. In addition, an equilibrium baseline is not reached before the 6th dynamic phase has been acquired in the phase data. The phase effect of Gd-DTPA is thus smaller than the R_2^* effect on the amplitude of the MR signal, and breathing-related background phase changes are of nearly 1/2 the magnitude of the Gd-DTPA induced phase shift.

Removal of the background gradient from the frequency maps is illustrated in Figure 2. In this example, frequency maps demonstrate a predominantly anterior-posterior gradient (Figure 3A–B) that is larger than the local frequency changes both at baseline (Figure 3A) and during the Gd bolus passage (Figure 3B). After removal of this gradient (Figure 3C), an

approximately 5 Hz range of frequency values is seen in this supraventricular brain section at baseline, consistent with prior static QSM studies at 3T (9). At the peak of the passage of the Gd-DTPA bolus (Figure 3D), the range of susceptibility contrast increases to 13 Hz.

The data shown in Figure 3C-D was used as input for the QSM analysis, performed separately on each dynamic followed by CSF referencing as described above. The resulting CSF-referenced susceptibility maps demonstrate the expected predominantly positive susceptibility changes during bolus pass, both in gray and white matter (Figure 4A-B). The negative susceptibility contrast of white matter at baseline with a mean value of about -0.04 ppm relative to CSF (Figure 4A) is the minimum in the entire dynamic series, as expected (9). Acceptable performance of the QSM processing using the lower resolution anisotropic data from the used EPI sequence compared to standard non-dynamic QSM imaging was confirmed using numerical simulations (not shown) and by the observed baseline susceptibility (before gadolinium arrival) being in good agreement with reported literature brain parenchymal susceptibility values. Small regions of artifactual decrease of the susceptibility during bolus pass, for example in the parasagittal subcortical white matter, are likely due to a reconstruction artifact (see discussion). Region of interest (ROI) analysis of the Gd-DTPA induced susceptibility changes during the imaging time is illustrated for several GM, WM and vascular ROIs in Figure 5A for scan 1. Distortions of the arterial curves (anterior (blue) and posterior (green) cerebral artery), are apparent, which preclude their direct use as AIF, and necessitate a semiautomatic vessel selection to generate an acceptable AIF as shown in Fig. 6B, and discussed further below. The remaining parenchymal curves demonstrate reasonable shape characteristics. Dynamic susceptibility curves for gray matter and white matter ROIs averaged for all five scans are shown in Figure 5B. Analogously for comparison, the corresponding dynamic ΔR_2^* changes in gray and white matter ROIs from all five scans are summarized in Figure 5C. For assessment of temporal variability, Figure 5D and 5E depict the time-courses of four representative voxels in the control scan, for susceptibility (Fig. 5D) and ΔR_2^* (Fig. 5E) respectively, plotted on the same scale as Figure 5B and 5C for comparison.

Arterial Input Function Determination

Typical AIF curves using the pixel selection criteria given in the methods section are shown in Figure 6 for both the $\Delta R_2^*(t)$ (Figure 6A) and $\Delta\chi_{ref}(t)$ data (Figure 6B). It is important to realize that these curves originate from pixels chosen using temporal criteria characteristic of arterial signal behavior, but nevertheless will still have significant partial volume effects with surrounding brain parenchyma. ΔR_2^* reaches a maximum of approximately 40 sec^{-1} during bolus peak (Figure 6A), while the maximum $\Delta\chi_{ref}$ value is approximately 6.10 ppm (Figure 6B). Interestingly, the general shape of both AIF's is similar, although the ΔR_2^* AIF has a higher signal-to-noise ratio.

Reconstructed Perfusion Images

Representative maps of CBF and CBV are shown in Figure 7 for perfusion processing based on both the magnitude (ΔR_2^*) and the phase (QSM) perfusion data. The ΔR_2^* -based AIF was used to calculate the ΔR_2^* perfusion maps, while for the QSM maps both the ΔR_2^* -based and the $\Delta\chi_{ref}$ -based AIFs were used, since the ΔR_2^* AIF has better SNR which may

benefit the QSM analysis. Overall, a good qualitative and quantitative (see colorbar) agreement between the CBF (Figure 7A) and CBV (Figure 7B) maps produced by both techniques was found. A voxel-by-voxel comparison of two slices for each scan (one at the level of the centrum semiovale, and one at the level of the internal capsule), yields a significant correlation ($p < 0.001$; $\rho = 0.61$), as shown in Figure 8. Data were smoothed with a Gaussian kernel (FWHM = 25 mm) to reduce the influence of noise and misregistration. The slope of the regression line is 0.81, indicating mild systematic underestimation of CBF by QSM PWI. Spearman correlation coefficients for all five scans are shown in Table 2.

Signal to Noise (CNR) Considerations

As depicted in Fig. 5D and 5E (scan without contrast administration), the variability between different time points is low for both ΔR_2^* and χ reconstructions. For the susceptibility reconstruction, the RMS noise was 0.015 ppm, compared to an average parenchymal peak signal change of 0.11 ppm in the bolus studies, leading to a contrast-to-noise (CNR) value of 7.3. For the ΔR_2^* reconstruction, RMS noise was 0.3 sec^{-1} , and the average parenchymal peak signal change 20 sec^{-1} , giving a CNR of 67. Thus, the CNR of QSM-based PWI is approximately one order of magnitude lower than that of the conventional ΔR_2^* reconstruction.

Discussion

This paper presents an algorithm and preliminary data to suggest that MR perfusion imaging based on measurement of quantitative changes in magnetic susceptibility associated with bolus injection of Gd contrast agent at 3T is feasible in the human brain. The resulting CBF and CBV parametric maps are in reasonable agreement with those produced by conventional ΔR_2^* analysis. Measurements of magnetic susceptibility have a theoretical advantage that they should be more linearly related to contrast agent concentration than methods based on changes in relaxation times or phase-shifts, and independent of vessel orientation. However, as this study shows, the contrast-to-noise ratio associated with susceptibility changes is far smaller than that associated with changes in the R_2^* relaxation rate, which may limit the practical application of this method. However, these limitations are partially attributable to the current standard PWI acquisition protocol used, and with pulse sequence optimization (e.g. choice of echo time, spatial resolution, and other factors, as well as optimization of contrast agent dose) it may be possible to increase the CNR of the QSM analysis in the future. This may require the development of new PWI acquisition protocols which combine high (isotropic) spatial resolution with the large coverage and high temporal resolution needed for clinical PWI.

Assuming other factors such as hematocrit do not change, the amount of susceptibility contrast observed in the brain depends on the contrast agent concentration and its molar susceptibility (2,4–8). In the current study a single dose of Gd-DTPA contrast agent was used (i.e. 0.1 mmol/kg body weight). On the 1st pass through the aorta, the peak vascular concentration of Gd-DTPA at this dosage is estimated to be of the order of 5–10 mM (7). In a long cylindrical vessel orientated parallel to the B_0 field, a 5 mM concentration of Gd-DTPA is estimated to cause a frequency shift of 1.7 ppm or approximately 220 Hz at 3T. This represents the maximum possible frequency shift which might be observed, for

instance, in the internal carotid artery. If the gray matter blood volume is assumed to be 4%–5.5% (35–37), and if the frequency shift scales proportionally to the blood volume, then a shift of at least 0.07 ppm (9 Hz at 3T) is predicted for gray matter. The peak susceptibility change in white matter is then expected to be at least 0.03 ppm (4 Hz), using a gray to white matter cerebral blood volume ratio of 2.2–2.5 (38). These numbers agree very well with the observed peak susceptibility shifts observed in parenchymal voxels in Figure 5. Severe peak distortions are observed in ‘arterial’ voxels which also show much smaller susceptibility shifts than predicted. This is likely primarily the result of excessive phase wrap in arterial voxels due to the acquisition parameters used in the current study (which were chosen with the primary aim of measuring tissue, rather than arterial, response). In gradient echo MR at a TE of 40 ms, the maximum frequency shift that can be measured (without phase unwrapping) is 25 Hz (~0.2 ppm), while the expected frequency shift in pure arterial blood may be as high as 220 Hz (~1.7 ppm) at 3T) based on literature values (7). Therefore, in the large arterial vessels, the use of this long TE undoubtedly leads to phase-wrap, and rapidly (spatially) varying phase-changes leading to signal loss. The result is that the 1st-pass arterial signal is distorted and almost certainly under-estimated, and that this also likely occurs (but to a lesser extent) on the 2nd pass also. It is important to realize however, that this is a consequence of the current acquisition parameters, and is not a fundamental limitation of the QSM-PWI technique itself; as already shown by others (1, 20, 21), by use of acquisition conditions optimized for the arterial signal (e.g. short TE, higher spatial resolution), susceptibility-based methods can be used to accurately determine AIFs. In the future interleaving of a short TE acquisition for AIF determination with a long TE acquisition for measuring tissue response might allow both to be measured optimally at the same time.

For all these reasons [which are well known problems in determining AIFs also using ΔR_2^* -based methods (26, 29)], it is not surprising that the ‘arterial’ voxels in Figure 5 are distorted and show lower susceptibility shifts than predicted by theory. Therefore, a semi-automatic voxel-selection method in the vicinity of arteries was used to derive AIFs of similar shape to the ΔR_2^* -based technique. However, these AIF voxels are undoubtedly affected by partial volume with brain parenchyma and therefore underestimate the true arterial concentration. Although underestimation of the AIF will result in over-estimation of CBF and CBV in tissue, its effect in the absence of curve shape distortion results in a mere scaling of the result, and the amplitude could in principle be fixed by area normalization to, for example, a venous curve. Alternative data acquisition methods are required for better determination of the AIF without partial volume or phase unwrapping issues, e.g. shorter TE and higher spatial resolution (Xu et al., 2012). Comparing dynamic changes in χ_v (Figure 5B) and ΔR_2^* (Figure 5C), the peak estimation is better for QSM-PWI (relatively smaller error bars, specifically in the gray matter), while after peak passage, the QSM-PWI data show more variability, indicating a higher noise level. The mean white matter dynamic χ_v changes are relatively larger compared to ΔR_2^* , likely due to certain brain regions retaining residual non-local susceptibility effects (QSM reconstruction artifact) with the current QSM-PWI method. While direct comparison of QSM-PWI and ΔR_2^* -data shows significant correlation (Figure 8), the QSM data are currently limited compared to the ΔR_2^* -data in identifying the clinically relevant perfusion abnormalities. However, none of the included clinical cases (consecutive patients enrolled with our protocol) had an outcome of a large confluent

territorial stroke, likely as a result from good arterial collateralization, and the presented case studies are thus more challenging for perfusion analysis than strokes that result in large territorial parenchymal necrosis. The above quantitative analysis is promising, in that QSM may allow to make perfusion imaging more quantitative and may provide complementary information. Further work is required to develop it into a clinically relevant tool.

In addition to the small magnitude of the Gd-DTPA-associated susceptibility shift, other factors also make reconstruction of QSM-based perfusion images challenging. As can be seen from Figure 2, a periodic phase angle variation of the dynamic phase data with a temporal frequency of approximately 0.3 Hz is present. This corresponds to a peak-to-peak local resonance frequency change of 2.5 Hz (which is equal to 0.02 ppm of the B_0 field strength). The most likely origin of this effect is a bulk susceptibility shift associated with inflation and deflation of the lungs during normal breathing; it can be seen that the amplitude of this effect is comparable to that associated with the Gd-DTPA bolus itself. This effect has been previously observed in other high field MR studies of the brain with similar amplitudes (40–42). In the current study, the effects of breathing were addressed by removing the background gradient in the frequency image for each dynamic and by CSF calibration. The CSF calibration is nearly unaffected by inter-individual differences (age, many disease processes), compared to the calibration to normal appearing white matter commonly used in ΔR_2^* -approaches, providing a better quantitative measurement. In addition, it is additive (the scale intervals remain unchanged) compared to a multiplicative correction in ΔR_2^* -techniques, thus QSM difference measurements remain fully quantitative. Intraventricular hemorrhage or ventriculitis would affect the calibration, but would be detected on other imaging sequences. Residual nonideal effects and partial volume effects limit the CSF referencing technique, as residual bolus effects are detected. We have reduced these effects maximally by semi-automatically detecting CSF voxels with minimal signal change, as well as avoiding as much as possible voxels with partial volume with brain tissue or sub-ependymal veins. Other approaches to resolve the breathing related background changes might be to fit the periodic phase variation in the pre-bolus images to a model function (on a regional basis, since the effect is location dependent), and then extrapolate and correct the expected breathing related phase-changes to the subsequent dynamics of the acquisition. Such an approach would however require higher temporal resolution data to work optimally. Other potential approaches might be to use a breath hold acquisition (not practical for patients) or to compensate for the variations using periodic adjustment of the scanner shim coils (40).

It is well known that the solution of the inverse problem to generate susceptibility maps from MR frequency measurements is underdetermined (11), and that the reconstructed susceptibility maps can contain artifacts as a result. Thus, appreciable errors can occur using the current method, particularly at the interfaces between different tissue types. One solution to this problem, which has been demonstrated to work well for conventional static QSM, is to collect multiple images with different head positions relative to the B_0 field direction (12,43). Simulations (unpublished data, not shown) indicated that such an approach would also work well for dynamic PWI QSM; however, because of the high temporal resolution required for dynamic PWI, as well as the difficulty in giving multiple Gd-DTPA injections such an approach is unlikely to be feasible for dynamic PWI. In addition, a more

sophisticated inverse method that utilizes a priori tissue structure information for regularization (17) may help reduce such kind of artifacts and further improve the accuracy and image quality of the QSM-based PWI. The SNR of QSM-PWI is currently lower than that of ΔR_2^* -based PWI, however, is expected to increase with implementation of the above discussed sequence and processing improvements.

Solving the QSM inverse problem is inherently a 3-dimensional calculation – frequency shifts seen in one slice depend not only on the susceptibility of the tissue in that slice, but also on that in regions above and below the observed slice (9,11,12). Typically, PWI is performed (as in the current example here) with relatively thick slices (4.4–5 mm) as well as moderate in-plane resolution (here 1–2 mm but commonly 2–3 mm) in order to have both good brain coverage and high temporal resolution. This is in contrast to static QSM which usually uses isotropic, high-resolution 3D acquisitions, since high temporal resolution is not a concern. It is likely that QSM PWI would in the future benefit from the use of 3D acquisitions with higher spatial resolution (albeit at the expense of decreased coverage, and perhaps temporal resolution) in order to reduce QSM associated reconstruction artifacts. The optimal technique for deconvolution of the QSM-derived perfusion data remains to be determined, including a systematic evaluation of both deconvolution techniques and regularization parameters, which is beyond the scope of this study.

In summary, this pilot study demonstrates that susceptibility based analysis of dynamic perfusion data is feasible and can be used to reconstruct CBF maps. The optimum acquisition and processing methods remain to be determined since the major limitation is the small effect of Gd on bulk tissue susceptibility (in remarkable contrast to its large effects on R_2^*), efforts to increase contrast are particularly needed, such as the use of contrast agents with higher molar susceptibility (e.g. dysprosium (1)), or higher concentration Gd agents, and/or higher magnetic field strengths. Perhaps the most likely role for QSM PWI is a complementary analysis method when ΔR_2^* analyses may be ambiguous; for example, when changes in both tissue R_1 and R_2^* occur, which can confound the estimation of Gd concentration (44), or, as previously described (20), as an alternative method for AIF determination. It may also supplement the analysis when blood-brain barrier (BBB) breakdown occurs (due to expected smaller effects of extravascular Gd on the signal change in QSM compared to relaxation time based methods), however the exact effects of intravoxel Gd distribution on the observed QSM signal remain to be further evaluated, for example using microvascular simulations. It should be noted that the method can be equally applied to the calculation of CBV, which is the most commonly used metric evaluated in brain tumor imaging. The method has the advantage of not requiring any additional scanner hardware or scan time, and can be readily applied on standard clinical systems so long as complex (as opposed to magnitude) image data is available for analysis. Higher contrast doses may benefit the assessment of the tissue response, while lower contrast doses and the selection of a shorter TE can alleviate the phase wrap and allow a more accurate determination of the AIF. In the future, an isotropic 3D acquisition would lead to an improvement in the QSM solution compared to the current 2D sequence, if it can be obtained at sufficient temporal resolution and brain coverage. More work is required to investigate optimization of data acquisition protocols and analysis methods for QSM-based

PWI, and also to investigate the effects (if any) of BBB breakdown on dynamic QSM measurements.

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Abbreviations

Gd	Gadolinium
DTPA	Diethylene triamine pentaacetic acid
QSM	Quantitative susceptibility mapping
PWI	Perfusion weighted imaging
CBF	Cerebral blood flow
CBV	Cerebral blood volume
MTT	Mean transit time
BBB	Blood brain barrier
ROI	Region of interest

References

1. Conturo TE, Barker PB, Mathews VP, Monsein LH, Bryan RN. MR imaging of cerebral perfusion by phase-angle reconstruction of bolus paramagnetic-induced frequency shifts. *Magn Reson Med*. 1992; 27(2):375–390. [PubMed: 1334207]
2. Petridou N, Wharton SJ, Lotfipoor A, Gowland P, Bowtell R. Investigating the effect of blood susceptibility on phase contrast in the human brain. *NeuroImage*. 2010; 50(2):491–498. [PubMed: 20026280]
3. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. *Magn Reson Med*. 1995; 34(4):555–566. [PubMed: 8524024]
4. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). *Magn Reson Med*. 2004; 52(3):612–618. [PubMed: 15334582]
5. Langham MC, Magland JF, Floyd TF, Wehrli FW. Retrospective correction for induced magnetic field inhomogeneity in measurements of large-vessel hemoglobin oxygen saturation by MR susceptometry. *Magn Reson Med*. 2009; 61(3):626–633. [PubMed: 19107914]
6. Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K. Functional brain mapping by blood oxygenation level dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophysical journal*. 1993; 64(3):803–812. [PubMed: 8386018]
7. de Rochefort L, Nguyen T, Brown R, Spincemulle R, Choi G, Weinsaft J, Prince MR, Wang Y. In vivo quantification of contrast agent concentration using the induced magnetic field for time-resolved arterial input function measurement with MRI. *Medical physics*. 2008; 35(12):5328–5339. [PubMed: 19175092]
8. Li L. Magnetic susceptibility quantification for arbitrarily shaped objects in inhomogeneous fields. *Magn Reson Med*. 2001; 46(5):907–916. [PubMed: 11670642]
9. Li W, Wu B, Liu C. Quantitative susceptibility mapping of human brain reflects spatial variation in tissue composition. *NeuroImage*. 2011; 55(4):1645–1656. [PubMed: 21224002]

10. Schweser F, Deistung A, Lehn DW, Reichenbach JR. Quantitative imaging of intrinsic magnetic tissue properties using MRI signal phase: an approach to in vivo brain iron metabolism? *NeuroImage*. 2011; 54(4):2789–2807. [PubMed: 21040794]
11. de Rochefort L, Liu T, Kressler B, Liu J, Spincemaille P, Lebon V, Wu J, Wang Y. 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. [PubMed: 19953507]
12. Wharton S, Bowtell R. Whole-brain susceptibility mapping at high field: a comparison of multiple- and single-orientation methods. *NeuroImage*. 2010; 53(2):515–525. [PubMed: 20615474]
13. Langhammer C, Schweser F, Krebs N, Deistung A, Goessler W, Scheurer E, Sommer K, Reishofer C, Yen K, Fazekas F, Ropele S, Reichenbach JR. Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study. *NeuroImage*. 2012; 62(3):1593–1599. [PubMed: 22634862]
14. Li W, Wu B, Avram AV, Liu C. Magnetic susceptibility anisotropy of human brain in vivo and its molecular underpinnings. *NeuroImage*. 2012; 59(3):2088–2097. [PubMed: 22036681]
15. Li X, Vikram DS, Lim IA, Jones CK, Farrell JA, van Zijl PC. Mapping magnetic susceptibility anisotropies of white matter in vivo in the human brain at 7 T. *NeuroImage*. 2012; 62(1):314–330. [PubMed: 22561358]
16. Liu C. Susceptibility tensor imaging. *Magn Reson Med*. 2010; 63(6):1471–1477. [PubMed: 20512849]
17. Liu J, Liu T, de Rochefort L, Ledoux J, Khalidov I, Chen V, Tsiouris AJ, Wisnieff C, Spincemaille P, Prince MR, Wang Y. Morphology enabled dipole inversion for quantitative susceptibility mapping using structural consistency between the magnitude image and the susceptibility map. *NeuroImage*. 2012; 59(3):2560–2568. [PubMed: 21925276]
18. Klocke J, Deistung A, Schweser F, Grandjean J, Dominiano M, Waschkes C, Nitsch RM, Knuesel I, Reichenbach JR, Rudin M. Detection of cerebral microbleeds with quantitative susceptibility mapping in the ArcAbeta mouse model of cerebral amyloidosis. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2011; 31(12):2282–2292.
19. Kiselev VG. On the theoretical basis of perfusion measurements by dynamic susceptibility contrast MRI. *Magn Reson Med*. 2001; 46(6):1113–1122. [PubMed: 11746577]
20. Kotys MS, Akbulut E, Markham J, Conturo TE. Precision, signal-to-noise ratio, and dose optimization of magnitude and phase arterial input functions in dynamic susceptibility contrast MRI. *J Magn Reson Imaging*. 2007; 25(3):598–611. [PubMed: 17226084]
21. Xu B, Liu T, Spincemaille P, Thimmappa ND, Prince MR, Wang Y. Dynamic Quantitative Susceptibility Mapping for Cerebral Arterial Concentration. 2015.3847.
22. Duyn JH, van Gelderen P, Li TQ, de Zwart JA, Koretsky AP, Takahaga M. High-field MRI of brain cortical substructure based on signal phase. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 104(28):11795–11801. [PubMed: 17586684]
23. Smith SM. Fast robust automated brain extraction. *Human brain mapping*. 2002; 17(3):143–155. [PubMed: 12391562]
24. Chu SC, Xu Y, Balschi JA, Springer CS Jr. Bulk magnetic susceptibility shifts in NMR studies of compartmentalized samples: use of paramagnetic reagents. *Magn Reson Med*. 1997; 38(2):239–262. [PubMed: 2156127]
25. Salomir R, De Senneville BD, Moonen CTW. A fast calculation method for magnetic field inhomogeneity due to an arbitrary distribution of bulk susceptibility. *Concepts Magn Reson B Magn Reson Eng*. 2003; 19B(1):26–34.
26. van Osch MJ, Vonken EJ, Viergever MA, van der Grond J, Bakker CJ. Measuring the arterial input function with gradient echo sequences. *Magn Reson Med*. 2003; 49(6):1067–1076. [PubMed: 12768585]
27. Knutsson L, van Westen D, Petersen EF, Bloch KM, Holvas S, Stahlberg F, Wirestam R. Absolute quantification of cerebral blood flow: correlation between dynamic susceptibility contrast MRI and model-free arterial spin labeling. *Magnetic resonance imaging*. 2010; 28(1):1–7. [PubMed: 19695822]

28. Zierler KL. Equations for Measuring Blood Flow by External Monitoring of Radioisotopes. *Circulation research*. 1965; 16:309–321. [PubMed: 14270567]
29. Grigic K, van Zijl PC, Qin Q. Hematocrit and oxygenation dependence of blood (1)H(2)O T(1) at 7 tesla. *Magn Reson Med*. 2012 [Epub ahead of print].
30. Gall, P.; Emerich, P.; Kjølby, B.; Kellner, E.; Mader, I.; Kiselev, VG. *Magma*. Vol. 23. New York, NY: 2010. On the design of filters for Fourier and oSVD-based deconvolution in bolus tracking perfusion MRI; p. 137-195.
31. Gall, P.; Mader, I.; Kiselev, VG. *Magma*. Vol. 22. New York, NY: 2009. Extraction of the first bolus passage in dynamic susceptibility contrast perfusion measurements; p. 241-249.
32. Kind T, Houtzager I, Faes TJ, Hofman ML. Evaluation of model-independent deconvolution techniques to estimate blood perfusion. *Conf Proc IEEE Eng Med Biol Soc*. 2010; 2010:2602–2607. [PubMed: 21096179]
33. Ostergaard L, Sorensen AG, Wong KK, Weisskoff RM, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intra-vascular tracer bolus passages. Part II: Experimental comparison and preliminary results. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 1996; 35(5):726–736.
34. Biagi L, Abbazzese A, Bianchi MC, Alsop DC, Del Guerra A, Tosetti M. Age dependence of cerebral perfusion assessed by magnetic resonance continuous arterial spin labeling. *J Magn Reson Imaging*. 2007; 25(4):696–702. [PubMed: 17275531]
35. Ulatowski JA, Oja JM, Suarez JJ, Kauppinen RA, Traystman RJ, van Zijl PC. In vivo determination of absolute cerebral blood volume using hemoglobin as a natural contrast agent: an MRI study using altered arterial carbon dioxide tension. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 1999; 19(7):809–817.
36. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJ, Gibbs JM, Wise RJ, Hatazawa J, Herold S, et al. Cerebral blood flow, blood volume and oxygen utilization. Normal values and effect of age. *Brain*. 1990; 113(Pt 1):27–47. [PubMed: 2302536]
37. Lu H, van Zijl PC. Experimental measurement of extravascular parenchymal BOLD effects and tissue oxygen extraction fractions using multi-echo VASO fMRI at 1.5 and 3.0 T. *Magn Reson Med*. 2005; 52(4):808–816. [PubMed: 15799063]
38. Lee MC, Cha S, Chang SM, Nelson SJ. Partial-volume model for determining white matter and gray matter cerebral blood volume for analysis of gliomas. *J Magn Reson Imaging*. 2006; 23(3):257–266. [PubMed: 16430821]
39. Calamante F, Vonken EJ, van Osch MJ. Contrast agent concentration measurements affecting quantification of bolus-tracking perfusion MRI. *Magn Reson Med*. 2007; 58(3):544–553. [PubMed: 17763347]
40. van Gelderen P, de Zwart JA, Starewicz P, Timis RS, Duyk JH. Real-time shimming to compensate for respiration-induced B0 fluctuations. *Magn Reson Med*. 2007; 57(2):362–368. [PubMed: 17260378]
41. Van de Moortele PF, Pfeuffer J, Glover GH, Ugurbil K, Hu X. Respiration-induced B0 fluctuations and their spatial distribution in the human brain at 7 Tesla. *Magn Reson Med*. 2002; 47(5):888–895. [PubMed: 11979567]
42. Barry RL, Menon RS. Modeling and suppression of respiration-related physiological noise in echo-planar functional magnetic resonance imaging using global and one-dimensional navigator echo correction. *Magn Reson Med*. 2005; 54(2):411–418. [PubMed: 16012661]
43. Liu T, Spincemaille P, de Rochefort L, Kressler B, Wang Y. Calculation of susceptibility through multiple orientation sampling (COSMOS): a method for conditioning the inverse problem from measured magnetic field map to susceptibility source image in MRI. *Magn Reson Med*. 2003; 61(1):196–204. [PubMed: 19097105]
44. Boxerman JL, Schmainda KM, Weisskoff RM. Relative cerebral blood volume maps corrected for contrast agent extravasation significantly correlate with glioma tumor grade, whereas uncorrected maps do not. *AJNR American journal of neuroradiology*. 2006; 27(4):859–867. [PubMed: 16611779]

Figure 1

Flow chart showing the processing steps to OSM-based perfusion maps. Example dynamic images at the level of corona radiata are shown before, during and after the Gd-DTPA induced bolus peak. In the 'Reference ROI' box, the selected ventricular CSF regions to be used for susceptibility reference are shown as red areas superimposed on the magnitude image. The blue curve shows the average signal magnitude in the selected reference ROIs. In the '3D frequency maps' box, the gray scale images are in units of Hz and in the range of -5 to 5 Hz. The gray scale quantitative susceptibility maps are in units of ppm and in the range of -0.15 to 0.15 ppm. The inset in the "Reference ROI" box displays the flat profile of the ventricular susceptibility over time (average magnitude on the ordinate, dynamics number on the abscissa, scale ranges from 3×10^4 to 10×10^4).

Figure 2

(A) Magnitude compared to (B) phase data from an ROI including the mesial gray matter of the supraventricular region. The dashed curve represents the measured data, while the solid curve is smoothed (6-point coverage). Note the periodic phase changes attributable to breathing in the phase data at a frequency of approximately 0.3 Hz. The contrast-to-background ratio associated with the Gd-DTPA bolus in the phase images is much smaller than in the magnitude data. The maximum phase change during the bolus passage is about 35°, corresponding to a frequency shift of about 2.5 Hz (TE 40 ms).

Figure 3

Frequency maps before (A/B) and after (C/D) background removal by dipole fitting of a single slice at the level of the corona radiata are shown at baseline (A/C) and during peak bolus passage (B/D). In (A) and (B), a strong, predominantly anterior-posterior background gradient is superimposed on the intrinsic frequency changes caused by tissue susceptibility differences in the brain. The contrast-induced phase changes are difficult to appreciate in (A) and (B), however can be noted in the gray matter and pial vessels. In (A), a 29 Hz difference between anterior and posterior brain regions is present, larger than the expected 10 Hz difference of intrinsic unenhanced brain tissue susceptibility contrast at 3 Tesla. C,D: The background gradient has been subtracted from each phase to generate local frequency maps (units Hz) at baseline (C) and during peak bolus pass (D). At baseline, the intrinsic susceptibility contrast at the level of the centrum semiovale is 5 Hz, which is expected given the included brain structures (C). At bolus peak (D), the range of susceptibility contrast increases to 13 Hz, indicating the presence of the Gd-LTPA effect on the frequency distribution.

Figure 4
 (A) CSF-referenced susceptibility maps $\chi_{ref}(t)$ (ppm) at baseline (6 sec), during peak bolus passage (36 sec), and during recirculation (90 sec). (B) Susceptibility difference images ($\Delta\chi_{ref}(t)$, ppm) at the same time points. During the bolus passage a moderate susceptibility increase is seen in both white and gray matter regions.

Figure 5

A: Representative susceptibility-time curves for selected white matter, gray matter and large arteries taken from figure 4B. Note that the maximum susceptibility change (in the vicinity of the anterior cerebral artery) is approximately 0.15 ppm. The smallest changes are in the selected white matter regions. Severe distortions of the arterial peaks are related to the inability of the sequence to resolve the large phase shifts related to the arterial Gd concentration (blue and green curves). B: Gray matter (red) and white matter (green) ROI averages (curves) for all five scans for QSM-PWT ($\Delta\chi_{ref}$). C: ΔR_2^* -data, analogous to B. D and E: Temporal variability for susceptibility (D) and ΔR_2^* (E) (plotted on the same scale as in B and C) for four representative voxels in the control scan performed without administration of contrast agent. The variability relative to the average peak in the bolus measurements is smaller for ΔR_2^* compared to $\Delta\chi_{ref}$.

Figure 6
Comparison of arterial input functions (AIF) derived from (A) ΔR_2^* and (B) $\Delta\chi_{ref}$ data. Both AIFs were determined by averaging the signal of semi-automatically selected voxels in the vicinity of the arteries, to avoid the distortions shown in Figure 5A. Crosses represent individual time points, whereas the curves are the smoothed AIFs (5-point sliding averages). It can be seen that the general appearance of the AIFs is similar in (A) and (B).

Figure 7
Comparison of (A) CBF and (B) CBV images reconstructed using classical ΔR_2^* analysis (left columns) or dynamic QSM perfusion [middle columns: using the ΔR_2^* -derived AIF (AIF₁); right columns: using the QSM-derived AIF (AIF₂)]. Representative slices at the level of the head of the caudate nuclei (upper rows) and the centrum semiovale (lower rows) are shown. Overall, good qualitative and quantitative agreement between DSC and QSM processing is shown for CBF (A) and CBV (B).

Figure 8
 Parity plot between CBF values calculated from ΔR_2^* (abscissa) and QSM-PWI (ordinate). For clarity, data are shown for two slices of each subject only, with reduction of the in-slice voxel number by a factor of 4, using down sampling of the image resolution. See text for further details. The solid line indicates the regression over all data points. Significant correlation ($p < 0.001$) with a Spearman's correlation coefficient of $\rho = 0.61$ is found. The slope is 0.81, indicating mild underestimation of CBF by QSM-PWI as compared to ΔR_2^* estimation.

Table 1

Patient characteristics

Scan ID/ Subject ID/ age / gender	Clinical	Diffusion	Perfusion	MRA/CTA
1/1/8/M	History of coronary artery disease; Transient double vision	Small subacute stroke in the right thalamus	Normal	MRA: No large vessel stenosis or occlusion
2/2/86/F	History of hypertension and prior stroke; Acute onset confusion and dizziness, dysarthria, left lower extremity predominant weakness	Small focal acute infarcts in the ACA territory	Hypoperfusion of right ACA distribution	CTA: Stenosis of right A1 segment
3/3/57/M	History of hypertension and diabetes; Aphasia, right-sided weakness improving when lying flat	Left MCA watershed focal infarctions	Perfusion deficit in left MCA territory	Left ICA thrombosis
4/3/57/M	Repeat scan 1 days later	Evolving watershed infarctions and new small embolic infarcts	Perfusion deficit in left MCA territory	Persistent left ICA thrombosis
5/4/63/M	History of hypertension and diabetes; Right-sided weakness; 1 week of memory and gait difficulty	Left PCA small focal infarcts	Perfusion deficit left PCA territory	High grade stenosis P2/P3 segments of left PCA

Table 2

Quantitative comparison of QSM-PWI and ΔR_2^* using Spearman's correlation coefficient and linear regression.

Sc. n ID	Spearman's rho	Linear regression (CBF)
1	0.64 (p<0.001)	$CBF_{QSM}=0.82CBF_{\Delta R_2^*}+0.25$
2	0.47 (p<0.001)	$CBF_{QSM}=0.87CBF_{\Delta R_2^*}+0.89$
3	0.70 (p<0.001)	$CBF_{QSM}=0.82CBF_{\Delta R_2^*}+1.07$
4	0.60 (p<0.001)	$CBF_{QSM}=0.77CBF_{\Delta R_2^*}+1.15$
5	0.62 (p<0.001)	$CBF_{QSM}=0.87CBF_{\Delta R_2^*}+1.44$