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On the Measurement of Absolute Cerebral Blood Volume (CBV) Using Vascular-Space-Occupancy (VASO) MRI

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Abstract

Recently, a vascular-space-occupancy (VASO) MRI technique was developed for quantitative assessment of cerebral blood volume (CBV). This method uses the T_1 -shortening effect of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) with imaging parameters chosen that null the precontrast blood magnetization but allow the postcontrast blood magnetization to recover to equilibrium. A key advantage of VASO CBV estimation is that it provides a straightforward procedure for converting MR signals to absolute physiologic values. However, as with other T_1 -based steady-state approaches, several important factors need to be considered that influence the accuracy of CBV values obtained with VASO MRI. Here, the transverse relaxation (T_2/T_2^*) effect in VASO MRI was investigated using multiecho spin-echo and gradient-echo experiments, resulting in underestimation of CBV by $14.9\% \pm 1.1\%$ and $16.0\% \pm 2.5\%$ for spin echo (TE = 10 ms) and gradient echo (TE = 6 ms), respectively. In addition, the influence of contrast agent clearance was studied by acquiring multiple postcontrast VASO images at 2.2-min intervals, which showed that the concentration of Gd-DTPA in the first 14 min (single dose) was sufficient for the blood magnetization to fully recover to equilibrium. Finally, the effect of vascular Gd-DTPA leakage was assessed for scalp tissue, and signal extrapolation as a function of postinjection time was demonstrated to be useful in minimizing the associated errors. Specific recommendations for VASO MRI acquisition and processing strategies are provided.

Keywords

cerebral blood volume; brain; perfusion; VASO; MRI

Quantitative measurement of cerebral blood volume (CBV, defined as ml blood in 100 ml brain) is useful for advancing our understanding of brain physiology and pathophysiology (1, 2). It has been reported that many brain disorders, including stroke (1,3,4) and Alzheimer's disease (5–8), are associated with abnormal CBV. Compared to cerebral blood flow (CBF), CBV has been less extensively studied, but it was recently shown to be particularly sensitive to brain tumor grade (9), and it may be a useful marker for angiogenesis and synaptogenesis (10,11). In addition, CBV is an important parameter for quantitative functional MRI (fMRI) and investigation of the blood oxygenation level-dependent (BOLD) signal mechanism (12–14).

We recently developed a vascular-space-occupancy (VASO) MRI technique for quantitative assessment of CBV. This technique uses the T_1 -shortening effect of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) and is based on pre/post image subtraction,

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in which the imaging parameters are chosen such that the precontrast blood signal is zero and the postcontrast blood signal corresponds to equilibrium magnetization (15). VASO MRI has several potential advantages in comparison to the dynamic susceptibility contrast (DSC) MRI (16–18) method: It does not require the arterial input function (AIF). It does not use single-shot EPI acquisition, and thus the image distortion is minimal and higher resolution is feasible. In contrast to other T_1 -based steady-state methods (19–22), VASO MRI does not need a whole blood voxel for signal reference, it utilizes fully the T_1 relaxivity of the Gd-DTPA contrast agent, and it has a relatively small inflow effect when using a long TR (>6000 ms) (23).

Despite these features, VASO MRI shares common limitations of T_1 -based CBV methods in that several confounding factors can cause bias in the estimated CBV values. First, this technique utilizes the T_1 -relaxivity effect on blood (not on tissue because of the blood–brain barrier [BBB]), but the contrast agent will also shorten T_2/T_2^* of blood and possibly those of tissue. Consequently, the acquired image is weighted by T_2 or T_2^* even with the use of the shortest attainable echo time (TE). This can partly offset the T_1 effect and result in an underestimation in CBV. Second, extravasation of Gd-DTPA can occur in patients with a damaged BBB. This will increase the fraction of water molecules affected by the contrast agent and cause an overestimation of CBV. Third, the theoretical framework of VASO MRI is based on the assumption that the concentration of Gd-DTPA is sufficiently high to allow the blood magnetization to return to equilibrium. Therefore, it would be useful to determine the time window during which this assumption is valid. Finally, water exchange between blood and tissue across the BBB, which was not included in the previous study (15), may influence the quantification of CBV.

The purpose of this work is to quantify the effect of these factors on the estimation of CBV in VASO MRI and to provide recommendations for optimal data acquisition and analysis strategies. We investigate TE dependence, acquisition timing dependence, and acquisition scheme dependence (gradient echo [GE] vs. spin echo [SE]) in VASO MRI. In addition, scalp tissue is used as a “model tissue” to study the effect of Gd-DTPA leakage. Effect of water-exchange is assessed using numerical simulations.

Materials And Methods

MRI Experiment

All MRI experiments were conducted on 3T MR system (Philips Medical System, Best, The Netherlands). We recruited 10 healthy subjects (24 ± 2 years old, five men and five women) for this study. Each subject gave informed written consent before participating in the study. The Health Insurance Portability and Accountability Act (HIPAA)-compliant protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

The 10 subjects were equally divided into two groups, with one group undergoing the SE studies and the other group GE studies. For each study we performed one precontrast VASO scan and 10 consecutive postcontrast VASO scans, resulting in 10 CBV maps as a function of postinjection time. The same precontrast scan was used for these calculations. For each scan, depending on the SE or GE study, an eight-echo SE (i.e., Carr-Purcell-Meiboom-Gill [CPMG] sequence) with an echo interval, τ_{CPMG} , of 10 ms or a multiecho GE sequence with an echo interval of 6 ms was used, thereby allowing us to assess the effect of transverse relaxation times. The Gd-DTPA contrast agent (Magnevist, Berlex Laboratories, Wayne, NY, USA) was administered intravenously at a single dosage (0.1 mmol/kg) with a rate of 5 ml/s via a power injector (Medrad, Pittsburgh, PA). It was followed by a saline flush of twice the volume of Gd-DTPA solution with the same injection rate. Figure 1 shows a diagram of the experimental protocol.

The VASO MRI pulse sequence is a non-slice-selective inversion recovery sequence with the inversion time (TI) chosen to null the blood signal as described previously (12,15). At 3T, blood $T_1 = 1624$ ms (24), resulting in a TI = 1088 ms for TR = 6000 ms. Other imaging parameters were: TE = 10 ms (SE)/6 ms (GE), field of view (FOV) = 230×230 mm², scan matrix size = 128×128 , single slice with slice thickness = 5 mm, and EPI factor = 7, duration per scan = 2.2 min. The first postcontrast VASO scan was initiated 51 s after the injection to avoid signal fluctuations due to bolus passes. In addition, a proton density (PD)-weighted image (TR/TE = 20,000 ms/11 ms) was acquired for estimation of MR signal at equilibrium, M_0 , which is needed to convert the MR signal to physiologic values (15). The inhomogeneity of head coil sensitivity was accounted for by referencing against the body coil signal profile, assuming the body coil has a homogeneous sensitivity within the brain and the dielectric effect is minimal.

In an additional healthy subject (26-year-old female), we assessed the time course of contrast agent clearance by performing a long DSC scan (T_2^* -weighted, single-shot EPI) continuously for 47 min (TR = 4000 ms, 700 volumes). This provided an estimate of the plasma Gd-DTPA concentration decay, which was needed for the simulations. Other imaging parameters were: FOV = 240×240 mm², matrix size = 64×64 , slice thickness = 5 mm, number of slices = 5, slice orientation = transverse, TE = 30 ms, and flip angle = 90° .

Data Processing

Magnitude and phase images were reconstructed on the scanner. The phase of the first echo (TE = 10 ms for SE, and TE = 6 ms for GE) was used to determine the sign of the magnetizations. This is important because in an inversion recovery sequence like VASO, the magnetization may be positive or negative depending on the T_1 of the tissue type. For short- T_1 tissue such as gray or white matter, the magnetization will be positive, whereas for CSF the magnetization will be negative. For mixed voxels with partial volumes, the sign of the total magnetization will depend on the volume fraction of each tissue type, and the phase of the image, ϕ , can be used to determine the sign by thresholding of $-90^\circ \leq \phi < 90^\circ$ as positive and $90^\circ \leq \phi < 270^\circ$ as negative.

The sign-corrected pre- and postcontrast VASO images were coregistered using FSL (FMRIB Centre, University of Oxford, Oxford, UK). Then CBV was calculated by (15):

$$CBV = \frac{S_{\text{post}} - S_{\text{pre}}}{M_0 \cdot C_b} \times 100 \quad (\text{ml}/100 \text{ ml brain}), \quad [1]$$

where S_{pre} and S_{post} are the MRI signals before and after the contrast agent injection, respectively; M_0 is the MRI signal for a pure-water voxel at equilibrium magnetization; and C_b is the water content of blood and is assumed to be 0.87 ml water/ml blood (25). The M_0 for each subject was estimated from the ventricular voxels of the PD images. In-house MATLAB routines were used to calculate CBV maps corresponding to each of the eight echoes for each of the 10 postinjection times.

Region-of-interest (ROI) analysis was also performed. While CBV maps were calculated for the whole brain, the ROI analyses were based on tissue masks. To obtain a mask, the precontrast VASO image was first edited to remove ventricles and deep gray matter regions. Then the histogram of the remaining voxels was fitted to the summation of two Gaussian curves. Because of the T_1 -weighted contrast of the VASO images, the Gaussian curve with lower signal intensity was assigned as gray matter, while the other was assigned as white matter. The voxels having

intensities within mean $\pm 0.5 \times$ standard deviation (SD) of the Gaussian curve were included in the ROI.

The signals from the long DSC scan were used to estimate the blood Gd-DTPA concentration, $[\text{Gd-DTPA}]_b$, as a function of time. The voxels within the entire (skull-stripped) brain were used for the spatial averaging in order to achieve the highest possible signal-to-noise ratio (SNR). The MR signals were first converted to relaxation rates by:

$$\Delta R_2^*(t) = R_2^*(t) - \tilde{R}_2^* = - \frac{\ln(S(t) / \tilde{S})}{\text{TE}}, \quad [2]$$

where $R_2^*(t)$ is the transverse relaxation rate at time point t , $\tilde{R}_2^*$ is the precontrast relaxation rate, and $S(t)$ and $\tilde{S}$ are the corresponding MR signal intensities. $\Delta R_2^*(t)$ was then converted to $[\text{Gd-DTPA}]_b(t)$ according to the Monte Carlo simulation results of Boxerman et al. (26):

$$[\text{Gd-DTPA}]_b(t) = n \cdot \Delta R_2^*(t)^m, \quad [3]$$

where m was assumed to be 0.56 at $[\text{Gd-DTPA}]_b(t) = 1.2$ mM and decrease linearly to 0.50 at $[\text{Gd-DTPA}]_b(t) = 0$ mM. The parameter m is the reciprocal of the exponent used in Fig. 6 of Boxerman et al. (26). We note that these simulation results were based on a specific model of vascular network (26) and are the closest data in the literature matching our experimental conditions. However, the actual relationship between the contrast agent concentration and the R_2^* effect could be different from the assumed equation. In Eq. [3], n is a constant related to voxel composition and will be canceled out in relative comparisons.

Simulation

To compare the experimental data with theoretical predictions, numerical simulations were performed using a kinetic model similar to that considered by Tofts and Kermode (27). We assumed the following four compartments: plasma, blood cell, extravascular extracellular space (EE), and extravascular intracellular space (EI). When the BBB is intact, the contrast agent is only distributed in plasma. In leaky vasculature, Gd-DTPA will be distributed in plasma and EE, but not EI. When considering the T_1 relaxation effects, the plasma and blood cell compartments are considered together, as are the EE and EI compartments. This is equivalent to assuming a fast water exchange between plasma and blood cell and between EE and EI, similar to models used previously (28,29). We believe this is applicable (30,31) given the long TI (1088 ms) used in the VASO sequence. The blood Gd-DTPA concentration time course is based on the long-duration DSC scan described above. With these assumptions, simulations were performed for leaky and nonleaky tissues and for various water exchange rates between intravascular and extravascular compartments. VASO signal time courses (as a function of postinjection time), as well as the time derivatives, were calculated for comparison with experimental data and to understand the different signal contributions. The theoretical framework for the simulations is detailed in the Appendix.

Results

Figure 2 illustrates the VASO CBV maps of two subjects (for SE and GE experiments, respectively) at different postinjection times and echoes. Figure 3 shows the averaged gray matter CBV for SE (Fig. 3a, $N = 5$) and GE (Fig. 3b, $N = 5$) experiments. In addition to the

eight echoes acquired experimentally, analysis was also done to first extrapolate the MRI signal intensity to an effective TE of 0 ms and then calculate the CBV. This set of values was denoted as “extrapolated CBV” in the plot. Since the extrapolated estimation is expected to have minimal T_2/T_2^* effect, we consider this to be our best estimation of CBV, and all other CBV values were normalized against the extrapolated CBV values during the plateau period ($t = 8.6, 10.8, \text{ and } 13.0 \text{ min}$). The estimated CBV values were $4.1 \pm 0.3 \text{ ml/100 ml}$ (mean $\pm$ standard error of the mean [SEM], $N = 10$) and were not different between SE and GE data ($P = 0.19$). We believe this estimation has a minimal transverse relaxation effect as well as a minimal water exchange effect, as supported by the simulation results below.

Compared to the extrapolated estimation, the CBV measured with the first echo (10 ms for SE and 6 ms for GE) was underestimated by $14.9\% \pm 1.1\%$ and $16.0\% \pm 2.5\%$ for SE and GE acquisitions, respectively. The T_2 and T_2^* values calculated from the eight echoes of the pre- and postcontrast images are plotted in Fig. 4. The precontrast gray matter T_2 and T_2^* values were $77.9 \pm 0.7 \text{ ms}$ and $53.0 \pm 1.6 \text{ ms}$, respectively, comparable to previous reports (32,33); however, it should be noted that the blood signal was suppressed in these measurements, so these values reflect the relaxation of intracellular and interstitial fluid in the presence of influences from venous blood (i.e., the BOLD effect). Upon contrast agent injection, T_2^* shows a significant decrease (paired t -test, $P < 0.05$ for all postcontrast time points) and then slowly recovers toward the precontrast value. T_2 did not show a significant drop at any of the postcontrast time points ($P > 0.5$ for all time points). We believe that the T_2 change of pure tissue will be even smaller than what Fig. 4 shows, since the postcontrast signal contains blood and extravascular tissue and the major contribution to the T_2 change is likely from blood. The extravascular tissue will, in principle, also experience a T_2 reduction because the water diffusion will prevent the magnetization from being perfectly refocused, and such an effect is more pronounced when the field inhomogeneity is greater (with contrast agent). This mechanism is similar to that of SE BOLD fMRI (26). However, our experimental result suggests that this effect is quite small at a refocusing interval of 10 ms.

The pattern of estimated CBV as a function of postinjection time (Fig. 3) appears to suggest that the signal is not a simple linear or exponential decay and multiple components may be involved in this time course. During the first four time points after the injection, the estimated CBV has a sharp decrease (analysis of variance [ANOVA], $P = 0.002$). For time points 8.6, 10.8, and 13.0 min, the values show very slow, if any, decay ($P = 0.790$). After 14 min, the estimates further decrease gradually ($P = 0.001$).

Numerical simulations were performed to understand this time course. Figure 5a shows the estimated CBV as a function of blood Gd-DTPA concentration in tissues with intact BBB. Under the assumption of no water exchange (solid curve), the estimated CBV is relatively insensitive to Gd-DTPA concentration beyond a certain threshold (e.g., $[\text{Gd-DTPA}]_b = 0.5 \text{ mM}$), which is an advantage of the VASO sequence. This is because the magnetization of spins in blood has reached equilibrium and the blood volume effect has plateaued. The water exchange effect, however, will continue to increase with higher concentration (dotted and dashed curves in Fig. 5a). Using the Gd-DTPA concentration decay curve, one can simulate the estimated CBV as a function of time (Fig. 5b). It can be seen that the no-water-exchange curve (solid line) shows a gradual CBV decrease, but this does not explain the initial rapid decay as seen in the experimental data (Fig. 3). With the inclusion of water exchange for typical brain tissue (permeability-surface product $[\text{PS}] = 80\text{--}130 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$) (34), the simulated time-course also shows the initial decay pattern. Therefore, we explain the VASO signal time-course by a combined effect of CBV contributions and water-exchange contributions. Figure 5c shows the fraction of water-exchange contributions in the total VASO signal. It can be seen that the contribution is reduced to less than 10% of the total effect after

approximately 7.0 min postinjection, at which time the CBV signal is 95.8% of the true CBV effect. This value reduces to 92.1% at 14 min postinjection. In addition, the 7- to 14-min period has the weakest time dependence as shown by the time-derivative plot (Fig. 5d), which is useful to ensure that the VASO signal is constant within the imaging time (2.2 min). Taking these factors together, the period of 7–14 min appears to be optimal for VASO image acquisitions in terms of minimizing the water-exchange effect, maximizing the CBV effect, and ensuring that the effect is relatively constant within the scan duration. In our experimental data, the 8.6- to 13.0-min time points were acquired during this period (note that it takes 2.2 min to acquire each VASO image, thus the 8.6- to 13.0-min time points were actually acquired during the period of 7.5–14.1 min).

The effect of Gd-DTPA leakage was investigated using the scalp as a “model” for leaky tissue. Figure 6a shows an example of the manually drawn ROI for the scalp tissue, and Fig. 6b and c plot the time courses of the estimated BV for the SE and GE data, respectively (symbols in Fig. 6b and c, mean $\pm$ SEM, $N = 5$ in each plot). Note that we still use the term “BV” for easy comparison with other plots. However, this signal is no longer a true BV signal. Instead, it is a combined effect of BV and vessel permeability. It can be seen that, in contrast to the pattern of CBV (Fig. 3), the scalp signal increased as a function of time, especially during the first several minutes after the injection. By including an additional permeability parameter, K^{trans} , in the kinetic model, simulations can be performed to estimate the BV in the presence of vascular leakage (curves in Fig. 6b and c). It can be seen that the experimental data are qualitatively similar to the predictions from simulations. We have also found that a quadratic extrapolation to time zero can considerably reduce the overestimation in CBV due to Gd-DTPA leakage. This was tested with simulation data in which the true CBV was assumed to be 5 ml/100 ml. For K^{trans} values ranging from 0.005 to 0.025 min^{-1} , the extrapolated values were 4.75–6.97 ml/100 ml, which are comparable to the true CBV.

Discussion

In this study we investigated potential confounding factors that may affect the accuracy of CBV estimation using VASO MRI. These factors can cause underestimation or overestimation. However, the acquisition and processing procedures can be optimized to minimize such spurious contributions. Specifically, multiecho data acquisition is recommended to reduce the transverse relaxation effect. In order to preserve >90% of the CBV effect, the Gd-DTPA concentration needs to be sufficiently high, and this corresponds to the first 14 min after injection, when a single dosage is used. Within this period, 7–14 min postinjection is optimal for a tradeoff between minimizing the water exchange effect and preserving the CBV effect. Leaky vasculature (to Gd-DTPA) results in overestimation in CBV, the extent of which is a function of postcontrast time. This overestimation may be corrected by extrapolating to postinjection time of zero.

In our previous study (15), the theory did not account for the effect of water exchange. Here, we considered this effect and found that the water exchange contribution is concentration dependent and can be up to 30% of the total signal if the postcontrast scan is performed immediately after the contrast agent injection. But this fraction decreases quickly (compared to the decrease of CBV effect) as a function of postinjection time. Thus the optimal timing of the postcontrast VASO is to wait for a few minutes before the VASO scan starts. This “waiting” time can be utilized to acquire other postcontrast scans, such as DSC and postcontrast T_1 -weighted scans. If these other scans are not of interest and shortening the exam time is critical, one can consider using a slightly lower dosage to achieve the target concentration immediately. However, the blood Gd-DTPA concentration will decay after the initial injection. Thus, follow-up infusion (at a much slower rate) after the initial dose is needed to maintain the Gd-DTPA concentration throughout the VASO scan.

Our simulations showed time courses similar to the experimental data. However, it should be noted that many assumptions are used in the simulations. We analyzed the sensitivity of the simulation results to each of these assumptions. It was found that the exponent m in Eq. [3] is important for the explanation of the plateau period in the time course. According to the work of Boxerman et al. (26), m is dependent on Gd-DTPA concentration, and thus is time-variant in our simulation. In this study, the value of m is assumed to decrease linearly from 0.56 to 0.50 when the Gd-DTPA concentration changes from 1.2 mM to 0. If the value of m is assumed to be constant with time, the middle plateau period in Fig. 5b will not be as evident. The other assumed parameters do not have a significant impact on the curvature of the time course, although the curve tends to shift up and down slightly when the parameter value changes. For a 10% variation in the assumed values of Gd-DTPA concentration, T_1 of blood, T_1 of extravascular tissue, and the relaxivity of Gd-DTPA, the simulated CBV varied by 2.8%, 5.2%, 0.92%, 2.5%, respectively.

From the multiecho data, we observed a clear decrease in T_2^* of the parenchyma (blood + tissue), which is due to a combined intravascular and extravascular effect of the contrast agent. The T_2 reduction as estimated from the CPMG data is much more subtle. In vivo blood R_2 measurements using the same contrast agent, dosage, and τ_{CPMG} have shown that the pure blood R_2 increases by about 3.6 s^{-1} (35). Assuming that the parenchyma contains 5% blood, the Gd-DTPA effect on pure blood would by itself translate to a 1-ms reduction in the parenchyma T_2 , which is about the amplitude of the T_2 change in Fig. 4. This suggests that additional contributions from tissue T_2 reduction are minimal and that the intravascular Gd-DTPA has negligible effect on extravascular tissue's CPMG- T_2 . According to this result, a τ_{CPMG} of 10 ms is sufficiently short to refocus any dephasing effect due to water diffusion.

If multiecho VASO acquisition is not feasible, the shortest attainable TE should be used. In this case, the CBV effect, which is based on the T_1 relaxivity of Gd-DTPA, will be reduced by T_2/T_2^* effects, which originate from both intrinsic transverse relaxation and change of relaxation rate due to the contrast agent. The intrinsic transverse relaxation will affect both SE and GE acquisitions, whereas the change of relaxation rate will only affect a GE acquisition, as described above (also see Fig. 4). These underestimations in single-echo data may be minimized by assuming a T_2/T_2^* value from the literature and performing an extrapolation to TE of zero. We tested this using our experimental data and found that, by assuming $T_2 = 78 \text{ ms}$ and $T_2^* = 53 \text{ ms}$, the underestimation using the single-echo data was only $3.4\% \pm 1.2\%$ and $6.0\% \pm 2.8\%$, for SE and GE, respectively. This is much smaller than the value without using extrapolation ($\sim 15\%$). The amount of underestimation in GE data can be further reduced by assuming separate T_2^* values for pre- and postcontrast conditions. In our data, using $T_2^{\text{pre}} = 53 \text{ ms}$ and $T_2^{\text{post}} = 46 \text{ ms}$, the underestimation was reduced to $1.8\% \pm 2.7\%$. Since T_2/T_2^* values would show slight variations across subjects and across brain regions, we performed simulations to test the bias in CBV due to errors in the assumed T_2 values. It was found that, for every 1 ms of deviation in T_2 , the CBV value will be biased by 0.17%. Thus, the effect of T_2 variation is relatively small. The single-echo SE data still showed some underestimation after T_2 extrapolation. The reason is that the first echo signal intensity in our data is always lower than the expected signal from a monoexponential fitting, which is due to imperfect refocusing RF pulses and the presence of stimulated echoes (36). This was verified by performing the extrapolation with the later echoes, and the residual bias was found to be reduced ($<2\%$). In this work we used sinc-shaped noncomposite RF pulses for refocusing. In principle, composite RF pulses would be useful to achieve better refocusing (37). However, the use of composite pulses will increase the interval between refocusing pulses, which lengthens the echo train.

In this work we studied only young healthy controls, who are expected to have minimal BBB leakage. Thus, to assess the effects of leaky vasculature on the CBV estimation, we used scalp tissue as our “model” tissue for Gd-DTPA extravasation and compared the experimental data with simulation results. The simulations were performed with parameters comparable to those in the brain (Table 1). The extent of leakage (K^{trans}) was based on literature values for brain tumors (9,38). From the simulation results, it was found that the K^{trans} in scalp tissue is similar to that in lymphoma (38) and low-grade glioma (9) ($\sim 0.02 \text{ min}^{-1}$), but much lower than those in glioblastoma and meningioma (9,38). Thus, the vascular leakage data shown above is a reasonable model for low-grade tumors only.

One limitation of the present study is that the estimated CBV is not validated by a gold standard method. For human studies, the current CBV gold standard method is ^{11}CO positron emission tomography (PET), in which the subject takes a brief inhalation of ^{11}CO gas and, once the ^{11}CO concentration equilibrates in the blood pool, a PET image is taken. The PET image will then be calibrated using the blood tracer concentration measured from simultaneous blood sampling, and absolute CBV can be calculated. This was not performed in this study due to the short half-lives of the ^{11}CO tracer, which necessitates an onsite cyclotron in order to perform these measurements.

In this study, Gd-DTPA contrast agent was used in the VASO experiments to obtain the absolute values of CBV in ml blood/100 ml brain. Without the contrast agent, the VASO signal is CBV-weighted, but it is also affected by other parameters, such as tissue T_1 . Thus, while the noncontrast VASO image is sensitive to CBV changes during brain activation (12), the signal itself does not provide a quantitative measure of CBV. More recently, a method to quantify absolute CBV using noncontrast VASO was proposed, but the estimation was limited to ROI analysis due to the low sensitivity, despite the scan duration of approximately 45 min (39).

Conclusions

Estimation of absolute CBV using VASO MRI may contain contributions from several confounding factors. However, many of these effects can be minimized by optimal acquisition and processing strategies. The transverse relaxation effect of the contrast agent can result in underestimation of CBV, which can be compensated for by extrapolation of multiecho data. The water-exchange and Gd-DTPA leakage effects may cause overestimation of CBV. We found that the water-exchange effect is considerably reduced during a 7- to 14-min interval following contrast agent administration, at which time the blood volume effect is largely preserved. Gd-DTPA leakage can lead to overestimation, and a multi-time-point acquisition may be useful for correcting this effect when the leakage is mild. Our findings suggest that, with careful selection of the experimental protocol, accurate CBV estimation is feasible with VASO MRI.

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Appendix

Appendix

Simulation of VASO MRI Signals With Considerations of Water-Exchange and Gd-DTPA Leakage Effects

We assume that the MR signals in brain parenchyma can be separated into two compartments: an intravascular (containing plasma and blood cells, denoted by b) and an extravascular (containing EE and EI, denoted by t) space. The VASO signal can be written in terms of the T_1 of each compartment, $T_{1,b}$ and $T_{1,t}$ (15):

$$S = S_t + S_b = M_0 [(C_{par} - V_b C_b) (1 - 2e^{-TI/T_{1,t}} + e^{-TR/T_{1,t}}) + V_b C_b (1 - 2e^{-TI/T_{1,b}} + e^{-TR/T_{1,b}})], \quad [A1]$$

where M_0 is the equilibrium magnetization for pure water; C_{par} and C_b are the PD of parenchyma and blood vessels, respectively; V_b is the blood volume in ml blood/100 ml parenchyma; TI is the inversion time, and TR is the repetition time. In Eq. [A1], the transverse relaxation effect has been neglected. Equation [A1] is applicable for both pre- and postcontrast signals with different $T_{1,b}$ and $T_{1,t}$. Comparing pre- and postcontrast, the increase in relaxation rate, ΔR_1 , due to Gd-DTPA is proportional to the concentration, $[Gd-DTPA]_b$ or $[Gd-DTPA]_t$:

$$\frac{1}{T_{1,i}^{post}} - \frac{1}{T_{1,i}^{pre}} = \Delta R_{1,i} = J_i \cdot [Gd-DTPA]_i \quad (i=b, t), \quad [A2]$$

where J_i is the T_1 relaxivity of Gd-DTPA (40).

An estimate of $[Gd-DTPA]_b$ as a function of time, t , was obtained by fitting the DSC data to exponential functions (Fig. 7a). The DSC data up to 25 min were used for the fitting to match the duration for the VASO scans. We tested monoexponential and biexponential fittings for $[Gd-DTPA]_b$ decay and found that a biexponential function provides significantly better fits to the data. Figure 7a shows the experimental data as well as the biexponential fit. Figure 7b plots the estimated $[Gd-DTPA]_b$ as a function of time. The time constants were 1.2 min and 28.6 min for biexponential fitting and 11.3 min for monoexponential fitting. The time constant obtained from the monoexponential fitting is in good agreement with the “distribution half-life” (12 min) provided by the manufacturer.

For $[Gd-DTPA]_t$, since the contrast agent can only enter the EE when the vasculature is leaky, $[Gd-DTPA]_t$ is calculated by $[Gd-DTPA]_t = [Gd-DTPA]_{ee} \cdot f_{ee}$, in which f_{ee} is the fraction of EE space in the extravascular tissue. To estimate $[Gd-DTPA]_{ee}$ as a function of time, the following procedure was used. For impermeable vasculature, $[Gd-DTPA]_{ee}(t)$ was assumed to be 0. For leaky vasculature, $[Gd-DTPA]_{ee}(t)$ was calculated from $[Gd-DTPA]_p(t)$ at a given permeability K^{trans} following the work of Tofts and Kermode (27):

$$[\text{Gd-DTPA}]_{\text{ee}}(t) = \frac{K^{\text{trans}}}{V_{\text{ee}}} \int_0^t [\text{Gd-DTPA}]_p(\tau) \exp \left[-\frac{K^{\text{trans}}}{V_{\text{ee}}} (t - \tau) \right] d\tau, \quad [\text{A3}]$$

where $[\text{Gd-DTPA}]_p(t)$ is the Gd-DTPA concentration in plasma, estimated by $[\text{Gd-DTPA}]_p = [\text{Gd-DTPA}]_b / (1 - \text{hematocrit})$, and V_{ee} is the volume fraction of EE in the entire voxel. Table 1 summarizes the parameter values used in the simulation.

When the water exchange between the intra- and extravascular spaces is considered, three of the terms in Eq. [A1], namely V_b , $T_{1,b}$, and $T_{1,t}$, are replaced by a new set of terms. The analytical expressions of these new terms can be found in Hazlewood et al. (41) and are functions of water exchange rate, defined by the PS. These new terms are calculated for both the pre- and postcontrast conditions.

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Fig. 1. VASO MRI experiment protocol. A total of 11 VASO MRI scans were performed at the timing shown. For each VASO scan, a multiecho SE or GE acquisition scheme was used. The echo interval was 10 ms and 6 ms for SE and GE, respectively.

Fig. 2. Estimated CBV maps from the first, third, sixth, and eighth echoes for the postcontrast time (center of acquisition) of 2.0, 10.8, 15.2, and 19.6 min. **a:** SE data. **b:** GE data. The grayscale unit is ml blood/100 ml parenchyma.

Fig. 3.

Normalized CBV ($N = 5$) of gray matter as a function of echo number and postinjection time for SE (a) and GE (b). The extrapolated values from the multiecho data are also plotted and labeled as “Extrapolated”; $t = 0$ is defined as the time of contrast agent injection. The CBV data were normalized with respect to the extrapolated values at $t = 8.6, 10.8$, and 13.0 min, within which period no signal trend was observed ($P = 0.79$). The error bars indicate the SEM across subjects.

Fig. 4.

Time courses of T_2 (left axis) and T_2^* (right axis) changes for gray matter ($N = 5$). The data at $t = 0$ are precontrast values. The error bar indicates the SEM.

Fig. 5.

Simulation of estimated CBV using VASO MRI. **a:** CBV as a function of Gd-DTPA concentration. Since the Gd-DTPA concentration decays as a function of time, one can also plot CBV as a function of postinjection time (shown in **b**). **c:** The percentage contribution of the water-exchange effect to the estimated CBV as a function of time. **d:** The derivative of estimated CBV with respect to time, indicating how much the VASO signal would vary within the acquisition time. Simulations were performed at three different water exchange rates, shown by PS in ml/100 ml/min. The simulation was performed by assuming $CBV^{true} = 5$ ml/100 ml and was based on the concentration of the Gd-DTPA measured by the DSC experiment.

Fig. 6.

The effect of Gd-DTPA leakage on the VASO MRI signals. **a:** An ROI (red voxels) containing the scalp tissue was manually drawn on the precontrast VASO image. The ROI does not cover all the scalp tissue, but effort was made to ensure that all the voxels selected were located inside the scalp. **b** and **c:** Experimental results of the “BV” signals from SE (b) and GE (c) at different time points after the Gd-DTPA injection. Note that the curvature is different from that in the brain with intact BBB (see Fig. 3). Simulation results (right axis) using different permeability values, K^{trans} in min^{-1} , are also shown. The true BV in the simulation was assumed to be 5 ml/100 ml.

Fig. 7.

Results of a long-duration DSC scan. **a:** T_2^* -weighted MR signal as a function of time. Only the first 5 min are shown. Time 0 indicates the time of contrast agent injection. The signal is an average of whole-brain voxels. **b:** Estimated blood concentration of Gd-DTPA as a function of time. The MR signal was first converted to R_2^* change using Eq. [2], which was then converted to blood concentration using Eq. [3]. In the plots, the symbols indicate the experimental data, the dashed line is baseline obtained by averaging the signals before contrast agent injection, and the solid curves were obtained by performing biexponential fitting to the time points after 1.5 min, when the contrast agent concentration had reached a steady state.

Table 1
Parameter Values Used in the Numerical Simulations

Common Parameters Used in All Simulations (Reference)	Value
$T_{1,b}$ (24)	1624 ms
$T_{1,r}$ (brain) (32)	1166 ms
C_{par} (25)	0.83
C_b (25)	0.87
CBV (15)	5%
Hematocrit (25)	40%
J_b, J_t (40)	$5 \text{ s}^{-1} \text{mM}^{-1}$
PS (34)	80–130
$[\text{Gd-DTPA}]_b$ at $t = 0$	1.2 mM
Additional Parameters Used in Vascular Leakage Simulations (Reference)	Value
V_{ee}	40%
V_{ei}	55%
K^{trans} (9,38)	0.005–0.025 min^{-1}