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Quantitative Measurement of Cerebral Blood Volume using Velocity-Selective Pulse Trains

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Abstract

Purpose—To develop a non-contrast-enhanced MRI method for cerebral blood volume (CBV) mapping employing velocity-selective (VS) pulse trains.

Methods—The new pulse sequence applied velocity-sensitive gradient waveforms in the VS label modules and velocity-compensated ones in the control scans. Sensitivities to the gradient imperfections (e.g. eddy currents) were evaluated through phantom studies. CBV quantification procedures based on simulated labeling efficiencies for arteriolar, capillary and venular blood as a function of cutoff velocity (V_c) are presented. Experiments were conducted on healthy volunteers at 3T to examine the effects of unbalanced diffusion weighting, CSF contamination and variation of V_c .

Results—Phantom results of the employed VS pulse trains demonstrated robustness to eddy currents. The mean CBV values of gray matter and white matter for the experiments using $V_c = 3.5$ mm/s and velocity-compensated control with CSF-nulling were 5.1 ± 0.6 mL/100g and 2.4 ± 0.2 mL/100g, respectively, which were 23% and 32% lower than results from the experiment with velocity-insensitive control, corresponding to 29% and 25% lower in averaged temporal SNR values.

Conclusion—A novel technique utilizing VS pulse trains was demonstrated for CBV mapping. The results were both qualitatively and quantitatively close to those from existing methods.

Keywords

cerebral blood volume; arterial spin labeling; velocity-selective pulse train; eddy current

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INTRODUCTION

Quantitative measurement of cerebral blood volume (CBV) complements cerebral blood flow (CBF) and allows a thorough examination of cerebral circulation for both normal neurophysiology and various brain disorders. Baseline CBV is indispensable for understanding BOLD signal mechanisms when using biophysical models (1-3) and CBV changes during activation contribute to fMRI contrast (4-6). In patients with obstructed carotid arteries, increased CBV and oxygenation extraction fraction (OEF), yet at normal CBF (autoregulatory vasodilation), has been found to predict a higher risk of stroke (7). In patients with cerebral gliomas, the presence of angiogenesis marked by an elevated CBV has been correlated with higher tumor grade and poorer prognosis (8-10).

Regional CBV values have been estimated using dynamic susceptibility contrast (DSC)-MRI with injected Gadolinium (Gd)-based contrast agents (11,12). In clinical applications, DSC-MRI often reports qualitative perfusion measures, such as relative CBV compared to a normal white matter area. For absolute quantification of CBV, this technique faces several challenges, for example, identification of a global arterial input function (AIF) from a pure blood voxel, consideration of the delay and dispersion of the local AIF, non-linear response of intravascular Gd concentration, and reduction of arterial partial-volume effects (13-17). A newer Gd-based approach applies an inversion recovery pulse sequence with the blood signal nulled before the bolus administration and fully recovered after the contrast passage due to the shortening of blood T_1 (18,19), hence to generate the absolute CBV maps by normalizing pre/post-contrast difference images. However, risks of developing nephrogenic systemic fibrosis (NSF) limit using Gd-enhanced MRI techniques on patients with impaired renal function (20) and findings of gadolinium deposition in neural tissues even for individuals without kidney disease warrant caution for repetitive use of certain Gd-based contrast agents (21). The use of iron oxide nanoparticles has been suggested instead, allowing calculation of relative CBV maps through subtraction of pre/post contrast (22,23).

To minimize safety risks and cost, it is desirable to have noninvasive MRI methods for CBV measurements without requiring any exogenous contrast agent. Arterial spin labeling (ASL) methods acquire perfusion-weighted signal by subtracting arterial-blood-labeled images from control scans (24-27). ASL-based CBF measurement is becoming more standardized for clinical application (28). Spatially-selective ASL techniques with multiple labeling delays have been developed to estimate the arterial cerebral blood volume (29,30). Other approaches are to combine ASL with magnetization transfer effects (31,32) or to use the inflow-based Vascular-space-occupancy (VASO) MRI (33,34). A sophisticated T_2^* -based relaxation model has also been proposed for measuring venous cerebral blood volume (35). The intravoxel incoherent motion (IVIM) technique applies motion-sensitized gradients with multiple b values and extracts information of both the fraction of total blood compartment and diffusion constants of tissue and microvasculature by fitting a bi-exponential model (36-38).

An alternative approach applies paired velocity-sensitive and velocity-compensated gradient waveforms with matched diffusion weighting to isolate the signal of microvasculature by subtracting out the static tissue signal (39). This technique assumes coherent flow of moving

spins (no change of flow velocity and direction) during the motion-sensitized gradient waveforms and accounts for the dispersion of a velocity-modulated phase shift through cross-sections of blood vessels. Indeed, this is also the basis of the velocity-selective (VS) pulse trains proposed more recently for mapping CBF (40-44) and OEF (45,46). In this work we aim to develop a non-contrast-enhanced imaging protocol with VS magnetization preparation modules to quantify absolute CBV on human. Different configurations of VS pulse trains for the control/label modules are compared and potential systematic errors caused by eddy currents from gradients, CSF contamination and unbalanced diffusion weighting on static tissue are evaluated.

METHODS

Velocity-Selective (VS) pulse trains

A basic VS labeling module (47) of length T_{VS} consists of $\pm 90^\circ$ hard pulses enclosing a pair of adiabatic refocusing pulses with surrounding velocity-encoding gradients (Figure 1a). When assuming laminar flow, the VS module saturates the signal of blood flowing above the cutoff velocity (V_c) (47,48). In contrast, spins moving below the V_c , including the static tissue, only experience T_2 weighting and diffusion weighting during T_{VS} . The use of two refocusing pulses with alternating gradients was recommended in diffusion MRI for reducing eddy currents (49-51). For this work, double refocused hyperbolic tangent (DRHT) pulses (5.0 ms, tanh/tan, maximum amplitude of 575 Hz and a frequency sweep of 8 kHz) were employed and compared with double refocused composite (DRCP) pulses ($90^\circ_x 180^\circ_y 90^\circ_x$, 1.7 ms) on phantoms. The efficacy of the refocusing pulses was demonstrated through numerical simulations (Supporting figure S1). Four alternating triangular gradient lobes with a ramp time of 1.6 ms and maximum amplitude of $G_{VS} = 26$ mT/m yielded a $V_c = 3.5$ mm/s, which is within the range of the velocities of large capillary vessels (1 ~ 9 mm/s) (52,53). A gap of at least 4.0 ms between each gradient pulse and following RF pulse was kept to minimize the effect of eddy currents. For this VS module, $T_{VS} = 40$ ms. Note that the velocity-selective gradients were applied along one direction only and that the choice of the gradient direction was investigated in the phantom experiments. The effect of the single gradient orientation on various blood flowing directions is described in the Data Analysis section. For the corresponding control module, two negative gradient lobes were replaced with positive ones (red dashed lines in Figure 1a) to construct a velocity-compensated gradient waveform. A conventional velocity-insensitive control module with gradient lobes turned off (black lines in Figure 1a) was also tested for comparison.

Pulse Sequences

Inserting velocity-selective pulse trains right before acquisition while utilizing phase variations from laminar flow models has been demonstrated to depict blood vessels with high resolution in flow-sensitive dephasing (FSD) MR angiogram (MRA) studies (54,55). The pulse sequence diagram for measuring baseline CBV is shown in Figure 1b. A tailored hard-pulse train (65° , 83° , 143° , 162°) (56) was applied post-acquisition for global saturation. When CSF suppression is desired, a SNR-improved inversion recovery method can be implemented. This CSF-suppression module (the dashed box in Figure 1b) utilizes a

T_2 prep module (refocusing achieved with DRHT, $TE_{\text{prep}} = 300$ ms, $\tau_{\text{CPMG}} = 150$ ms) right before the inversion pulse (a 10 ms hyperbolic secant adiabatic pulse) to saturate tissues with relatively short T_2 values (e.g. blood and tissue) and thus rendering higher longitudinal magnetizations (Mz) for these spins during recovery (57). The T_2 prep module was applied 4.90 s after the global saturation and the recovery delay (duration between the global inversion pulse and the VS module) was set to $T_{\text{recover}} = 2.0$ s for this modified CSF-nulling sequence. In contrast, a sequence without CSF nulling modules had a recovery delay (duration between the global saturation pulse and the VS module) of $T_{\text{recover}} = 3.6$ s. Immediately following the VS pulse trains, a fat-suppression module (spectral presaturation with inversion recovery, SPIR) was inserted before data acquisition.

Experiments

Experiments were performed on a 3T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) using the body coil for RF transmission (maximum amplitude 13.5 μ T) and a 32-channel head-only coil for signal reception. The maximum strength and slew rate of our standard gradient coil are 40 mT/m and 200 mT/m/ms, respectively.

Phantom Experiments

Similar to previous VS-ASL studies (43,44), a spherical silicone oil phantom ($T_1 / T_2 = 1111 / 227$ ms) was scanned to evaluate the effects of eddy currents and other consequences of gradient imperfections. The sequence without CSF nulling modules was applied with 2D acquisition for 10 axial slices and the parameters were identical to the human studies detailed below. The gradients of the VS pulse trains were applied separately along the left-right (L-R), anterior-posterior (A-P), or superior-inferior (S-I) direction, and the phase encoding direction was A-P. VS pulse trains using either DRHT or DRCP were examined, at both $V_c = 3.5$ mm/s (described above) and 2.0 mm/s (3.2 ms duration of each trapezoidal gradient lobe, 0.7 ms ramp time and maximum amplitude of $G_{VS} = 30$ mT/m). Using a $TR = 4.0$ s, the total measurement time after 24 repetitions was about 3.4 min for each pulse train configuration. A proton density-weighted image of signal intensity (SI_{PD}) was also acquired with $TR = 10$ s. The averaged signal difference for the label/control pairs across repetitions was normalized to the SI_{PD} image. For each pulse train configuration, the mean and standard deviation (SD) of the normalized subtraction errors from all the pixels within the phantom (excluding the noisy background) were calculated. Note that the mean ratio could be very small since normalized subtraction errors of included pixels could be positive or negative and the SD values indicate the spatial variation. An ideal pulse train configuration needs both the mean and SD to be minimum.

In Vivo Experiments

Six healthy volunteers (range: 30-41 yrs, three males and three females) were enrolled after providing informed consent in accordance with the Institutional Review Board guidelines. In this study, 2D multi-slice single-shot echo-planar imaging (EPI) was performed in axial planes. Acquisition parameters: the transverse field of view (FOV) was 186×213 mm² with 10 slices acquired at a slice thickness of 4.4 mm without gaps from the level of the body of lateral ventricles to the vertex; the acquisition resolution was 3.3×3.5 mm² and the reconstructed voxel size was 1.9×1.9 mm²; phase encoding was along the A-P direction

with the EPI factor (the number of k -space lines collected per echo train) of 25 and sensitivity encoding (SENSE) factor of 2.5; the echo train duration per slice was 14.0 ms and the effective echo time (TE) was 8.7 ms. For sequences with the CSF-nulling modules, the repetition time (TR) was 7.7 s, and the total measurement time after 24 averages of interleaved label and control was about 6.4 min. For sequences without CSF-nulling, TR was 4.0 s as in the phantom experiments.

On each volunteer, four scans with $V_c = 3.5$ mm/s (velocity encoding along the L-R direction) were included: Exp.1, velocity-compensated control with CSF-nulling; Exp.2, velocity-insensitive control with CSF-nulling; Exp.3, velocity-compensated control without CSF-nulling; Exp.4, repeated Exp.3 where no CSF suppression module was present and added an extra T_2 prep module (DRHT, $TE_{prep} = 300$ ms) right before VS pulse train to suppress blood signal and visualize signal from CSF. On a subset of five subjects, Exp.1 was repeated with $V_c = 30.0$ mm/s ($G_{VS} = 3$ mT/m), 5.0 mm/s ($G_{VS} = 18$ mT/m) and 2.0 mm/s (described in the phantom experiments) as Exps.5-7, respectively. These different scans were randomly ordered and all participants were instructed to keep still with their head stabilized with foam pads.

In addition, a proton density-weighted image (SI_{PD}) (TR = 10 s) was acquired for CBV quantification purposes (0.3 min); a double inversion recovery (DIR) image was obtained to visualize gray matter only (TR = 10 s; first TI = 3.58 s; second TI = 0.48 s; 0.3 min); another scan with an extra T_2 prep module (DRHT, $TE_{prep} = 300$ ms) before acquisition was carried out to suppress tissue signal and visualize signal from CSF (TR = 5.5 s, 0.2 min). All of these images were collected with the same resolution and acquisition scheme.

Data Analysis

Experimental data were processed using Matlab (MathWorks, Inc., Natick, MA, USA). For tissue or blood, the contrast weightings by T_1 , T_2 and ADC are given by:

$$M(T_1) = 1 - \exp(-T_{recover}/T_1) \quad [1]$$

$$M(T_2) = \exp(-T_{vs}/T_2) \quad [2]$$

$$M(ADC) = \exp(-b \cdot ADC) \quad [3]$$

For the control sequence where both the tissue (t) and blood (b) signal are preserved, the signal intensity of a voxel can be described as the sum of multiple compartments with weightings of their particular T_1/T_2 and apparent diffusion constants (ADC):

$$SI_{control} = SI_{PD} \cdot (1 - x_b) \cdot M(T_{1,t}) \cdot M(T_{2,t}) \cdot M(ADC_t) \\ + SI_{PD} \cdot x_b \cdot \sum (x_i \cdot M(T_{1,i}) \cdot M(T_{2,i}) \cdot M(ADC_i)) \quad [4]$$

in which x_b is the water fraction of the blood in the voxel and $CBV = 100 \cdot \lambda \cdot x_b$. The CBV unit is mL blood/100g tissue and λ is the brain-blood partition coefficient, 0.9 mL blood/g tissue (58). x_i is the fraction of CBV in each microvessel compartment: arteriolar (a), capillary (cp) and venular (v).

Ideally, VS pulse trains in the labeling module suppress all the blood signal and only tissue signal is retained. However, with different flowing velocities in individual segments of the microvasculature and also limited gradient performance on the clinical scanners, the percentage of blood being suppressed in each microvascular compartment, or the labeling efficiency α_i varies with the VS pulse trains applying at different Vc. So for each labeled counterpart, realistically, the signal intensity still has contributions from unsuppressed blood:

$$SI_{label} = SI_{PD} \cdot (1 - x_b) \cdot M(T_{1,t}) \cdot M(T_{2,t}) \cdot M(ADC_t) \\ + SI_{PD} \cdot x_b \cdot \sum (x_i \cdot (1 - \alpha_i) \cdot M(T_{1,i}) \cdot M(T_{2,i}) \cdot M(ADC_i)) \quad [5]$$

And the subtraction of the control and label signal intensities is:

$$SI_{control} - SI_{label} = SI_{PD} \cdot x_b \cdot \sum (x_i \cdot \alpha_i \cdot M(T_{1,i}) \cdot M(T_{2,i}) \cdot M(ADC_i)) \quad [6]$$

Note that diffusion weighting by the motion-sensitized gradient can be omitted for the blood signal due to the rather small b-value used ($< 7 \text{ s/mm}^2$). Thus the CBV can be calculated as this difference normalized by the SI_{PD} image and a scaling factor related only to T_1 and T_2 of each blood compartment:

$$CBV = \frac{100 \cdot \lambda \cdot (SI_{control} - SI_{label})}{SI_{PD} \cdot \sum (x_i \cdot \alpha_i \cdot M(T_{1,i}) \cdot M(T_{2,i}))} \quad [7]$$

In order to have a plausible account of x_i and α_i for each compartment, we employed a previous microcirculation model derived using available morphological and physiological information (59,60), which consisted of 11 microvessel compartments with their respective volume fractions and velocities. For arteriolar, capillary and venular blood, $x_a = 0.21$, $x_{cp} = 0.33$, $x_v = 0.46$, as used before (1). Furthermore, the calculation of the Vc-specific labeling efficiency for each compartment was based on the projections of the 3-dimensional isotropic orientations of microvessels onto a single axis using a spherical coordinate. When the projected velocity was larger than Vc, it was considered being suppressed and the labeling efficiency α for the given velocity and Vc was computed as the ratio of the number of suppressed ones (label) to the total number of vessels (control). The compartmental volume fractions, velocities and labeling efficiencies for Vc = [0.5, 2.0, 3.5, 5.0] mm/s are listed in Table 1. The distributions of blood signal for the control and labeled conditions, out of the

total blood volume, are illustrated in both the 11-compartment model (Figure 2a) and 3-compartment (a , cp , v) model (Figure 2b). Based on this simulation, $V_c = 3.5$ mm/s did not label any capillary blood ($\alpha_{cp} = 0$) and partially labeled arterioles ($\alpha_a = 0.55$) and venules ($\alpha_v = 0.31$), respectively.

$T_{1,a}$ and $T_{1,v}$ at 3T were taken as 1.84 s and 1.70 s (61,62). Using the previously measured relationship between T_2 , oxygenation fraction (Y) and hematocrit (Hct) in blood samples (63), $T_{2,a}$ and $T_{2,v}$ were set to be 138 ms and 53 ms for the employed inter-echo spacing of the VS pulse train ($\tau_{CPMG} = 20$ ms) and $Y_a = 0.98$, $Y_v = 0.6$, $Hct = 0.42$ were assumed for a typical healthy adult.

Voxel-wise mean CBV maps from the CBV time courses measured repeatedly (24 times) and temporal SNR maps (ratio of the mean value to the SD of the CBV time courses) were produced for all the scans. For each subject, a binary gray matter mask (GM) was obtained from the DIR image using an empirical threshold and a ROI within the white matter (WM) was drawn manually using the SI_{PD} image. In addition, voxels with large vessels were identified, through thresholding the CBV map (> 12.5 mL/100g, as used in (17) as 2.5 times of the mean CBV) acquired in Exp.2 with the velocity-insensitive control and CSF-nulling. These were excluded for the calculation of the averaged CBV within GM under different methods. Averaged CBV and SNR values from GM and WM ROIs were calculated for each experiment.

RESULTS

Phantom Experiments

Figure 3 displays the effects of gradient imperfections for three orthogonal directions at $V_c = 3.5$ mm/s across 10 slices of the phantom. For the VS pulse trains using DRHT (Figure 3a), the normalized subtraction errors (mean $\pm$ SD) for velocity-encoding along L-R, A-P and S-I directions were $0.08 \pm 0.15\%$, $-0.17 \pm 0.18\%$, and $-1.37 \pm 0.46\%$, respectively, which showed lower sensitivity to eddy currents (slightly higher mean errors but much lower SD) than the corresponding ones with DRCP (Figure 3b), despite shorter gaps between gradient lobes and refocusing pulses (4.0 ms vs. 5.7 ms). The stripe patterns in the images acquired with gradients along L-R direction (Figure 3) is related to specific characteristics of the gradient imperfections in this direction (most likely eddy currents), as previously observed in VSASL work (42,44). It might also be partially caused by incomplete refocusing due to B1 inhomogeneities, as suggested in two MRA papers using VS pulse trains (54,64). The VS pulse trains with $V_c = 2.0$ mm/s also generated markedly higher gradient-related artifacts (data not shown) than their counterparts with $V_c = 3.5$ mm/s. For CBV measurements in vivo, the VS pulse train with DRHT, velocity encoding along the L-R direction and $V_c = 3.5$ mm/s was chosen for its overall resistance to eddy currents and other gradient imperfections.

In Vivo Experiments

Representative data from all ten slices for one female subject (#2) are shown in Figure 4: the images of SI_{PD} , the GM-only images from the DIR sequence, the CSF-only images using

the 300 ms T₂prep module, and quantified CBV maps estimated from Exps.1-6 using different sequences. Qualitatively, results of Exps.1-3 all showed CBV contrast similar to typical gradient echo-EPI based DSC-MRI images, where large vessels appeared in red with hyperintensity and regional CBV values exhibited relatively uniform distribution in cortical areas as well as deep brain regions. When comparing Exp.1 using velocity-compensated control and Exp.2 using velocity-insensitive control, large vessels were much less conspicuous and overall regional CBV values were noticeably lower in Exp.1 than in Exp.2. For Exp.3 with CSF not suppressed, artifactually high signal was visible in the lateral ventricles (the first two slices) and verified as originating from CSF with the extra 300 ms T₂prep in Exp.4. In addition, the close resemblance between CSF-only images and the results from Exp.4 indicated that the pulsatile flow of CSF in subarachnoid space also generated false contrast in CBV maps at the extracerebral convexities. Compared to Exp.1 using the same scaling factors for visual examination, Exp.5 displayed substantially reduced signal for V_c = 30.0 mm/s. For V_c = 5.0 mm/s (Exp.6), signal was slightly reduced and a similar CBV map was obtained with its corresponding labeling efficiency ($\alpha_a = 0.44$ for arterioles and $\alpha_v = 0.22$ for venules, Table 1). Results using V_c = 2.0 mm/s (Exp.7) illustrated not only higher signals in some regions but also artifacts supposedly related to eddy-currents (data not shown).

The CBV maps and SNR images from Exps.1-3 of the 5th slice (at the level of centrum semiovale) of all 6 subjects are arrayed in Figure 5. Characteristics of contrast were consistent for all participants in both CBV maps (Figure 5a) and SNR images (Figure 5b). In one subject (#4), signal fluctuations were found to be larger than for the others, leading to reduced SNR (Figure 5b), which might be due to higher physiological noise from cardiac pulsation or respiration.

Averaged CBV and SNR values within GM masks and WM ROIs and their GM/WM ratios are reported in Table 2 for Exps.1, 2, 3 and 6. For V_c = 3.5 mm/s with CSF-nulling, the averaged local CBV values from Exp.1 with velocity-compensated control were 5.1 ± 0.6 and 2.4 ± 0.2 mL/100g for GM and WM, respectively, which were 23% and 32% lower than those from Exp.2 with velocity-insensitive control. The averaged temporal SNR values for GM and WM from Exp.1 were 29% and 25% lower than the corresponding ones from Exp. 2, and 14% lower compared to Exp.3 without CSF-nulling, about. The averaged temporal SNR values from Exp.6 (V_c = 5.0 mm/s) were 25% and 33% lower than those from Exp.1 (V_c = 3.5 mm/s) for GM and WM, respectively, indicating reduced signal available for higher V_c.

DISCUSSION

Absolute CBV maps were obtained from pulse sequences with interleaved control and label modules for separating vascular signal. A proton density weighted image (SI_{PD}) was used for normalization, similar to ASL for CBF mapping. Several technical issues of this subtraction-based method for CBV quantification remain to be considered.

The obtained CBV contrast is qualitatively similar to typical DSC-MRI results. After being corrected using the simulated labeling efficiencies for the different microvascular

compartments, the mean CBV values in GM and WM using velocity-compensated controls (5.1 mL/100g and 2.4 mL/100g) are comparable to those reported in literature with different imaging modalities (16,17,19,65,66). However, the labeling efficiencies of the applied VS pulse train ($V_c = 3.5$ mm/s) are still relatively low for the microvessel compartments, especially in and close to the capillaries (Table 1), where blood moves as slow as 1.0 mm/s (52,53). Capillary blood is known to occupy approximately 33% of total CBV (1,59,60,67,68) and most of it was not labeled here. With the current technique demonstrated for CBV estimation, the signal from arteriolar and venular compartments being detected is therefore only around 1% of the signal in the tissue (using the simulated labeling efficiency for $V_c = 3.5$ mm/s and ignoring T1/T2 relaxations): within CBV, $0.55 \times 21\% + 0.31 \times 46\% = 25.8\%$; within tissue, $25.8\% \times 5.0\% = 1.3\%$). This is similar to the ASL effect size for CBF mapping, thus providing similar spatial and temporal resolution, for both clinical and fMRI applications. Indeed, the mean temporal SNR values (1.2 in GM and 0.6 in WM) are close to the recently recorded values for velocity- and acceleration-selective ASL methods (44,69,70). Ideally, if a V_c slower than capillary blood can be used, labeling efficiency will be much higher and uniform across different microvessel compartments, as indicated in Table 1. This would also reduce the need for the assumed compartmental model. Utilizing a smaller V_c value on clinical scanners is limited by the gradient performance (maximal strength, slew rate and eddy current), which can potentially be improved by more advanced gradient system design.

In addition to the various velocities in each compartment, another assumption of the adopted microvasculature model for calculating the labeling efficiency is that of isotropic orientations for the large number of vessels. Since the numbers of different vessels in Table 1 of (60) are for the whole brain (about 700,000 mm³, assuming these vessels occupying 5% of the parenchyma), scaling down for the voxel size used in this study (50 mm³) leads to [2, 14, 107, 364, 2793, 54992, 2793, 364, 107, 14, 2] vessels in [a5, a4, a3, a2, a1, cp, v1, v2, v3, v4, v5] per voxel, respectively. Given that there are a large number of vessels in most compartments (except a5, a4, v4, and v5), isotropic orientation seems to be a reasonable assumption for the majority of microvessels.

Although the pair of velocity-selective labeling and velocity-compensated control modules appear with balanced gradient lobes (Figure 1a), its diffusion weighting was only matched partially as calculation using the original integration equation for arbitrary gradient waveforms (Eq. [9.7] of (71)) yielded b-values of 6.6 s/mm² and 2.9 s/mm², respectively. To exactly match the b-values between the two counterparts, the second and third gradient lobe in the VS labeling module would need to be switched to have no overlap between the paired gradients (Supporting figure S2). Although this could be an ideal configuration for the VS pulse trains, much higher subtraction errors caused by gradient imperfections were found in phantom studies for this configuration (data not shown) and thus it was not further investigated in this study. The difference between CBV values from the methods using velocity-compensated and velocity-insensitive controls (5.1 mL/100g vs. 6.6 mL/100g) could partly be explained by the unbalanced diffusion weighting of the latter. When using velocity-insensitive controls, the control/label subtraction would have an extra term from static tissue: $SI_{PD} \cdot (1 - CBV/\lambda/100) \cdot M(T_{1,\rho}) \cdot M(T_{2,\rho}) \cdot (1 - M(ADC_\rho))$. Assuming CBV = 5.1 mL/100g, $T_{1,t} = 1.20$ s, $T_{2,t} = 80$ ms (72), $ADC_t = 0.8 \times 10^{-3}$ mm²/s, applying Eq.[1-7]

and a b-value of 6.6 s/mm² ($V_c = 3.5$ mm/s) would yield an overestimated CBV of 7.2 mL/100g, which is slightly larger than the averaged result of 6.6 mL/100g. When the control is velocity-compensated as used in this study ($b = 2.9$ s/mm²), the bias of overestimation is reduced from 42% to 23%.

Another difference between the two control methods was the amount of signal from large vessels being detected. It was later realized that the velocity-compensated pulse train for the control was actually acceleration-sensitive with a cutoff acceleration (A_c) of 0.57 m/s². Acceleration-selective ASL with similar A_c values has recently been demonstrated for CBF measurement (70,73). Thus pulsatile flow in large vessels would also cause blood suppression in the velocity-compensated control and lead to signal reduction in the final CBV images, whereas the velocity-insensitive control remains insensitive to acceleration and maintains the large vessel signal.

The calculated CBV values (Eq.[7]) depend on the T_1 and T_2 values of each microvessel compartment, which are functions of Hct and Y (63,74) and can be estimated for each subject (61,62,75). Note that the Hct values in microvascular segments are known to be approximately 75%-88% of that for large vessels (Fahraeus effect) (65,76). If $Hct = 0.42 \times 0.80 = 0.34$ were used in the calculations, $T_{1,a}$, $T_{1,v}$ (1.84 s, 1.70 s) should be increased by about 5% (77) and $T_{2,a}$, $T_{2,v}$ (138 ms, 53 ms) by about 10% (63). Raising the selected $T_{1,a}$, $T_{1,v}$ and $T_{2,a}$, $T_{2,v}$ for [+5%, +10%] would change CBV with [2.7%, 5.5%] and [-2.3%, -4.4%], respectively, assuming the other one unchanged.

Pulsatile CSF flow was found to generate signal in the CBV maps not only within ventricles but also in subarachnoid space (Figure 4). This is not surprising since the velocity of CSF in these areas ranges from 2 mm/s to 43 mm/s (78). Given that the CSF volume fraction typically varies from 10 to 20% in different brain cortical regions (79), a CSF suppression module is necessary to remove the nuisance and have reliable CBV measurement.

CONCLUSION

A novel non-contrast-enhanced method for quantifying absolute CBV values using velocity-selective spin labeling approach was developed at 3T. The technical feasibility was demonstrated and the quantified CBV values of gray matter and white matter of healthy subjects were consistent with literature reports. Further optimization of this reported technique is needed to boost the CBV signal, especially from the vessels with very slow flow, e.g. capillary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The pulse sequence diagram of the proposed method for absolute CBV measurement using velocity-selective (VS) pulse trains for control and labeling. (a) Diagram of the VS pulse train with gradients of alternating polarities surrounding refocusing pulses for velocity-sensitized waveform (red solid lines) and uni-polar gradients for velocity-compensated waveform (red dashed lines for the polarity-switched gradient lobes). The gradients are applied along one direction only. (b) The pulse sequence consists of a global saturation pulse train, an optional T₂prep prepared inversion for CSF suppression, and the VS control/label module followed by acquisition.

Figure 2.

Fraction of blood signal (with respect to the total blood volume) for control and each label condition ($V_c = [0.5, 2.0, 3.5, 5.0]$ mm/s, respectively) for both the 11-compartment model (a) and 3-compartment (a , cp , v) model (b).

Figure 3.

Errors of signal difference after employing VS control/label modules on a phantom caused by gradient imperfections (such as eddy currents) along different gradient orientations. Results of using DRHT pulses and DRCP pulses in the VS pulse trains with $V_c = 3.5$ mm/s are shown in the left (a) and right (b) columns. Error maps are normalized to SI_{PD} (percentage displayed). All acquired 10 slices are shown with the averaged error percentage (mean $\pm$ SD) displayed at the top of each row.

Figure 4.

Representative images of all 10 slices acquired from subject #2: the SI_{PD} images, the gray matter-only images, the CSF-only images, and quantified CBV maps from various experiments: Exp.1 using label with $V_c = 3.5$ mm/s, velocity-compensated control and CSF-nulling; Exp.2 using the same label but velocity-insensitive control and CSF-nulling; Exp.3 using velocity-compensated control without CSF-nulling; Exp.4 using the sequence of Exp.3 and an additional 300 ms T_2 prep module inserted right before the VS module; Exp.5 using the sequence of Exp.1 with $V_c = 30.0$ mm/s; Exp.6 using the sequence of Exp.1 with $V_c = 5.0$ mm/s.

Figure 5.

Comparison of the estimated CBV maps (a) and SNR images (b) on 6 subjects (only the 5th slice shown) from Exp.1-3 and 5 subjects from Exp.6. Characteristics of contrast are consistent for all participants.

Table 1

The simulated labeling efficiencies of velocity-selective pulse trains with different cutoff velocities (V_c) along a single direction, for individual compartments with various flow velocities along isotropic orientations. These are calculated based on a morphological and physiological microcirculation model consisting of 11 microvessel compartments in arteriolar, capillary and venular blood.

	arteriolar (a)					capillary (cp)	venular (v)				
	a5	a4	a3	a2	a1	cp	v1	v2	v3	v4	v5
	0.04	0.04	0.04	0.04	0.05	0.33	0.10	0.09	0.09	0.09	0.09
fraction of CBV (x_i)	0.21					0.33	0.46				
velocity (mm/s)	48.0	24.0	12.5	8.3	4.3	0.7	1.9	3.7	5.6	10.7	21.3
V_c (mm/s)	labeling efficiency in each microvessel compartment (α_i)										
0.5	97%	94%	90%	87%	78%	20%	60%	76%	82%	89%	94%
	89%					20%	80%				
2.0	90%	83%	72%	62%	40%	0%	0%	33%	50%	69%	82%
	70%					0%	46%				
3.5	85%	74%	58%	44%	13%	0%	0%	3%	26%	53%	72%
	55%					0%	31%				
5.0	80%	66%	46%	28%	0%	0%	0%	0%	7%	40%	63%
	44%					0%	22%				

Table 2

Averaged CBV and temporal SNR values (mean $\pm$ SD, n = 6) in GM and WM ROIs and their GM/WM ratios of different experiments using Vc = 3.5 mm/s (Exp.1-3) and Vc = 5.0 mm/s (Exp.6).

	CBV (mL/100g)			SNR		
	GM	WM	ratio	GM	WM	ratio
Exp.1, Vc = 3.5 mm/s, velocity-compensated control, with CSF-nulling,	5.1 $\pm$ 0.6	2.4 $\pm$ 0.2	2.1	1.2 $\pm$ 0.3	0.6 $\pm$ 0.1	2.0
Exp.2, Vc = 3.5 mm/s, velocity-insensitive control, with CSF-nulling,	6.6 $\pm$ 0.4	3.5 $\pm$ 0.4	1.9	1.7 $\pm$ 0.3	0.8 $\pm$ 0.1	2.1
Exp.3, Vc = 3.5 mm/s, velocity-compensated control, without CSF-nulling,	5.2 $\pm$ 0.4	2.4 $\pm$ 0.2	2.2	1.4 $\pm$ 0.3	0.7 $\pm$ 0.1	2.0
Exp.6, Vc = 5.0 mm/s, velocity-compensated control, with CSF-nulling,	5.9 $\pm$ 0.7	2.2 $\pm$ 0.3	2.7	0.9 $\pm$ 0.2	0.4 $\pm$ 0.1	2.3