Published in final edited form as:

Magn Reson Med. 2019 June ; 81(6): 3544–3554. doi:10.1002/mrm.27668.

Cerebral Blood Volume Mapping using Fourier-Transform based Velocity-Selective Saturation Pulse Trains

Qin Qin^{1,2}, Yaoming Qu³, Wenbo Li^{1,2}, Dapeng Liu^{1,2}, Taehoon Shin^{4,5}, Yansong Zhao⁶, Doris D. Lin¹, Peter C.M. van Zijl^{1,2}, Zhibo Wen³

¹The Russell H. Morgan Department of Radiology and Radiological Science, Division of MR Research, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

²F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland, USA

³Department of Radiology, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong Province, China

⁴Division of Mechanical and Biomedical Engineering, Ewha Womans University, Seoul, South Korea

⁵Department of Medicine, Case Western Reserve University, Cleveland, OH, USA

⁶Philips Healthcare, Cleveland, Ohio, USA

Abstract

Purpose: Velocity-selective saturation (VSS) pulse trains provide a viable alternative to the spatially selective methods for measuring cerebral blood volume (CBV) by reducing the sensitivity to arterial transit time. This study is to compare the Fourier-transform based velocity-selective saturation (FT-VSS) pulse trains with the conventional flow-dephasing VSS techniques for CBV quantification.

Methods: The proposed FT-VSS label and control modules were compared with VSS pulse trains employing double refocused hyperbolic tangent (DRHT) and eight-segment B1 insensitive rotation (BIR-8). This was done using both numerical simulations and phantom studies to evaluate their sensitivities to gradient imperfections such as eddy currents. DRHT, BIR-8 and FT-VSS prepared CBV mapping was further compared for velocity-encoding gradients along three orthogonal directions in healthy subjects at 3T.

Results: The phantom studies exhibited more consistent immunity to gradient imperfections for the employed FT-VSS pulse trains. Compared to DRHT and BIR-8, FT-VSS delivered more robust CBV results across the three VS encoding directions with significantly reduced artifacts along S-I direction and improved temporal SNR values. The average CBV values obtained from FT-VSS

*Corresponding Author: Qin Qin (Ph.D.), Department of Radiology, Johns Hopkins University School of Medicine, F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, 707 N. Broadway, Baltimore, Maryland, 21205, qin@mri.jhu.edu, Tel: 443-923-9516.

Prepared for submission as a Full Paper in *Magnetic Resonance in Medicine*

based sequences were 5.3 mL/100g for gray matter and 2.3 mL/100g for white matter, comparable to literature expectations.

Conclusion: Absolute CBV quantification employing advanced FT-VSS pulse trains had several advantages over the existing approaches using flow-dephasing VSS modules. A greater immunity to gradient imperfections and the concurrent tissue background suppression of FT-VSS pulse trains enabled more robust CBV measurements and higher SNR than the conventional VSS pulse trains.

Keywords

cerebral blood volume; arterial spin labeling; velocity-selective pulse train; Fourier-transform based velocity-selective saturation; eddy current

INTRODUCTION

The ability to estimate cerebral blood flow (CBF) and cerebral blood volume (CBV) quantitatively without relying on exogenous contrast agents provides a non-invasive and often preferred alternative to dynamic susceptibility contrast perfusion weighted imaging (DSC-PWI) (1,2), particularly when there is a contraindication to the use of Gadolinium based contrast agents, such as hypersensitivity reaction, risk of nephrogenic systemic fibrosis (3), and nowadays the growing concerns (even though with unknown health effects) of Gadolinium deposition in tissues after repeated contrast administration (4).

Arterial spin labeling (ASL) methods typically apply spatially selective labeling modules on the supplying arteries proximal to the imaging volumes for assessment of cerebral blood flow (CBF) (5,6) or arterial CBV (CBV_a) (7–9). However, spatially selective ASL is limited by the transit time of the labeled spins to various vascular compartments in the imaging volume. CBF and CBV measurements are affected by prolonged transit times caused by conditions such as arterial steno-occlusive cerebrovascular diseases.

To reduce the sensitivity to transit time, velocity-selective (VS) labeling modules, which dephase the magnetization of blood spins flowing above a cutoff velocity (V_c), have been employed for measuring absolute CBF (10–13) and recently CBV (14). Conventional VS saturation (VSS) pulse trains embed flow-sensitive gradients within a bracket of 90°_x - 90°_{-x} hard pulses and either double refocused hyperbolic secant (DRHS) (11–13) or hyperbolic tangent (DRHT) pulses (14). Newer pulse design utilizing eight-segment B1 insensitive rotation (BIR-8) have been proposed to alleviate artifactual CBF signal contributions due to gradient eddy currents (15,16). The magnetizations of static tissue and the spins moving below the V_c are preserved. The VS control modules negate the flow-sensitivity to all spins regardless of their velocities.

As an alternative, Fourier-transform (FT) based VS pulse trains have been developed by concatenating a series of small-flip-angle RF pulses interleaved with velocity-encoding gradients for MR angiography (MRA) (17–21) and quantitative CBF mapping (22). In contrast to the flow-dephasing VSS pulse trains, FT-VSS labeling modules saturate static

tissue while preserving spins flowing above V_c , while the control modules apply saturation universally on all spins.

Hence, FT-VSS label/control modules have the concurrent capability for background suppression, which would be potentially beneficial for ASL based CBV quantification given that CBV signal comprises only a few percent of overall tissue signal and therefore is susceptible to tissue signal fluctuations due to system instabilities and physiological motion. Here we evaluate the suitability of FT-VSS pulse trains for CBV quantification at 3T, and compare the results with DRHT and BIR-8 based methods.

METHODS

Velocity-Selective (VS) Pulse Trains

A DRHT pulse train consists of $\pm 90^\circ$ hard pulses enclosing paired refocusing pulses with surrounding triangular gradient lobes ($G_{VS} = 26$ mT/m; ramp time: 1.6 ms; $T_{VS} = 40$ ms; $V_c = 0.70$ cm/s) (Figure 1a), as utilized in the earlier CBV study (14). Additionally, a BIR-8 pulse train had with similar gradient design, the same T_{VS} and identical V_c (Figure 1b).

Both DRHT and BIR-8 pulse trains produce velocity-dependent cosine modulation of the longitudinal magnetization, $M_z = M_0 \cos(\gamma m_1 v)$, where γ is the proton gyromagnetic ratio and m_1 is the applied first gradient moment (23). Assuming a laminar flow distribution with a parabolic velocity profile from 0 at the vessel wall to a maximal velocity (v_{max}) at the vessel center, the integration of the cosine modulations within the blood vessel generates a sinc function, $M_z = M_0 \text{sinc}(\gamma m_1 v_{max})$ (24,25). In order to be consistent with the description below for the FT-VSS pulse train, V_c here refers to a v_{max} , which is twice the mean velocity used in (14). Figure 1c displays the integrated M_z as a function of v_{max} and the first zero-passing velocity is given as $V_c = \pi/(\gamma m_1)$ (dashed vertical lines in Figure 1c).

The FT-VSS pulse trains used in this CBV study were adapted from the ones used for MRA (19) and CBF mapping (22). The FT-VSS pulse train is composed of nine excitation pulses (10° hard pulses), interleaved with pairs of refocusing pulses (180° hard pulses) and gradients, that constitute eight velocity-encoding steps (16 ms each step; total duration $T_{VS} = 128$ ms, Figure 1d). The velocity-sensitive labeling module with triangular gradient lobes ($G_{VS} = 22$ mT/m; ramp time: 0.6 ms) of alternating polarity yields a targeted saturation band within ± 0.70 cm/s (dashed vertical lines in Figure 1e). Note that the $V_c = 0.70$ cm/s is calculated using the same equation, $V_c = \pi/(\gamma m_1)$, as for the conventional VSS pulse trains. The phase-cycling scheme for the refocusing pulses is MLEV-16 (26), which greatly improves the immunity to B0/B1 inhomogeneity and gradient imperfections such as eddy currents (19,22).

Specific parameters of DRHT, BIR-8 and FT-VSS labeling modules are listed in Table 1. The corresponding control modules also use velocity-compensated gradient waveforms (red dashed lines in Figures 1a,b,d) for a more balanced diffusion-weighting effect (14).

Numerical Simulation

Numerical simulations using the Bloch equations based on matrix rotation were performed to compare the effect of eddy currents on the static spins at the end of the DRHT, BIR-8 and FT-VSS pulse trains using Matlab (MathWorks, Inc., Natick, MA, USA). Responses of the M_z following both the label and control pulse trains with different eddy current amplitude of 0.01% – 0.25% and time constants of 10^{-4} – 1 s were calculated for distances from –23 cm to 24 cm with intervals of 1 cm, as described in (22). B_0/B_1 inhomogeneity and T_2 effects were not accounted for in this simulation.

Pulse Sequence

As described in (14), the pulse sequence for measuring CBV includes a global saturation module, a CSF-suppression module with T_2 prep ($TE_{\text{prep}} = 300$ ms) followed by a global inversion, and a VS labeling/control module immediately before a fat-suppression module and an acquisition module (Figure 1f). For global saturation of the moving spins within CSF and timing for the following CSF suppression, a tailored hard-pulse train (65° , 83° , 143° , 162°) (27) was applied right after the previous data acquisition. The T_2 prepared spatially nonselective inversion 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), thus ensuring saturation recovery of the signal of blood and tissue while maintaining inversion recovery of the CSF signal, based on their T_2 values, respectively (28,29). The repetition time was set to 6.1 s with the T_2 prep module applied at 3.5 s after the global saturation and the recovery delay (duration between the inversion pulse and the VS module) of $T_{\text{recover}} = 1.7$ s for CSF nulling. This allowed the total acquisition of each CBV protocol to be within 5 min when 24 repetitions were used.

Experiments

All the MR experiments were performed on a 3T Philips Achieva scanner (Philips Healthcare, 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 used for our standard gradients were 40 mT/m and 200 mT/m/ms, respectively.

Phantom Experiments

The phantom experiments were performed using a spherical oil phantom to evaluate the effects of gradient imperfections such as eddy currents. The sequence described above was applied without CSF nulling modules ($TR = 4.0$ s). VS pulse trains employing DRHT, BIR-8 and FT-VSS modules were compared with the VS gradients applied along the left-right (L-R), anterior-posterior (A-P), or superior-inferior (S-I) directions, respectively. Using a 2D single-shot echo-planar imaging (EPI) acquisition for 10 consecutive axial slices, 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 for normalization by keeping the same fat suppression and acquisition modules, removing the global saturation, the T_2 prepared inversion, and the VS modules, and extending the TR to 10 s.

In Vivo Experiments

In vivo studies were conducted under the approval of the local IRB. Six healthy volunteers (range: 26–54 yrs, three males and three females) provided informed consent. They were instructed to keep still with their head stabilized with foam pads. As in the phantom study, six 5-min-long CBV scans were acquired in random order using DRHT, BIR-8 and FT-VSS modules each with VS gradients along three orthogonal directions. The parameters for the axial EPI acquisition were identical with the ones applied in (14); Briefly: the transverse field of view (FOV) was $186 \times 213 \text{ mm}^2$; 10 continuous slices were acquired at 4.4 mm slice thickness; the acquisition resolution was $3.3 \times 3.5 \text{ mm}^2$ and the reconstructed voxel size was $1.9 \times 1.9 \text{ mm}^2$; EPI factor (the number of k -space lines collected per echo train) was 25 and sensitivity encoding (SENSE) factor was 2.5; the effective echo time (TE) was 8.7 ms. The reported specific absorption rate (SAR) percentages relative to the head averaged SAR limit of the scanner (3.2 W/kg) were comparable for DRHT, BIR-8 and FT-VSS scans (17%, 22% and 19%). With the same resolution and acquisition scheme, a SI_{PD} image for quantification as well as a double inversion recovery image (DIR, TR = 10s; TI_1 = 3.58 s; TI_2 = 0.48 s;) for visualizing gray matter were acquired as in previous studies (14,22), both at 0.3 min.

Data Analysis

Experimental data were processed using Matlab. For each pulse train configuration in the phantom study, the mean and standard deviation (SD) of the subtraction errors normalized to the SI_{PD} image from all the slices were calculated as before (14,22).

For in vivo studies, CBV values were computed using the model developed previously (14), with specific modifications of the equations for the FT-VSS based protocols. The main difference between the DRHT, BIR-8 and FT-VSS based quantification models lies in the T_2 weighting of tissue (t) and blood (b) signal during the corresponding label and control modules. For VSS modules (14) such as DRHT and BIR-8, it is a simple T_2 exponential decay, $M(T_2) = \exp(-T_{VS}/T_2)$, for static tissue and flowing blood in the control scans, or static tissue and blood moving below V_c in the label scans (Figures 2a,b); Signal for blood flowing above V_c is dephased by the VSS label modules and thus considered to be zero. For FT-VSS modules, the T_2 effects for label and control scans are slightly more complicated for both the passband and stopband in the label scans and nonzero for the control scans (19,22) (Figure 2c, described below).

Similar to the approach described in (14), the signal intensity of a voxel is described as the sum of multiple compartments with respective T_1 and T_2 weightings:

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

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

in which x_b is the water fraction of blood in the voxel and $M(T_1, t)$ is the fraction of CBV in each microvessel compartment: arteriolar (a), capillary (cp) and venular (v). Labeling efficiency α_i is the percentage of blood in each microvascular compartment flowing above the V_c , which would be in the passband of FT-VSS labeling modules. The remaining portion of the blood flowing below the V_c , $1 - \alpha_i$, experiences the same saturation effect as the control module. The relationship between CBV and x_b is:

$$CBV = 100 \cdot \lambda \cdot x_b \quad [3]$$

The unit for CBV is mL blood/100g tissue. λ is the brain-blood partition coefficient, 0.9 mL blood/g tissue (30). As described in (14), the fractions of CBV (x_i) and the labeling efficiencies (α_i) were calculated based on an 11-compartment microvessel model (31,32) with the projections of the 3-dimensional isotropic orientations of microvessels onto a single axis. Thus for the applied V_c , the estimated CBV include only arterioles ($x_a = 0.21$; $\alpha_a = 0.55$) and venules ($x_v = 0.46$; $\alpha_v = 0.31$), with negligible contribution from capillary blood ($x_{cp} = 0.33$; $\alpha_{cp} = 0$). The subtraction of the control and label signal intensities is:

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

Therefore, the CBV is calculated as this difference normalized by the SI_{PD} image and a scaling factor related only to the T_1 and T_2 effects of the applied VS pulse trains within each microvessel compartment:

$$CBV = \frac{100 \cdot \lambda \cdot (SI_{label} - SI_{control})}{SI_{PD} \cdot \sum (x_i \cdot \alpha_i \cdot M(T_{1,i}) \cdot (M(T_{2,i,label}) - M(T_{2,i,control})))} \quad [5]$$

The T_1 effect of the blood signal was set by the saturation recovery following the $T_{2,prep}$ -inversion module:

$$M(T_{1,i}) = 1 - \exp(-T_{recover}/T_{1,i}) \quad [6]$$

$T_{recover}$ was 1.7 s in this study. $T_{1,a}$ and $T_{1,v}$ at 3T were taken as 1.84 s (33) and 1.70 s (34), respectively.

The T_2 effects of blood signal under the label and control modules with duration of T_{VS} were characterized through Bloch equation simulations with 9 different T_2 values of [25, 50, 75, 100, 150, 200, 300, 400, 500] ms with the sampled T_{VS}/T_2 ratios as [0.26, 0.32, 0.43, 0.64, 0.85, 1.28, 1.71, 2.56, 5.12]. The averaged magnetizations in the maximal velocity range of [3.5, 7.5] cm/s were calculated as the responses for the label modules in the passband (Figure 2c, magenta stars); the magnetizations for zero velocity were taken as the results of the control modules (Figure 2c, green stars); the label and control data were subtracted for the differences (Figure 2c, black stars). These three datasets were each fitted

with different orders of polynomials and only these empirical 4-parameter models gave a reasonable fit for all three curves:

$$M(T_{2,i,label}) - M(T_{2,i,control}) = k_1 + k_2 \cdot k_3^{k_4 \cdot T_{VS}/T_{2,i}} \quad [7]$$

where $[k_1, k_2, k_3, k_4] = [0.12, 0.87, 0.72, 0.22]$ for label (Figure 2c, magenta line), $[0.51, -0.52, 0.24, 0.44]$ for control (Figure 2c, green line), and $[0.12, 0.86, 0.34, 0.38]$ for the label/control difference (Figure 2c, black line), respectively.

In order to estimate the exact T_2 effects of the applied VS pulse trains for arterial and venous blood compartments, $T_{2,a}$ and $T_{2,v}$ need to be set with different inter-echo spacing of the VS pulse trains to obtain T_{VS}/T_2 ratios within Eq. [7]. The dependence of $T_{2,a}/T_{2,v}$ on the CPMG inter-echo spacing is the result of both water exchange between plasma and red blood cells with their difference in magnetic susceptibility and diffusion through field gradients around these cells (35–37). Using the relationships between T_2 , oxygenation fraction (Y) and hematocrit fraction (Hct) established from ex vivo blood samples (36), $T_{2,a}$ and $T_{2,v}$ were set to be 154 ms and 68 ms for the employed 8 ms inter-echo spacing (interpolated from models with τ_{CPMG} of 5 ms and 10 ms) of the FT-VSS pulse train ($T_{VS} = 128$ ms). $Y_a = 0.98$, $Y_v = 0.6$, $Hct = 0.42$ were assumed for healthy adults (36,38). For DRHT and BIR-8, $T_{2,a}/T_{2,v}$ were set to be 138/53 ms and 146/60 ms for the employed 20 ms and 10 ms inter-echo spacings, respectively. The T_2 attenuations in the label/control differences for arterial and venous blood compartments were calculated to be 0.74 and 0.52 with FT-VSS pulse trains, which are comparable to 0.75 and 0.47 with DRHT and 0.76 and 0.51 with BIR-8 (Figure 2, red and blue squares).

Voxel-wise mean CBV maps from the repeated measures and temporal SNR maps were produced for all 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 of the CBV map (> 12.5 mL/100g) acquired in the FT-VSS pulse train with VS gradients applied along the S-I direction and were excluded for the calculation. Average CBV and SNR values from GM and WM ROIs were calculated for each experiment.

RESULTS

Numerical Simulations

The simulated effects of eddy currents (EC) for EC amplitude of 0.025% with various time constants static spins for the 40 ms DRHT, BIR-8 and 128 ms FT-VSS modules are shown in Figures 3a, b, c, respectively. The EC sensitivities of velocity-compensated control and velocity-sensitized label modules are shown as the subtraction of tissue's M_z affected by EC from M_z targeted by each pulse train (DRHT and BIR-8: 1; FT-VSS: 0) in the first two rows of Figure 3. The label/control differences are displayed in the third row. BIR-8 shows lower sensitivity to EC than DRHT as expected. For the simulated EC amplitude of 0.025%, FT-VSS shows an EC magnitude comparable to DRHT, but with an oscillating effect in the

spatial dimension (Figure 3c). When EC amplitude increases to higher values, FT-VSS yields lower sensitivity to EC than DRHT, but the overall magnitude of EC errors are far above the order of 1% observed in the phantom experiments (thus the data are not shown). The majority of these effects are caused by the velocity-compensated control (Figure 3). The range of time constants that the two pulse trains are sensitive to are 3–30 ms for DRHT, BIR-8 control, 10–30 ms for DRHT, BIR-8 label and 1–30 ms for FT-VSS label/controls, respectively. Note that for these pulse trains, EC effects are mainly off-center (> 10 cm).

Phantom Experiments

Figure 4 displays the effects of gradient imperfections along three orthogonal directions on DRHT, BIR-8 and FT-VSS label/control modules across 5 out of 10 slices of the phantom. The normalized subtraction errors (mean $\pm$ SD) along L-R, A-P and S-I directions are $0.12\pm0.22\%$, $-0.14\pm0.19\%$ and $-0.03\pm0.22\%$ for DRHT (Figure 4a), $-0.21\pm0.25\%$, $0.06\pm0.13\%$ and $0.02\pm0.10\%$ for BIR-8 (Figure 4b), vs. $0.06\pm0.12\%$, $0.07\pm0.11\%$ and $0.07\pm0.13\%$ for FT-VSS (Figure 4c), respectively. Compared to DRHT and BIR-8, FT-VSS generated least differences over three encoding directions. BIR-8 along A-P and S-I directions and FT-VSS results over all three encoding directions showed less spatial variation (SD), thus more resistance to gradient imperfections.

In Vivo Experiments

Representative data from 5 slices for one female subject (#3) are shown in Figure 5 with SI_{PD} , DIR, and CBV maps acquired using DRHT, BIR-8 and FT-VSS pulse trains. Figures 6 and 7 show the CBV maps and the corresponding temporal SNR images of the 5th slice obtained using DRHT, BIR-8, and FT-VSS in all 6 subjects. The DRHT and BIR-8 results showed noticeable and sometimes substantial artifacts in S-I directions (Figures 5,6). In contrast, FT-VSS produced CBV maps that were more consistent across all three directions with a higher temporal SNR in GM (Figures 6c, 7c).

Averaged CBV and SNR values within GM and WM ROIs and their GM/WM ratios are shown in Table 2 for DRHT, BIR-8 and FT-VSS with VS gradients along L-R, A-P and S-I directions, respectively. While the conventional VSS methods showed a large variation between L-R/A-P versus S-I velocity-encoding directions, FT-VSS yielded consistent mean CBV values: 5.5 ± 0.3 , 5.0 ± 0.2 and 5.3 ± 0.5 mL/100g for GM, and 2.8 ± 0.2 , 1.8 ± 0.1 and 2.3 ± 0.4 mL/100g for WM (Table 2). The mean temporal SNR values of GM CBV from FT-VSS based scans were 15–23% higher than the ones from DRHT based scans. The higher SNR values of WM from DRHT and BIR-8 methods are attributed to the artifacts related to gradient imperfections.

DISCUSSION

In this work, label and control modules with DRHT, BIR-8 and the proposed FT-VSS pulse trains were compared in simulations, phantom and *in vivo* experiments for CBV quantification. The FT-VSS based technique demonstrated significantly less susceptibility to gradient imperfections (Figure 4) as well as more robust CBV results with higher temporal SNR values across different VS encoding directions (Figures 5,6). The CBV values derived

from FT-VSS based sequences (averaged 5.3 mL/100g for GM and 2.3 mL/100g for WM) were comparable to those reported in the literature using other imaging modalities (39–43).

There are some obvious differences of the velocity-selective profiles between conventional VSS pulse trains such as DRHT and BIR8 (Figure 1c) and FT-VSS (Figure 1e). The most distinguished differences are the reversed saturation and pass bands. In addition, conventional VSS is based on the assumption of laminar flow, thus the velocity on the x-axis of Figure 1c is actually the maximal velocity, not the general velocity for FT-VSS as in Figure 1e. In order to reduce the T_2 effect, the relatively long durations of VSS and FT-VSS pulse trains can be shortened with a better RF coil (higher maximum B1 amplitude) and gradient system (higher maximum amplitude and slew rate, and less eddy currents). Furthermore, due to the limited velocity field of view, there are periodical aliasing sidebands for FT-VSS, potentially causing unintended saturation of some blood signal in large vessels. Reducing the gradient amplitudes or increasing the number of segments can move these sidebands further out, but at the cost of increasing V_c or T_{VS} , respectively. Nonetheless, signal loss in large vessels in this method is tolerable since the targeted CBV is that of microvessels.

For VS pulse trains, it is known that sensitivity to eddy currents can be reduced by lengthening the gaps between gradient lobes and the following refocusing pulses, which inevitably increases T_{VS} . A prolonged T_{VS} causes stronger T_2 based signal losses; thus, a compromise has to be made between gradient and T_2 effects. Compared to the 40 ms DRHT with 4 ms gaps, a 60 ms VSS, with the same gradient lobes as described in Table 1, except the lower G_{max} (17.4 mT/m), lengthened T_{gap} (9.0 ms) and (30 ms), reduced EC effects substantially (data not shown), but at the cost of signal loss of more than 13% for arterial blood and 31% for venous blood (Figure 2a). Conversely, the 128 ms FT-VSS with 2.2 ms T_{gap} (Table 1) yielded much better resistance to gradient imperfections (Figure 4) with matched T_2 effects for arterial and venous blood signal (Figure 2).

In simulations, the BIR-8 pulse train exhibited its advantage over DRHT in terms of reducing sensitivity to eddy currents (Figure 3). In phantom experiments, BIR-8 results were comparable to FT-VSS along A-P and S-I directions, but not L-R direction (Figure 4), indicating some mechanisms beyond eddy currents play a role. Furthermore, in vivo scans of both DRHT and BIR-8 revealed significant artifacts along the S-I direction in some cases (Figures 5,6), which are not fully explainable by the phantom results. Other gradient imperfections may include gradient-switching induced mechanical vibration, thermal variation and B0 field drifting (44).

We attribute the better performance of FT-VSS pulse trains over DRHT and BIR-8 to more effective background suppression related to their inherent velocity-selective profiles: static tissue signal in the saturation band and flowing spins in the passband, which are opposite from the M_z -velocity responses of flow-dephasing VSS pulse trains. Similar to CBF measurements using ASL, it is desirable for the subtraction-based CBV approach to minimize the effects of system fluctuations and physiological noise (45,46).

There are still artifacts in the FT-VSS prepared CBV results, for instance the observed higher signal in periventricular white matter in Figure 5c. This could be a result of gradient imperfections that affected the earlier slices obtained during the 2D multi-slice acquisition. Another possibility is the CSF pulsation effect from the ventricle. Further investigation is warranted for this question.

CONCLUSION

FT-VSS pulse trains enabled more robust CBV measurements between encoding directions and increased temporal SNR compared to the conventional method based on flow-dephasing VSS pulse trains, as demonstrated by phantom studies and *in vivo* imaging. The inherent velocity-selective profiles of FT-VSS provide greater immunity to gradient imperfections and simultaneously superior tissue background suppression. Its clinical value will be further investigated in patients with cerebrovascular diseases.

Acknowledgments

We are grateful to Mr. Joseph Gillen, Ms. Terri Brawner, Ms. Kathleen Kahl, and Ms. Ivana Kusevic for their experimental assistance. Dr. van Zijl is a paid lecturer for Philips Healthcare and has technology licensed to Philips. This has been approved by the Committee on Conflict of Interest of Johns Hopkins University.

Grant support from NIH R01 HL138182 (QQ), NIH K25 HL121192 (QQ), Scholar Award of American Society of Hematology (QQ), NIH P41 EB015909 (PVZ), NIH R01 HL135500 (TS), National Research Foundation of Korea 2018R1D1A1B07045267 (TS).

REFERENCES:

1. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. *Magn Reson Med* 1996;36(5):715–725. [PubMed: 8916022]
2. Ostergaard L, Sorensen AG, Kwong KK, Weisskoff RM, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. *Magn Reson Med* 1996;36(5):726–736. [PubMed: 8916023]
3. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* 2007;242(3):647–649. [PubMed: 17213364]
4. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. *Radiology* 2015;275(3):772–782. [PubMed: 25742194]
5. Wong EC, Buxton RB, Frank LR. Quantitative imaging of perfusion using a single subtraction (QUIPSS and QUIPSS II). *Magn Reson Med* 1998;39(5):702–708. [PubMed: 9581600]
6. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med* 2008;60(6):1488–1497. [PubMed: 19025913]
7. Hua J, Qin Q, Pekar JJ, van Zijl PC. Measurement of absolute arterial cerebral blood volume in human brain without using a contrast agent. *NMR in biomedicine* 2011;24(10):1313–1325. [PubMed: 21608057]
8. Yan L, Li C, Kilroy E, Wehrli FW, Wang DJ. Quantification of arterial cerebral blood volume using multiphase-balanced SSFP-based ASL. *Magn Reson Med* 2012;68(1):130–139. [PubMed: 22127983]
9. Hua J, Liu P, Kim T, Donahue M, Rane S, Chen JJ, Qin Q, Kim SG. MRI techniques to measure arterial and venous cerebral blood volume. *Neuroimage* 2018(in press).

10. Duhamel G, de Bazelaire C, Alsop DC. Evaluation of systematic quantification errors in velocity-selective arterial spin labeling of the brain. *Magn Reson Med* 2003;50(1):145–153. [PubMed: 12815689]
11. Wong EC, Cronin M, Wu WC, Inglis B, Frank LR, Liu TT. Velocity-selective arterial spin labeling. *Magn Reson Med* 2006;55(6):1334–1341. [PubMed: 16700025]
12. Qiu D, Straka M, Zun Z, Bammer R, Moseley ME, Zaharchuk G. CBF measurements using multidelayer pseudocontinuous and velocity-selective arterial spin labeling in patients with long arterial transit delays: Comparison with xenon CT CBF. *Journal of magnetic resonance imaging* : JMIR 2012;36(1):110–119. [PubMed: 22359345]
13. Zun Z, Hargreaves BA, Pauly J, Zaharchuk G. Near-contiguous spin echo imaging using matched-phase RF and its application in velocity-selective arterial spin labeling. *Magn Reson Med* 2014;71(6):2043–2050. [PubMed: 23857667]
14. Liu D, Xu F, Lin DD, van Zijl PC, Qin Q. Quantitative measurement of cerebral blood volume using velocity-selective pulse trains. *Magn Reson Med* 2017;77(1):92–101. [PubMed: 27797101]
15. Meakin JA, Jezzard P. An optimized velocity selective arterial spin labeling module with reduced eddy current sensitivity for improved perfusion quantification. *Magn Reson Med* 2013;69(3):832–838. [PubMed: 22556043]
16. Guo J, Meakin JA, Jezzard P, Wong EC. An optimized design to reduce eddy current sensitivity in velocity-selective arterial spin labeling using symmetric BIR-8 pulses. *Magn Reson Med* 2015;73(3):1085–1094. [PubMed: 24710761]
17. Shin T, Hu BS, Nishimura DG. Off-resonance-robust velocity-selective magnetization preparation for non-contrast-enhanced peripheral MR angiography. *Magn Reson Med* 2013;70(5):1229–1240. [PubMed: 23192893]
18. Shin T, Woters PW, Hu BS, Nishimura DG. Non-contrast-enhanced renal and abdominal MR angiography using velocity-selective inversion preparation. *Magn Reson Med* 2013;69(5):1268–1275. [PubMed: 22711643]
19. Qin Q, Shin T, Schar M, Guo H, Chen H, Qiao Y. Velocity-selective magnetization-prepared non-contrast-enhanced cerebral MR angiography at 3 Tesla: Improved immunity to B0/B1 inhomogeneity. *Magn Reson Med* 2016;75(3):1232–1241. [PubMed: 25940706]
20. Shin T, Qin Q, Park JY, Crawford RS, Rajagopalan S. Identification and reduction of image artifacts in non-contrast-enhanced velocity-selective peripheral angiography at 3T. *Magn Reson Med* 2016;76(2):466–477. [PubMed: 26308243]
21. Li W, Xu F, Schar M, Liu J, Shin T, Zhao Y, van Zijl PC, Wasserman BA, Qiao Y, Qin Q. Whole-brain arteriography and venography: Using improved velocity-selective saturation pulse trains. *Magn Reson Med* 2018;79(4):2014–2023. [PubMed: 28799210]
22. Qin Q, van Zijl PC. Velocity-selective-inversion prepared arterial spin labeling. *Magn Reson Med* 2016;76(4):1136–1148. [PubMed: 26507471]
23. Bernstein MA, King KF, Zhou XJ. *Handbook of MRI Pulse Sequences*: Elsevier Academic Press; 2004.
24. Duhamel G, de Bazelaire U, Alsop DC. Evaluation of systematic quantification errors in velocity-selective arterial spin labeling of the brain. *Magnetic Resonance in Medicine* 2003;50(1):145–153. [PubMed: 12815689]
25. Wong EC, Cronin M, Wu WC, Inglis B, Frank LR, Liu TT. Velocity-selective arterial spin labeling. *Magnetic Resonance in Medicine* 2006;55(6):1334–1341. [PubMed: 16700025]
26. Levitt MH, Freeman R, Frenkiel T. Broad-Band Heteronuclear Decoupling. *J Magn Reson* 1982;47(2):328–330.
27. Sung K, Nayak KS. Design and use of tailored hard-pulse trains for uniformed saturation of myocardium at 3 Tesla. *Magn Reson Med* 2008;60(4):997–1002. [PubMed: 18816833]
28. Wong EC, Liu TT, Luh WM, Frank LR, Buxton RB. T-1 and T-2 selective method for improved SNR in CSF-attenuated imaging: T-2-FLAIR. *Magnetic Resonance in Medicine* 2001;45(3):529–532. [PubMed: 11241715]
29. Qin Q. A simple approach for three-dimensional mapping of baseline cerebrospinal fluid volume fraction. *Magn Reson Med* 2011;65(2):385–391. [PubMed: 21264932]

30. Herscovitch P, Raichle ME. What is the correct value for the brain--blood partition coefficient for water? *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 1985;5(1):65–69.
31. Sharan M, Jones MD Jr., Koehler RC, Traystman RJ, Popel AS. A compartmental model for oxygen transport in brain microcirculation. *Annals of biomedical engineering* 1989;17(1):13–38. [PubMed: 2919811]
32. Piechnik SK, Chiarelli PA, Jezzard P. Modelling vascular reactivity to investigate the basis of the relationship between cerebral blood volume and flow under CO₂ manipulation. *Neuroimage* 2008;39(1):107–118. [PubMed: 17920935]
33. Li W, Liu P, Lu H, Strouse JJ, van Zijl PCM, Qin Q. Fast measurement of blood T₁ in the human carotid artery at 3T: Accuracy, precision, and reproducibility. *Magn Reson Med* 2017;77(6):2296–2302. [PubMed: 27436420]
34. Qin Q, Strouse JJ, van Zijl PC. Fast measurement of blood T₁ in the human jugular vein at 3 Tesla. *Magn Reson Med* 2011;65(5):1297–1304. [PubMed: 21500258]
35. Jensen JH, Chandra R. NMR relaxation in tissues with weak magnetic inhomogeneities. *Magn Reson Med* 2000;44(1):144–156. [PubMed: 10893533]
36. Lu H, Xu F, Grgac K, Liu P, Qin Q, van Zijl P. Calibration and validation of TRUST MRI for the estimation of cerebral blood oxygenation. *Magn Reson Med* 2012;67(1):42–49. [PubMed: 21590721]
37. Grgac K, Li W, Huang A, Qin Q, van Zijl PC. Transverse water relaxation in whole blood and erythrocytes at 3T, 7T, 9.4T, 11.7T and 16.4T; determination of intracellular hemoglobin and extracellular albumin relaxivities. *Magn Reson Imaging* 2017;38:234–249. [PubMed: 27993533]
38. Qin Q, Grgac K, van Zijl PC. Determination of whole-brain oxygen extraction fractions by fast measurement of blood T₂ in the jugular vein. *Magn Reson Med* 2011;65(2):471–479. [PubMed: 21264936]
39. Sakai F, Nakazawa K, Tazaki Y, Ishii K, Hino H, Igarashi H, Kanda T. Regional cerebral blood volume and hematocrit measured in normal human volunteers by single-photon emission computed tomography. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 1985;5(2):207–213.
40. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJR, Gibbs JM, Wise RJS, Hatazawa J, Herold S, Beaney RP, Brooks DJ, Spinks T, Rhodes C, Frackowiak RSJ, Jones T. Cerebral Blood-Flow, Blood-Volume and Oxygen Utilization-Normal Values and Effect of Age. *Brain* 1990;113:27–47. [PubMed: 2302536]
41. Uh J, Lewis-Amezcu K, Varghese R, Lu H. On the measurement of absolute cerebral blood volume (CBV) using vascular-space-occupancy (VASO) MRI. *Magn Reson Med* 2009;61(3):659–667. [PubMed: 19097238]
42. Bjornerud A, Emblem KE. A fully automated method for quantitative cerebral hemodynamic analysis using DSC-MRI. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2010;30(5):1066–1078.
43. Knutsson L, Lindgren E, Ahlgren A, van Osch MJ, Bloch KM, Surova Y, Stahlberg F, van Westen D, Wirestam R. Dynamic susceptibility contrast MRI with a prebolus contrast agent administration design for improved absolute quantification of perfusion. *Magn Reson Med* 2014;72(4):996–1006. [PubMed: 24285621]
44. Vannesjo SJ, Haeberlin M, Kasper L, Pavan M, Wilm BJ, Barmet C, Pruessmann KP. Gradient system characterization by impulse response measurements with a dynamic field camera. *Magn Reson Med* 2013;69(2):583–593. [PubMed: 22499483]
45. Ye FQ, Frank JA, Weinberger DR, McLaughlin AC. Noise reduction in 3D perfusion imaging by attenuating the static signal in arterial spin tagging (ASSIST). *Magn Reson Med* 2000;44(1):92–100. [PubMed: 10893526]
46. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, Lu H, Macintosh BJ, Parkes LM, Smits M, van Osch MJ, Wang DJ, Wong EC, Zaharchuk G. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med* 2015;73:102–116. [PubMed: 24715426]

Figure 1:

Diagrams of (a) DRHT, (b) BIR-8, (d) FT-VSS pulse trains with a velocity-sensitized waveform (red solid lines) and a velocity-compensated waveform (red dashed lines for the polarity-switched gradient lobes). Simulated M_z -velocity responses of (c) DRHT, BIR-8 and (e) FT-VSS pulse trains in the range of ± 15 cm/s are displayed as a saturation above or below the cutoff velocity (V_c), along with the range of ± 1.5 cm/s zoomed out in the subfigures to the right. The V_c at ± 0.7 cm/s are indicated by the vertical black dashed lines. The red horizontal dashed lines illustrate the universal preservation or saturation response of the control modules for DRHT/BIR-8 and FT-VSS, respectively. (f) The pulse sequence

diagram for CBV quantification using VS labeling and control modules, combined with a global post-acquisition saturation and T₂prep prepared inversion for CSF suppression.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 2:

Comparison of the T_2 effects for DRHT, BIR-8 and FT-VSS pulse trains as M_z of blood signal following label/control modules with various T_{VS}/T_2 ratios. For (a) DRHT and (b) BIR-8 pulse trains, the subtraction of control and label is shown in black. For (c) FT-VSS label/control modules, the responses for the label modules in the passband are in magenta; the results of the control modules are in green; the label and control differences are in black; the stars represent the sampled T_{VS}/T_2 ratios and the lines are the fitted models. The red and blue squares in (a), (b) and (c) correspond to arterial and venous blood, respectively, all with comparable T_2 effects from the three pulse trains.

Figure 3:

Simulated differences of the M_z of static spins in the presence of eddy current (EC) effects with the EC amplitude of 0.025% under different time constants, with the M_z at EC-free conditions, at different distances to isocenter, following (a) DRHT, (b) BIR-8 and (c) FT-VSS control (the first row) and label (the second row) modules. The results of subtraction of control and label are displayed in the third row.

Figure 4:

Errors in the signal difference caused by gradient imperfections after employing VS control/label modules on a phantom along different orientations (L-R, A-P, S-I) of velocity-encoding gradients. Results for the DRHT, BIR-8 and FT-VSS pulse trains are shown in the left (a) and right (b) columns. Error maps are normalized to SI_{PD} (percentage displayed). 5 out of 10 slices (from inferior to superior: 1, 3, 5, 7, 9) are shown with the error percentage averaged across all 10 slices (mean $\pm$ SD) displayed at the top of each row. Compared to DRHT, FT-VSS generated least differences over three encoding directions. BIR-8 with A-P and S-I directions and FT-VSS pulse trains of all three directions yielded significantly smaller effects of gradient errors.

Figure 5:

Representative images of 5 out of 10 slices (from inferior to superior: 1, 3, 5, 7, 9) acquired from subject #3: the SI_{PD} images, the DIR images for visualizing gray matter only, and CBV maps calculated from experiments using DRHT, BIR-8 and FT-VSS pulse trains with various velocity-encoding directions. DRHT and BIR-8 both generated significant artifacts throughout all slices for S-I direction. FT-VSS produced more consistent CBV contrast across different velocity-encoding directions with significantly reduced artifacts.

Figure 6:

Comparison of the estimated CBV maps on 6 subjects (only the 5th slice of each subject is shown) based on (a) DRHT, (b) BIR-8 and (c) FT-VSS pulse trains with velocity-encoding gradients along L-R, A-P, and S-I directions. CBV quantification employing FT-VSS pulse trains yielded much less artifacts and more consistent CBV contrast than with DRHT and BIR-8 modules.

Figure 7:

Comparison of the temporal SNR images on 6 subjects based on (a) DRHT, (b) BIR-8 and (c) FT-VSS pulse trains with velocity-encoding gradients along L-R, A-P, and S-I directions. CBV quantification employing FT-VSS pulse trains yielded higher temporal SNR than with DRHT and BIR-8 modules.

Table 1:

Parameters for the labeling modules with DRHT, BIR-8 and FT-VSS pulse trains.

	T _{VS} (ms)	N _{step}	T _{step} (ms)	T _{ref} (ms)	T _G (ms)	T _{ramp} (ms)	G _{max} (mT/m)	T _{gap} (ms)	(ms)	V _c (cm/s)	b-value (s/mm ²)
DRHT	40.0	1	40.0	5.00	3.2	1.6	26.0	4.0	20.0	0.7	6.6 / 2.9
BIR-8	40.0	1	40.0	5.00	3.2	1.6	26.0	1.7	20.0	0.7	7.2 / 2.3
FT-VSS	128.0	8	16.0	0.87	1.2	0.6	22.0	2.2	8.0	0.7	2.3 / 0.8

T_{VS}: duration for the entire VS pulse train; T_{step}: duration for each velocity encoding step; T_{ref}: duration of each refocusing pulse; T_G: duration of each gradient lobe; T_{ramp}: ramp time for each gradient lobe; G_{max}: maximum gradient strength of gradient lobes; T_{gap}: the gap between the gradient and the following RF pulse; : the separation between the bipolar gradient lobes when assuming the refocusing pulses are not applied; V_c: cut-off velocity; The b-values of velocity-selective labeling and velocity-compensated control modules are shown in the last column.

Table 2:

Average CBV (mL/100g) and temporal SNR values (mean $\pm$ SD, n = 6) in GM and WM ROIs and their GM/WM ratios for using DRHT, BIR-8 and FT-VSS pulse trains with velocity-encoding gradients along L-R, A-P, and S-I directions.

		DRHT			BIR-8			FT-VSS		
		GM	WM	ratio	GM	WM	ratio	GM	WM	ratio
CBV	L-R	5.8 $\pm$ 0.5	4.6 $\pm$ 0.8	1.3	5.6 $\pm$ 0.5	3.9 $\pm$ 0.6	1.4	5.5 $\pm$ 0.3	2.8 $\pm$ 0.2	2.0
	A-P	5.5 $\pm$ 0.4	3.4 $\pm$ 0.9	1.6	6.5 $\pm$ 0.2	4.4 $\pm$ 0.4	1.5	5.0 $\pm$ 0.2	1.8 $\pm$ 0.1	2.7
	S-I	7.4 $\pm$ 1.4	5.9 $\pm$ 1.9	1.2	8.8 $\pm$ 2.5	6.1 $\pm$ 2.0	1.4	5.3 $\pm$ 0.5	2.3 $\pm$ 0.4	2.3
tSNR	L-R	1.4 $\pm$ 0.1	0.9 $\pm$ 0.2	1.6	1.3 $\pm$ 0.1	0.8 $\pm$ 0.1	1.7	1.7 $\pm$ 0.2	0.6 $\pm$ 0.1	2.6
	A-P	1.3 $\pm$ 0.2	0.6 $\pm$ 0.1	2.1	1.7 $\pm$ 0.2	0.8 $\pm$ 0.2	2.0	1.5 $\pm$ 0.2	0.4 $\pm$ 0.1	3.4
	S-I	1.3 $\pm$ 0.2	0.8 $\pm$ 0.1	1.6	1.4 $\pm$ 0.2	0.9 $\pm$ 0.1	1.6	1.6 $\pm$ 0.2	0.5 $\pm$ 0.1	3.2