Three-dimensional whole-brain mapping of cerebral blood volume and venous cerebral blood volume using Fourier transform–based velocity-selective pulse trains

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Purpose: To develop 3D MRI methods for cerebral blood volume (CBV) and venous cerebral blood volume (vCBV) estimation with whole-brain coverage using Fourier transform–based velocity-selective (FT-VS) pulse trains.

Methods: For CBV measurement, FT-VS saturation pulse trains were used to suppress static tissue, whereas CSF contamination was corrected voxel-by-voxel using a multi-readout acquisition and a fast CSF T2 scan. The vCBV mapping was achieved by inserting an arterial-nulling module that included a FT-VS inversion pulse train. Using these methods, CBV and vCBV maps were obtained on 6 healthy volunteers at 3 T.

Results: The mean CBV and vCBV values in gray matter and white matter in different areas of the brain showed high correlation (r = 0.95 and P < .0001). The averaged CBV and vCBV values of the whole brain were 5.4 ± 0.6 mL/100 g and 2.5 ± 0.3 mL/100 g in gray matter, and 2.6 ± 0.5 mL/100 g and 1.5 ± 0.2 mL/100 g in white matter, respectively, comparable to the literature.

Conclusion: The feasibility of FT-VS-based CBV and vCBV estimation was demonstrated for 3D acquisition with large spatial coverage.

KEYWORDS
arterial nulling, cerebral blood volume, CSF suppression, velocity-selective pulse train, venous cerebral blood volume

INTRODUCTION

Quantitative estimation of the total cerebral blood volume (CBV) is important to better characterize microvascular physiology in both healthy brains and brain disease. The venous CBV (vCBV), which primarily includes the volume of venules, is an important indicator for the venous microvascular homeostasis of the brain.1,2 The increased vCBV could be an indicator of the venous expansion induced by venous congestion,3,4 which could cause leakage of venules and capillaries.
and in turn lead to brain swelling,\textsuperscript{5} hyperemia,\textsuperscript{6,7} or disruption of the blood–brain barrier.\textsuperscript{8} Meanwhile, vCBV is critical to further interpret the extravascular BOLD effect,\textsuperscript{9-11} which results primarily from the change of deoxyhemoglobin concentrations in deoxygenated capillaries, venules, and veins. Noninvasive mapping of CBV and vCBV using 3D acquisition with large spatial coverage is desired for both physiological and clinical applications. The main challenge in measuring CBV or vCBV is to confine the blood signal to the corresponding vascular compartments,\textsuperscript{2} which requires suppressing static tissue, mitigating CSF contamination, as well as (for vCBV measurement) nulling arterial, arteriolar, and capillary blood.

As an important addition to the technical arsenal of spin-tagging MRI, velocity-selective (VS) pulse trains\textsuperscript{12} have been developed for direct separation of vascular signal from static tissues. A basic VS saturation (VSS) pulse train consists of ±90° hard pulses enclosing a pair of adiabatic inversion pulses with surrounding velocity-encoding gradients, which produce a velocity-dependent “cos” modulation. When assuming a laminar flow pattern within the vessels, this VSS module generates a “sine” modulation, so that the signal of blood flowing above a cutoff velocity (V\textsubscript{CUTOFF}) gets dephased and the signal of slow-moving spins, including static tissue, is largely preserved. Conventional VSS pulse trains have been used for measuring cerebral blood flow,\textsuperscript{13,14} venous oxygenation,\textsuperscript{15-18} arterial CBV,\textsuperscript{19-21} total CBV,\textsuperscript{22} and vCBV.\textsuperscript{23}

Static tissue signal can be eliminated with VSS modules applied right before acquisition of the interleaved label and control scans.\textsuperscript{15,16,22,23} However, the static tissue signal is retained with conventional VSS pulse trains, and system instability and physiological motion could induce fluctuation of the tissue signal. This would generate considerable background error in subtraction, strongly affecting quantification as microvascular signal is only a few percent of static tissue’s signal. A different method applied VS excitation with a “sin” modulation to specifically excite moving spins.\textsuperscript{17} This would alleviate the CSF contamination from different diffusion weightings, as well as interference from eddy current effects. However, more than 20% of available blood signal is lost by this scheme.\textsuperscript{17}

To reduce the CSF contamination of the vascular signal from the pulsatile effect, a CSF suppression module can be applied before the acquisition that nulls residual CSF signal.\textsuperscript{22} The scheme of inserting a relatively long T\textsubscript{2prep} before inversion yields higher vascular signal as a result of saturation recovery compared with using an inversion pulse alone.\textsuperscript{24} However, the blood signal is still attenuated due to the limited time available for magnetization recovery of the blood signal. Alternatively, a multi-readout acquisition scheme,\textsuperscript{25} which takes advantage of large T\textsubscript{2} differences between CSF and blood, can be used to correct for the CSF partial volume while maintaining high blood signal.

When only the venous signal is targeted, different strategies have been used for nulling arterial blood. A slab-selective inversion under the imaging plane can be applied for nulling the incoming arterial blood.\textsuperscript{17,18} However, this method is sensitive to the arterial transit time, which is not ideal for large spatial coverage or patients with occluded vessels. Instead, a conventional VSS module followed by a nonselective inversion (NSI) pulse after a preceding delay can be used to null all recovering arterial blood.\textsuperscript{15,16} Another recent study proposed using a single NSI pulse to null fresh incoming arterial blood together with CSF through careful timing.\textsuperscript{23} However, this use of NSI pulses in the last two schemes also attenuates the available signal of venous blood at acquisition.

As an alternative to the conventional flow-dephasing VSS pulse trains, Fourier transform–based velocity-selective (FT-VS) pulse trains are designed by concatenating a series of small flip-angle RF pulses followed by paired refocusing pulses with surrounding velocity-encoding gradients.\textsuperscript{26-28} These either saturate (FT-VSS) or invert (FT-VSI) static tissue while preserving spins flowing above V\textsubscript{CUTOFF}. Various FT-VS pulse trains have been applied successfully for MRA\textsuperscript{27,29-34} and quantitative mapping of cerebral blood flow,\textsuperscript{26,35} as well as total CBV.\textsuperscript{28} The FT-VSS label/control modules offer a concurrent capability of suppressing the tissue background for more robust CBV measurements.\textsuperscript{28}

In this work, we aimed to conduct 3D-CBV mapping by combining both the FT-VSS pulse train for better tissue suppression\textsuperscript{28} and a multi-readout acquisition scheme\textsuperscript{25} to remove CSF contamination. Furthermore, we developed a sequence for vCBV quantification by incorporating an arterial blood nulling module that appended the FT-VSI pulse train\textsuperscript{26} with an NSI pulse to obtain higher venous blood signal. The CBV and vCBV were measured for healthy volunteers with whole-brain coverage at 3 T.

2 METHODS

2.1 Fourier transform–VS pulse trains

The FT-VSS and FT-VSI pulse trains\textsuperscript{26-28} consist of nine excitation pulses (10° hard pulses for saturation and 20° hard pulses for inversion), interleaved with paired and phase-cycled refocusing pulses (180° hard pulses) surrounded by gradients with alternating polarity (Figure 1A). The VS-label modules (total duration T\textsubscript{VS} = 96 ms) with triangular gradient lobes (G\textsubscript{VS} = 29 mT/m; length: 1.2 ms; ramp time: 0.6 ms) yield a targeted saturation or inversion band within ±0.70 cm/s (V\textsubscript{CUTOFF}; dotted vertical lines in Figure 1B,C). The corresponding control module for FT-VSS also uses velocity-compensated gradient waveforms (dashed lines in Figure 1A) for a more balanced diffusion-weighting effect and achieves universal saturation regardless of the velocity
The NSI pulse applied immediately after the FT-VSI pulse train with a spoiling gradient flips the VSI profile such that the flowing spins within the passing band get inverted and the static spins within the inversion band are restored (Figure 1C, red).

### 2.2 Pulse sequence

The pulse sequence diagrams for CBV and vCBV mapping are shown in Figure 2A. A slab-selective presaturation pulse train is used at the start for erasing any magnetization from previous history (yellow square in Figure 2B). For CBV mapping, the FT-VSS label/control modules are applied following a post-saturation delay of 3500 ms. Preceded by fat suppression, a segmented 3D gradient and spin-echo (GRASE) readout is used as acquisition. To detect the residual CSF signal and correct its contamination in the blood volume analysis, the 208-ms GRASE readout is played out four times after the 90° slab-selective excitation, in which the last readout starting at 624 ms only contains CSF signal and could be used for CSF correction (see Supporting Information Figure S1).

For vCBV mapping, a spatially nonselective arterial-nulling module, which consists of a FT-VSI segment plus an NSI pulse followed by an inversion time (TI), is inserted between the post-saturation delay and the FT-VSS label/control modules. The NSI pulse is a hyperbolic tangent adiabatic pulse (6 ms, maximum amplitude of 13.5 μT, frequency sweep of 12 kHz). The post-saturation delay is set as 2500 ms to allow adequate signal recovery of blood signal after the slab-selective presaturation, while letting the fresh incoming arterial blood fill the intracranial arteries in the imaging slab.

Figure 3 illustrates the idealized evolution of the microvascular signal through the preparation phase of the sequence.
Based on the compartmental microcirculation model previously adopted by other human MRI studies modeling the cerebrovascular network, the velocity ranges in arterioles and venules are [0.4, 4.8] cm/s and [0.2, 2.1] cm/s, while the blood velocity in capillaries is as slow as 0.1 cm/s. Therefore, immediately after FT-VSI plus NSI pulses (Figure 3A), the spins flowing above the VCUTOFF (0.7 cm/s), such as those within the arteries, veins and large arterioles, and venules, would be inverted, while the spins moving below the VCUTOFF, such as those within the capillaries and small arterioles and venules, would be preserved (Figure 1C). As shown in Figures 3B and 4A, the inverted blood spins in arteries and large arterioles (velocity > VCUTOFF) would recover and flow into the small arterioles and capillaries, and finally be nulled at the end of TI. Meanwhile, the preserved blood spins in capillaries and small venules (velocity < VCUTOFF) would outflow into the large venules during TI while recovering, to yield relatively high signal for vCBV measurement.

2.3 Experiments

All experiments were conducted on a 3T scanner (Ingenia; Philips Healthcare, Best, the Netherlands) using the body coil for RF transmission (maximum amplitude = 13.5 µT) and a 32-channel head coil for signal reception. The maximum strength and slew rate of the gradient coils were 45 mT/m and 200 mT/m/ms, respectively. The protocol was approved by the institutional review board of Johns Hopkins University School of Medicine. All 6 healthy volunteers (5 females, 1 male; 49 ± 12 years old) provided written, informed consent.

The 3D-GRASE readout (Supporting Information Figure S1) was applied with low–high acquisition order. Following the 90° slab-selective excitation pulse, a series of nonselective sinc 180° refocusing pulses were applied. The acquisition parameters were as follows: FOV = 220 × 220 × 100 mm³ with acquisition resolution of 3.5 × 3.8 × 5.0 mm³; slice oversampling factor of 1.6, turbo spin-echo factor of 16, EPI factor of 15 along left–right direction, SENSE factor of 2 for phase encoding, echo spacing of 13 ms, and echo train length of 208 ms. The full k-space was acquired with 4 interleaves.
This acquisition scheme was performed for all of the following scans. For CBV and vCBV mapping, three additional GRASE readouts were concatenated so that the last readout starting at 624 ms could be used to correct for the remaining CSF signal. These two scans were acquired with a TR of 4.6 seconds, eight dynamics, and a total scan time of 5.5 minutes. A proton density–weighted image (SIPD) was acquired for CBV/vCBV quantification purposes (TR = 10 seconds; 1.1 minutes). Two double inversion recovery (DIR)\textsuperscript{41} images were collected to visualize gray matter (TI\textsubscript{1} = 3.58 seconds; TI\textsubscript{2} = 0.48 seconds) and white matter (TI\textsubscript{1} = 4.05 seconds, TI\textsubscript{2} = 0.77 seconds), respectively (TR = 10 seconds; 1.1 minutes).

The CSF T\textsubscript{2} was estimated using a method modified from a previous work\textsuperscript{42} (Supporting Information Figure S2). The post-saturation delay was set as 9000 ms. A 600-ms T2prep was applied before the acquisition to suppress all other signal except CSF. Eight consecutive GRASE readouts with the same acquisition parameters as the GRASE readout used in vCBV measurement were acquired to obtain the T\textsubscript{2} relaxation decay of CSF signal (TR = 10 seconds; 1.1 minutes).

In addition, the arterial-nulling module in the vCBV measurement was incorporated into a VS-MRA sequence previously developed\textsuperscript{30} to evaluate the arterial nulling effect on 1 volunteer. Meanwhile, the outflow territories of

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**FIGURE 4**  
A. Simulated magnetization evolution during the preparation for vCBV measurement of the spins before moving into the arterioles and venules. The arterial spins flowing above the V\textsubscript{CUTOFF} would be inverted by the FT-VSI plus NSI module (efficiency 0.86; see text), then recover while flowing into the small arterioles, and finally get nulled at the end of TI (in red). The blood spins initially within the capillaries (in black), with velocity below the V\textsubscript{CUTOFF} largely flowing out into the venules (in blue) during TI with the preserved signal magnetization. Meanwhile, the rest of the capillary blood staying within the capillary during TI is removed by the FT-VSS pulse. The Mz-velocity responses after the FT-VSI + NSI pulse trains are simulated separately by considering the T\textsubscript{2} relaxation effect during FT-VSI pulse trains for arterial (B) and capillary blood (C), respectively. The small signal losses right after FT-VSI + NSI and FT-VSS pulses in (A) are caused by the T\textsubscript{2} effect (Equations 5 and 8), as shown in (C)
retained capillary blood during the arterial-nulling module was evaluated using a similar velocity-selective MRA sequence with a modified preparation module, in which the FT-VSI + NSI pulses in the arterial-nulling module were replace by a FT-VSI pulse (Supporting Information Figure S5A).

2.4 Data analysis

MATLAB (MathWorks, Natick, MA) was used for data processing. Before analyzing the CBV data, CSF T₂ maps were first derived by fitting the eight data sets voxel-by-voxel as a function of TE using a single exponential decay (Supporting Information Figure S2), as follows:

\[ S_{CSF} = S_{0,CSF} \times e^{-TE/T_{2,CSF}} \]  

(1)

This was used to estimate and remove the CSF contamination in the difference images (\( SI_{diff} \)) between label and control scans in the CBV measurements at the first and last readouts (\( \Delta TE = 624 \) ms) using a weighted subtraction (Figure 5), as follows:

\[ SI_{diff} = SI_{diff, first \ readout} - e^{\Delta TE/T_{2,CSF}} \times SI_{diff, last \ readout} \]  

(2)

After correcting for the residual CSF signal, the total CBV map was calculated following the process described in our previous paper:

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

(3)

where the unit for CBV is milliliters of blood/100-g tissue; \( \lambda \) is the brain–blood partition coefficient (0.9 mL of blood/g tissue); \( SI_{PD} \) is the signal intensity of the proton density images. For \( V_{CUTOFF} = 0.70 \) cm/s, the compartmental fractions of CBV (\( x_i \)) and their labeling efficiencies (\( \alpha_i \)) are \( x_a = 0.21, \alpha_a = 0.55 \) for arterioles and \( x_v = 0.46, \alpha_v = 0.31 \) for venules (with negligible contribution from capillary blood: \( x_c = 0.33; \alpha_c = 0 \)).

The \( T_1 \) effects on the blood signals of the three microvascular compartments are determined by the post-saturation recovery, as follows:

\[ M(T_{1,i}) = 1 - \exp \left( -T_{recovery}/T_{1,i} \right) \]  

(4)

Arterial and venous blood \( T_1 \) values were taken as \( T_{1,a} = 1888 \) ms and \( T_{1,v} = 1707 \) ms, assuming a Hct of 0.42 and \( Y_a \) of 0.98, and \( Y_v \) of 0.6 for healthy adults. Based on the post-saturation delay of \( T_{recovery} = 3.5 \) seconds in this
study, the $T_1$ effects were calculated as 0.85 for arterial blood and 0.87 for venous blood.

The $T_2$ effects of blood signal under the label and control modules with duration of $T_{VS}$ can be characterized by\(^ {28}\)

\[
M(T_{2,i,\text{label}}) - M(T_{2,i,\text{control}}) = k_1 + k_2 \cdot k_3 \cdot \frac{T_{VS}/T_2}{k_3},
\]

where $[k_1, k_2, k_3, k_4] = [0.12, 0.86, 0.34, 0.38]$. Arterial and venous blood $T_2$ were set as $T_{2,a} = 163$ ms and $T_{2,v} = 71$ ms, respectively, based on our $T_2$ model\(^ {39,46}\) for the used 6-ms inter-echo spacing of the FT-VS pulse trains, assuming Hct of 0.42, $Y_a$ of 0.98, and $Y_v$ of 0.6 for healthy adults\(^ {34,45}\). For the FT-VSS pulse lengths ($T_{VS}$) of 96 ms, the $T_2$ effects were calculated as leading to the normalized magnetization fractions of 0.80 for arterial blood and 0.61 for venous blood.

Regarding the vCBV experiment, the inserted arterial-nulling module (green dashed box in Figure 2A) removes the arterial blood signal. Therefore, vCBV values can be calculated from the CSF-corrected signal $S_{diff,\text{CBV}}$ as

\[
v_{\text{CBV}} = \frac{100 \cdot \lambda \cdot \alpha_v \cdot M_{\text{prep}} \cdot (M(T_{2,v,\text{label}}) - M(T_{2,v,\text{control}}))}{S_{PD} \cdot \alpha_v \cdot M_{\text{prep}}},
\]

where the labeling efficiency $\alpha_v$ (0.31) and the normalized magnetizations after considering the $T_2$ effect during the FT-VSS pulse trains $M(T_{2,v})$ are from Equation 5; and $M_{\text{prep}}$ is the magnetization modulation by the post-saturation delay and arterial-nulling module:

\[
M_{\text{prep}} = 1 + \left(- M(T_{1,c}) \cdot M_{\text{VSI}}(T_{2,c}) - 1\right) \cdot e^{-TI/T_1},
\]

where $M(T_{1,c})$ represents the normalized blood magnetization after post-saturation recovery (Equation 4). The negative sign before $M(T_{1,c})$ reflects the inversion by NSI. The value of $M_{\text{VSI}}(T_{2,c})$ is the normalized magnetization considering the $T_2$ effect of FT-VSI pulses. As indicated in Figures 3 and 4, the water in the venules at the time of acquisition was originally in the capillary bed when they experienced the FT-VSI pulse train. Therefore, the $T_1$ and $T_2$ values of the blood in the capillary will be used to estimate $M_{\text{prep}}$. To estimate $T_1$ and $T_2$ values of the blood in the capillary, we used a capillary oxygen delivery model\(^ {10}\) to calculate the blood oxygenation fraction distribution along the capillary and calculated the mean $T_{1,c}$ and $T_{2,c}$ values of the capillary blood as 1861 ms and 118 ms, respectively (Supporting Information Figure S3).

As done in our precious study for the FT-VSS pulse trains,\(^ {28}\) this $T_2$ effect was simulated using the Bloch equation for the FT-VSI pulse train ($T_{VS} = 96$ ms) with nine different $T_2$ values of $[25, 75, 100, 150, 200, 300, 400, 500]$ ms, corresponding to sampled $T_{VS}/T_2$ ratios of $[3.84, 1.28, 0.96, 0.64, 0.48, 0.32, 0.24, 0.19]$. The averaged magnetizations in the maximal velocity range of $[3.5, 7.5]$ cm/s were calculated as the responses for the FT-VSI module in the passband; the magnetizations for zero velocity were taken as the results of the inversion band (Figure 6A). For convenience of the calculation with different $T_2$ values, the two data sets were fitted using an empirical four-parameter model:

\[
M_{\text{VSI}}(T_2) = a_1 + a_2 \cdot (T_{VS}/T_2) + a_3 \cdot (T_{VS}/T_2)^2 + a_4 \cdot (T_{VS}/T_2)^3,
\]

where $[a_1, a_2, a_3, a_4] = [0.92, -0.10, 0.0061, 0.0002]$ for pass-band (Figure 6B, magenta line) and $[-0.97, 0.52, -0.11, 0.011]$ for inversion band (Figure 6B, green line), respectively.

Therefore, $M(T_{1,c})$, $M_{\text{VSI}}(T_{2,c})$ (inversion band for capillary blood), and $M_{\text{prep}}$ in Equation 7 were calculated as 0.74, -0.62 and 0.69, respectively. Meanwhile, using $T_{2,a} = 163$ ms, the magnetization modulation of FT-VSI on arterial blood (in passband) $M_{\text{VSI}}(T_{2,a})$ was calculated as 0.86, which was used to calculate the value of TI for arterial nulling.

Following these equations, the mean CBV and vCBV maps could be obtained from the repeated dynamics. The voxels with large vessels were identified and excluded by

**FIGURE 6** A, Simulated $T_2$ effect on the magnetization modulation of the FT-VSI pulse train, $M_{\text{VSI}}(T_2)$, for different velocities. B, The fits of $M_{\text{VSI}}(T_2)$ for the passband (magenta) and inversion band (green) as a function of the ratio between FT-VSI pulse train length ($T_{VS}$) and $T_2$. 
thresholding the CBV map using 12 mL/100 g and vCBV map using 6 mL/100 g.

For each volunteer, binary gray matter (GM) and white matter (WM) masks were obtained from the GM-only and WM-only DIR images using an empirical threshold. The GM and WM regions of interest from frontal lobe, temporal lobe, parietal lobe, occipital lobe, and cerebellum were also segmented out. The averaged CBV and vCBV values in GM and WM, both from these individual ROIs and the whole brain, were calculated.

3 | RESULTS

The CSF correction process is illustrated in Figure 5 using the images acquired with a long effective TE and the separately obtained CSF T₂ map. It can be seen from the figure that the label/control difference image from the first readout still contained a significant portion of CSF signal, likely due to its pulsatile motion, whereas the label/control difference image from the last readout (ΔTE = 624 ms) only had the remaining CSF signal. Therefore, the CSF contamination in the first readout image was effectively removed by subtracting the label/control difference image of the last readout considering the T₂,CSF decay between the first and last readout (Equation 2), and the vascular signal was retained as compared with the corresponding DIR GM image. The periventricular GM signal (red arrow), which was obscured in the first readout, was represented correctly after the CSF correction.

Axial, coronal, and sagittal planes from 3D whole-brain CBV, vCBV, and DIR GM are shown in Figure 7 for 2 representative subjects. Tissue background was suppressed well,

![Figure 7](image_url)

**FIGURE 7** Example slices from 3D maps of total CBV, vCBV, and DIR (GM) for the three orthogonal planes in 2 subjects (subjects 1 and 3). Note that the image scale for total CBV images is twice that for the vCBV images.
and no obvious artifacts related to eddy currents are apparent. When comparing these images, both CBV and vCBV maps have a contrast pattern similar to the DIR-GM image due to the high blood volume in the GM, and the blood-volume values in the vCBV maps are about half of the values in the CBV maps. Meanwhile, the CSF signals in both CBV and vCBV maps appear to be effectively removed, especially apparent in the ventricular regions. Figure 8 shows five axial CBV and vCBV slices for all 6 subjects at different locations. The GM/WM contrast of the two maps is largely consistent across subjects.

Figure 9 shows a high correlation ($r = 0.95$ and $P < 0.0001$) between the mean CBV and vCBV values in GM and WM regions of interest within the frontal lobe, temporal lobe, parietal lobe, occipital lobe, and cerebellum of all our volunteers. The CBV and vCBV values averaged from the whole-brain GM and WM tissue masks of each subject are summarized in Table 1. The averaged CBV values in GM and WM are $5.4 \pm 0.6$ mL/100 g and $2.6 \pm 0.5$ mL/100 g, whereas the averaged vCBV values in GM and WM are $2.5 \pm 0.3$ mL/100 g and $1.5 \pm 0.2$ mL/100 g, respectively.

4 | DISCUSSION

In this work, we optimized a CBV mapping method based on the FT-VSS pulse trains to suppress the static tissue signal and an additional readout with prolonged effective TE, to directly detect CSF contamination. Built on this sequence, a novel technique for quantifying venous CBV was developed by embedding an arterial-nulling module containing a FT-VSI pulse train. The feasibility of both techniques for 3D acquisition with large FOV was demonstrated for a group of healthy volunteers.
Extending from a previous study using 2D acquisition, the capability of our new methods is shown in Figures 8 and 9 for 3D-CBV quantification with whole-brain coverage. The obtained CBV values (Table 1, averaged 5.4 mL/100 g for GM and 2.6 mL/100 g for WM) are comparable to those reported previously in the literature. The derived vCBV in GM (2.5 ± 0.3 mL/100 g) is 46% of the CBV in GM, and comparable to the $x_v = 0.46$ (used in calculating CBV in Equation 3) obtained from the previously mentioned compartmental microcirculation model based on animal brain morphological data. For WM, the measured vCBV (1.5 ± 0.2 mL/100 g) is about 58% of the CBV, which is a little higher than physiologically plausible, but within error. The inherently low vascular signal in WM inevitably leads to less accuracy and precision for the CBV/vCBV quantification in WM regions compared with GM regions.

To detect and then remove the CSF contamination, we adopted a multi-readout strategy previously proposed for a 2D-VSASL study. Instead of only acquiring two images with a short TE and a very long TE, our implementation acquired four consecutive images (Figure 2A and Supporting Information Figure S1), with the second and third images not used in the analysis. This consecutive acquisition scheme was chosen, in particular, for the 3D-GRASE readout to keep the echo spacing between the refocusing pulses within each readout the same as the interval between the readouts, and thus alleviate potential artifacts from stimulated echoes.

To estimate the CSF signal attenuation between the first and last readout images, additional CSF $T_2$ mapping was performed using the same successive GRASE acquisitions (Supporting Information Figure S2). The measured average CSF $T_2$ for all of our volunteers was 2020 ± 231 ms in the ventricles and 1732 ± 288 ms within the cortical lobes, which are close to respective values of 2062 ms and 1573 ms reported in a previous study measuring CSF $T_2$ using a separately acquired data set with different durations of $T_2$ preparation. Admittedly the CSF $T_2$ mapping in the current work may have bias induced by $B_1$ inhomogeneities and a consequent imperfect refocusing of the sinc refocusing pulses used in GRASE readout. However, as the CSF $T_2$ map sequence shared the same acquisition as the CBV/vCBV sequences, the fitted CSF $T_2$ values would better reflect the signal decay between the first and last readouts in CBV/vCBV sequences. Instead of using an extra scan to map CSF $T_2$, it would be faster and simpler to just apply a single CSF $T_2$ value for all voxels. If cortical $T_2,_{CSF} = 1732$ ms was presumed, the CSF correction factor, $e^{\Delta T_E/T_{2,CSF}}$, would be only overestimated by 5.3% for ventricle $T_2,_{CSF} = 2020$ ms.

To isolate venous blood signal for vCBV quantification, a new arterial-nulling module that combines a FT-VSI pulse train and a NSI pulse (Figure 2A) was applied to preserve the magnetization of the slow-flowing blood in capillaries that would flow into the venular vessels during TI (Figures 3 and 4). Supporting Information Figure S4 shows that, in this limited data set, velocity-selective MRA using this

### Table 1

| Subject | Age (years) | CBV (mL/100 g) | vCBV (mL/100 g) |
|---------|-------------|----------------|-----------------|
|         |             | GM  | WM  | GM  | WM  |
| #1 (F)  | 38          | 6.0 | 2.8 | 2.8 | 1.5 |
| #2 (M)  | 35          | 5.8 | 3.0 | 3.0 | 1.9 |
| #3 (F)  | 61          | 5.4 | 2.3 | 2.4 | 1.5 |
| #4 (F)  | 45          | 4.9 | 1.9 | 2.4 | 1.4 |
| #5 (F)  | 56          | 5.4 | 3.2 | 2.6 | 1.5 |
| #6 (F)  | 61          | 4.5 | 2.3 | 2.1 | 1.4 |
| Mean ± SD | 49 ± 12 | 5.4 ± 0.6 | 2.6 ± 0.5 | 2.5 ± 0.3 | 1.5 ± 0.2 |

Abbreviations: F, female; M, male.
arterial-nulling module confirms its effectiveness to suppress the signal in distal arteries to a level of less than 10%. This ensured a very minimal vCBV signal contribution from small arteries and arterioles, because the arterial blood bolus containing inverted spins (Figure 3A) would flow downstream and fill both small arteries and arterioles during TI and finally get nulled at the time of acquisition, as illustrated in Figure 3B. Notably, as shown in Supporting Information Figure S4A, some signal remains in large arteries such as middle cerebral arteries, due to the fast inflow of fresh arterial blood during TI. However, these large vessels, which could not be fully suppressed by the arterial-nulling module, would be removed through thresholding, as described in section 2.4, and thus have little effect on vCBV measurement. Another possible limitation of the arterial-nulling module is that imperfect inversion by the FT-VSI plus NSI pulses, caused for instance by $B_1$ inhomogeneity, could induce a residual arterial signal. If the inversion efficiency was 0.66, 23% lower than 0.86 used previously, an 11% arterial signal will be left after the TI. Considering that the arterial blood volume fraction is less than half of the venous blood volume fraction (0.21 vs 0.46 based on the compartmental microcirculation model), this remaining 11% arterial signal would induce only about 5% overestimation of vCBV.

In addition, in the arterial-nulling module for our vCBV estimation, we also assumed that the capillary blood retained by the FT-VSI and NSI pulses will move out and fill the venules and small veins during the TI, as depicted in Figure 3. To visualize the correctness of this assumption regarding the outflow territory of the capillary blood during TI, we designed a velocity-selective MRA sequence with a modified preparation module, in which the FT-VSI + NSI pulses in the arterial-nulling module were replaced by the FT-VSI pulse (Supporting Information Figure S5A). In this sequence, the FT-VSI pulse will invert the capillary blood below the $V_{\text{CUTOFF}}$ (Figure 1C, black line) and the inverted capillary blood will flow out into the venules and cortical veins during TI and be nulled at acquisition (Supporting Information Figure S5B). Then the outflow territories of the capillary blood can be illustrated by comparing the velocity-selective MRA with and without this modified preparation module. As shown in Supporting Information Figure S5C, most of the visible cortical veins were nulled, which indicates that the outflowing capillary blood reached these large cortical veins during TI. This suggest that our vCBV estimation targeting the venules and small veins may not be very susceptible to variations in venous flow velocity, which would require further validation over a larger population. Of course, for reduced flow situations such as in the presence of the venous congestion, our method could underestimate vCBV values.

In the quantitative CBV/vCBV maps (Equations (3-8)), the signal evolution during the post-saturation delay or the following arterial-nulling module and FT-VSS module is estimated based on the $T_1$ and $T_2$ values of arterial and venous blood calculated from the population-averaged Hct (0.42) and $Y_v$ (0.60) values. To evaluate the sensitivity of the CBV/vCBV measurements to Hct and $Y_v$, variations, Hct and $Y_v$ were sampled from the range [0.39, 0.50] with interval of 0.005 and [0.50, 0.70] with interval of 0.01, respectively. For a given combination of Hct and $Y_v$, the blood $T_1$ and $T_2$ values were derived based on our published models. The corresponding CBV/vCBV results were compared with the ones obtained using Hct of 0.42 and $Y_v$ of 0.60. As shown in Supporting Information Figure S6, the variation of Hct in the range of [0.39, 0.50] and $Y_v$ in the range of [0.50, 0.70] could cause deviations of up to $[-6\%, 9\%]$ and $[-15\%, 24\%]$ in the CBV and vCBV estimations, respectively. To minimize these potential biases, individual measurements of arterial blood $T_1$ and venous blood $T_2$ values could be measured with each taking about 1 minute, respectively. These can be used to calculate Hct and $Y_v$, respectively, using an available online calculator. Meanwhile, in the vCBV estimation, $T_1$ and $T_2$ values of capillary blood (1861 ms and 118 ms, Supporting Information Figure S3) were used to calculate the magnetization modulation imposed by the post-saturation delay and arterial-nulling module. However, due to the fast water exchange between the capillary bed and tissue, the relaxation of tissue water would also affect the venous signal. If the $T_1$ and $T_2$ values of GM ($T_1 = 1165$ ms and $T_2 = 83$ ms) and WM ($T_1 = 738$ ms and $T_2 = 75$ ms) were used, there would be a 11% and 20% difference in the estimated vCBV values, respectively.

Furthermore, to calculate the labeling efficiency $\alpha_i$ in Equations (3) and (6), the volume fractions of arterial, venous, and capillary blood and their corresponding velocities were also assumed based on a compartmental microcirculation model. However, this assumption may not be valid under conditions such as brain pathologies, cerebrovascular reactivity challenges, or functional stimulation. Given these considerations, we calculated the labeling efficiency $\alpha_i$ in Equations (3) and (6), and found that a 20% change in blood velocity could lead to 8% deviation in the arterial labeling efficiency $\alpha_a$ and 14% deviation in the venous labeling efficiency $\alpha_v$. Meanwhile, the arterial and venous compartmental fractions ($x_i$ in Equation (3)) would change under hypercapnia and visual stimulation challenges, due to the different vascular response among arterioles, capillaries, and venules/veins. Previous studies have shown that vCBV change would contribute about 36%-50% of total CBV change under hypercapnia and visual stimulation. Based on these results and the assumption that the capillary has little change during the stimulation, there would be an approximate 10%-13% overestimation of our CBV measurement if the total CBV increases 20% under certain stimulation. Certainly, if brain capillary is also involved in cerebral blood flow regulation and dilates under stimulations as indicated by a recent study, the
overestimation of our CBV measurement will decrease due to the less change of $x_i$ values. Note that our $vCBV$ computation (Equation (6)) does not depend on venous compartment fraction $x_v$, and thus would not be affected by its change in the stimulation.

The $T_2$ effect during the FT-VSS and FT-VSI pulse trains can in principle be lowered by shortening their duration ($T_{VS}$), such as when having availability of higher maximum $B_1$ amplitude and a higher maximum amplitude and slew rate for the gradient system. If $T_{VS}$ was reduced from 96 ms to 64 ms, the normalized magnetization difference $M(T_2,\text{label}) - M(T_2,\text{control})$ (Equation (5)) would be raised from 0.79 to 0.85 for arterial blood ($T_{2a} = 163$ ms) and from 0.61 to 0.71 for venous blood ($T_{2v} = 71$ ms); $M_{VS}(T_2)$ (Equation 8) for the capillary blood ($T_{2c} = 118$ ms) would be improved from $-0.62$ to $-0.72$; and $M_{\text{prep}}$ would be improved from 0.69 to 0.74.

Note that the duration of each GRASE readout was relatively long ($T_{\text{acq}} = 208$ ms) compared with venous blood $T_2$ ($T_{2v} = 71$ ms). The optimum $T_{\text{acq}}/T_2$ ratio to mitigate $T_2$ decay–induced blurring and achieve maximum SNR efficiency is 1.2. Therefore, a $T_{\text{acq}}$ of 100 ms would be more desirable, especially for $vCBV$ mapping. More advanced acceleration techniques could further improve the temporal resolution of the acquisition.

5 | CONCLUSIONS

We extended the FT-VSS-based CBV mapping technique from 2D to 3D acquisition with suppression of static tissue and mitigation of CSF contamination. We further demonstrated a $vCBV$ quantification method with preservation of high venular signal by applying a FT-VSI pulse train. The clinical value of these approaches is expected to be especially pertinent for patients with cerebrovascular disease, in whom blood transit times are unknown. In addition, the ability to determine $vCBV$ should be helpful for the quantitative interpretation of BOLD effects.

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CONFLICT OF INTEREST

Dr. van Zijl is a paid lecturer for Philips Healthcare, has research support from Philips, and has technology licensed to Philips. This has been approved by the Committee on Conflict of Interest of Johns Hopkins University.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

FIGURE S1 Diagram of the gradient and spin-echo (GRASE) acquisition for 3D cerebral blood volume (CBV)/venous CBV (vCBV) measurement. The GRASE readout was repeated 3 additional times so that the last readout could detect residual CSF signal.

FIGURE S2 A. Pulse sequence for 3D-CSF T2 mapping. After a 600-ms T2 preparation to suppress other tissues with short T2s, the multishot GRASE readout was used to acquire images with concatenated eight readouts with different effective TEs. The signals acquired at different effective TEs were fitted using a voxel-by-voxel mono-exponential decay (B) to obtain the CSF T2 maps (C).

FIGURE S3 Capillary blood oxygenation fraction (A), capillary blood T2 (B), and T1 (A) as a function of its relative position in the capillary (I/L).

FIGURE S4 Investigation of arterial-nulling module using velocity-selective MRA (VSMRA). A. The VSMRA was conducted without and with the arterial-nulling module (Fourier transform [FT] velocity-selective inversion [LSI] plus nonselective inversion [NSI] followed by inversion time [TI]) before FT velocity-selective saturation (VSS) and acquisition, to test its effectiveness for suppressing the arterial blood signal. When the arterial-nulling module was used, most of the visible arterial signal in distal arteries was suppressed.

To quantify the nulling efficiency, several regions of interest (ROIs) of the anterior cerebral arteries (ACAs), middle cerebral arteries (MCAs), and posterior cerebral arteries (PCAs) were drawn on the maximum intensity projection (MIP) of areas above the circle of Willis. B. The ratio of the intensities of these ROIs with and without the arterial-nulling module were calculated, and the residual arterial blood intensities with the arterial-nulling module were 7.0 ± 2.5% compared with the signal obtained without applying this module.

FIGURE S5 Investigation of capillary outflow using VSMRA. A. The pulse-sequence diagram of VSMRA with a modified preparation module (FT-VSI followed by TI, which is the same as the TI used in the vCBV measurement) inserted before FT-VSS and acquisition. B. Evolution of the longitudinal magnetization of water in different compartments: The FT-VSI pulse train inverts spins in the capillaries flowing below the Vcutoff and the inverted capillary blood will outflow to the small veins during TI and be nulled at acquisition, whereas the spins with preserved magnetization in arteries will move into the capillaries during TI and get saturated by the FT-VSS at acquisition.

C. The VSMRA was conducted without and with this modified preparation module to visualize the outflow territories of the capillary blood. When this module was used, most of the visible venous signal in small cortical veins was nulled. To quantify the nulling efficiency, three ROIs of the cortical veins were drawn on the MIP of cortical veins. D. The ratio of the intensities of these ROIs with and without the modified preparation module was calculated, and the residual venous blood intensities with this modified preparation module were less than the 5% level compared with the signal obtained without applying this module. This indicates that the outflowing capillary blood reaches these large cortical veins during TI.

FIGURE S6 Error analysis of the CBV (A) and vCBV (B) measurements at different hematocrit (Hct) and venous oxygenation fractions (Yv). For a given combination of Hct and Yv, the signal evolution of arterial and venous blood was calculated with respective T1 and T2 values of arterial and venous blood, and the corresponding CBV/vCBV results were compared with the ones obtained using Hct of 0.42 and Yv of 0.60. The Hct and Yv variations could cause up to [−6%, 9%] and [−15%, 25%] bias in CBV and vCBV measurements, respectively. To minimize these potential biases, individual measurements of blood T1 and T2 values could be applied, with each taking about 1 minute, respectively.

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