INTRODUCTION

Since its introduction,\(^1\)\(^2\) arterial spin labeling (ASL) has gained popularity for cerebral perfusion imaging over contrast-enhanced methods due to its noninvasive nature, suitability for use in longitudinal studies, and concerns about links between Gadolinium-based contrast agents and nephrogenic systemic fibrosis in patients with kidney dysfunction.\(^3\) There is a wide range of potential applications for ASL, including acute stroke, chronic vascular disease, dementia, and assessment of tumor blood flow.

Advances in magnetic field strength, multichannel receive coils, background suppression,\(^4\) and the use of improved labeling schemes, such as pseudocontinuous ASL (PCASL),\(^5\) have all improved the signal-to-noise ratio (SNR) in ASL acquisitions, priming their transition into clinical use. However, standard ASL methodologies provide information only about the total perfusion in each voxel of the brain without regard to its arterial source. An apparently normal perfusion map may be the result of efficient collateral flow (e.g., around the circle of Willis), masking the presence of disease. In addition, the cause of any observed perfusion deficit cannot be accurately assigned to a particular feeding artery due to common variations in the morphology of the cerebral vasculature.\(^6\) Vessel-selective information may also be of use in assessing the arterial supply to lesions such as tumors.

To address this, a number of ASL techniques capable of generating perfusion maps arising from individual arteries have been developed. These include methods that label blood in a single artery\(^7\)\(^–\)\(^11\) and those that label multiple arteries before separating the vascular territories in postprocessing.\(^12\)\(^–\)\(^15\) The vessel-encoded PCASL (VEPCASL) approach of Wong\(^14\) benefits from the comparatively high SNR of the PCASL labeling scheme along with the flexibility of tagging arteries within a single plane. This is in contrast to the use of pulsed ASL techniques for vessel-selective ASL that require a complex planning procedure to position a three-dimensional (3D) slab over the artery or arteries of interest. If the vascular geometry is such that an encoding scheme can be designed which ‘tags’ or ‘controls’ each artery an equal number of times, then theoretically the SNR of the VEPCASL technique should match that of standard PCASL,\(^14\) although to our knowledge this has not yet been shown experimentally.

Thus far the VEPCASL approach has been implemented using a single postlabeling delay (PLD). This necessitates the choice of a long PLD to ensure the entire bolus has arrived at the tissue,\(^16\) during which the labeled blood decays considerably, reducing the SNR. It also removes the possibility of estimating the bolus arrival time (BAT) of the blood in each voxel by fitting a kinetic model to the data, which may be an interesting physiologic parameter in its own right.\(^17\) In addition, with separate signals from each artery it would be possible to fit the kinetic model to each component. This may produce more accurate cerebral blood flow (CBF) estimates than a standard, nonselective ASL acquisition in voxels fed by multiple arteries with different BATs, such as in patients with a significant collateral flow.

The aim of this study was to evaluate multi-PLD VEPCASL for quantitative cerebral perfusion imaging and to assess its advantages and disadvantages relative to standard PCASL, building on the work previously presented in abstract form.\(^19\) Simulations were performed to determine whether VEPCASL could produce more accurate CBF estimates than standard PCASL when multiple...
arteries contribute to perfusion in the voxel. Estimates of CBF in healthy volunteers from the two techniques were then compared to determine whether there is any systematic bias in VEPCASL relative to PCASL. The SNR of perfusion maps derived from the two techniques was also assessed and compared with theoretical expectations.

**MATERIALS AND METHODS**

**Simulations**

To test the hypothesis that VEPCASL would produce more accurate CBF estimates than standard PCASL in voxels supplied by multiple arteries, simulations of the general kinetic model for ASL\(^2\) were performed using Matlab (Mathworks, Natick, MA, USA). It was assumed that the simulated voxel was supplied by two arteries. Blood from the first artery had a fixed BAT, \(J_t\), equal to 1 second. The BAT of blood from the second artery was varied over the range of 0.5 to 2 seconds. The total CBF was fixed at 60 ml/100 g per minute, but the ratio of CBF contributed by the two arteries was varied between 1:4 and 4:1. The simulated PCASL signal was then calculated by summing the signals from these two arterial components.

Two different SNR regimes were simulated to ascertain whether the observed trends were a result of the perfusion signal being lost within the noise floor, or whether they represented systematic errors. Here, we define SNR using perfusion images that have been averaged over all repeats and all PLDs. The ‘signal’ is defined as the average gray-matter (GM) perfusion signal and the ‘noise’ as the standard deviation in a background region of interest. The two regimes tested were a ‘high’ SNR of 250, and a more realistic ‘low’ SNR of 30, comparable to that measured in our experiments (see Results). Note that to make the simulations as realistic as possible the interest. The two regimes tested were a ‘high’ SNR of 250, and a more realistic ‘low’ SNR of 30, comparable to that measured in our experiments (see Results). Note that to make the simulations as realistic as possible the

**Experiments**

Seven healthy volunteers (two female, mean age 28.9, range 25 to 37) were recruited and scanned on a 3T TIM Verio system (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. All experiments were performed under an agreed technical development protocol approved by the Oxford University Clinical Trials and Research Governance office, in accordance with International Electrotechnical Commission and United Kingdom Health Protection Agency guidelines. A 3D multiblab time-of-flight (TOF) angiography sequence was performed to enable labeling plane selection and vessel localization.

A schematic of the ASL pulse sequence is shown in Figure 1A. Both standard PCASL and VEPCASL acquisitions were performed in each subject and shared a common labeling plane positioned ~ 8 cm below the circle of Willis, through the proximal V3 segment of the vertebral arteries (VAs). In this plane, the four main brain-feeding arteries all run in the inferior–superior direction and form an approximately rectangular arrangement in the axial plane (Figure 1C). Other than the vessel-encoded preparation all parameters were kept constant between the two scans, as listed in Table 1. Pseudocontinuous ASL was achieved using 600\(\mu\)s duration Gaussian RF pulses once per ms over the labeling duration (\(\tau\)) of 1.4 seconds. A single-shot echo planar imaging readout was used with repetition time (TR) = 4.05 seconds and echo time (TE) = 14 ms. Slices were acquired sequentially from inferior to superior, giving whole brain coverage with voxel size = 3.4 \(\times\) 3.4 \(\times\) 5 mm. Images were acquired in separate blocks for six PLDs, ranging from 0.25 to 1.5 seconds, giving a total acquisition time of 6.5 minutes.

Background suppression was achieved by combining a water suppression enhanced through T\(_1\) effects presaturation module (similar to Goly et al\(\text{a}\)) applied to the imaging region with two global hyperbolic secant inversion pulses that followed the PCASL pulse train, which were timed\(\text{b}\) to perfectly null tissues with \(T_{1}\) equal to \(T_{1}\text{opt}\) or \(2T_{1}\text{opt}\). Due to the restricted time available to play out the global inversion pulses, \(T_{1}\text{opt}\) is bounded by an upper value that is PLD dependent. We therefore chose the largest \(T_{1}\text{opt}\) available up to a maximum of 500 ms (see Table 1), as used by Günther et al\(\text{c}\). Although this gives imperfect suppression of static tissue for some PLDS, simple simulations show that tissues with \(T_{1}\) greater than \(2T_{1}\text{opt}\) are still effectively suppressed (Figure 1B).

Vessel encoding of the right and left internal carotid arteries (ICAs) (RICA and LICA) and right and left VAs (RVA and LVA) was performed with eight paired encoding cycles (see Figure 1C): nonelective tag and control; two left–right encodings tagging first the arteries on the right while controlling those on the left, then tagging those on the left while controlling those on the right; two anterior–posterior encodings tagging first the anterior arteries while controlling the posterior arteries, then tagging the posterior arteries while controlling the anterior arteries; and finally two diagonal encodings where first the RICA and LVA were tagged while the LICA and RVA were controlled, then the LICA and RVA were tagged while the RICA and LVA were controlled.

Using the encoding matrix description of Wong\(\text{d}\), this set of encoding cycles gives rise to measured data in a single voxel, \(y\), such that for a perfectly rectangular arrangement of arteries within the labeling plane:

\[
y = Ax = \begin{pmatrix} -1 & -1 & -1 & -1 & 1 \\ -1 & 1 & 1 & 1 & 1 \\ -1 & -1 & 1 & 1 & 1 \\ -1 & -1 & -1 & 1 & 1 \\ -1 & 1 & -1 & -1 & 1 \\ 1 & -1 & -1 & -1 & 1 \end{pmatrix} \begin{pmatrix} R_{ICA} \\ L_{ICA} \\ R_{VA} \\ L_{VA} \\ 5 \end{pmatrix}
\]

where \(A\) is the encoding matrix and \(x\) is the vector of the signals arising from the right (R) and left (L) ICAs and VAs as well as static tissue (5). This encoding matrix is full rank and has a theoretical SNR efficiency equal to that of a standard PCASL acquisition because each artery is tagged and controlled for an equal number of times.\(\text{e}\) To ensure a fair comparison between VEPCASL and PCASL, the same number of volumes (96) was acquired for both techniques, meaning that a greater number of averages were acquired for PCASL at each PLD.

Additional calibration scans were acquired using identical imaging parameters to the PCASL and VEPCASL sequences, but with background suppression and labeling turned off and a longer TR (6 seconds). Three volumes after dummy scans were acquired in two separate calibration scans that used both the head coil and the body coil for signal reception.

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**Table 1. Parameters used for simulations, experiments, and analysis**

| Parameter                              | Value                                      |
|----------------------------------------|--------------------------------------------|
| Experimental                           |                                            |
| Radiofrequency (RF) labeling pulses    | Gaussian, 600 \(\mu\)s duration            |
| RF labeling pulse separation           | 1 ms                                       |
| Mean tagging gradient                  | 0.8 mT/m                                   |
| Tagging gradient during RF pulses      | 6 mT/m                                     |
| Labeling duration (\(\tau\))          | 1.4 seconds                                |
| Postlabeling delays (PLDs)             | 0.25, 0.5, 0.75, 1.0, 1.25, 1.5 seconds    |
| Background suppression \(T_{1}\text{opt}\) | 80, 170, 280, 390, 500, 500 ms\(^a\)       |
| Voxel size                             | 3.4 \(\times\) 3.4 \(\times\) 5 mm         |
| Matrix size                            | 64 \(\times\) 64                           |
| Partial Fourier factor                 | 6/8                                        |
| Echo time (TE)                         | 14 ms                                      |
| Number of slices                       | 24                                         |
| Time per slice                         | 45.2 ms                                    |
| Volume repetition time (TR)            | 4.05 seconds                               |
| Number of volumes                      | 96                                         |
| Acquisition time                       | 6.5 minutes                                |
| Analysis                               |                                            |
| Inversion efficiency                   | 0.88\(b\)                                 |
| Longitudinal relaxation time of tissue \(T_{1}\) | 1.3 seconds                              |
| Longitudinal relaxation time of blood \(T_{1}\) | 1.6 seconds                              |
| Blood/tissue water partition coefficient | 0.9 mL/g                                   |
| Longitudinal relaxation time of CBF \(T_{1c}\) | 4.3 seconds                               |
| Transverse relaxation time of CBF \(T_{2c}\) | 750 ms                                    |
| Transverse relaxation time of CBF \(T_{2c}\) | 50 ms                                     |
| Cerebral blood flow prior (mean \(\pm\) s.d.) | \(0 \pm 10^6\) mL/100 g per minute       |
| Bolus arrival time (mean \(\pm\) s.d.)  | 1.3 \(\pm\) 0.5 seconds                    |

CSF, cerebrospinal fluid; s.d., standard deviation.

*The chosen \(T_{1}\text{opt}\) value is dependent on the PLD. \(b\)Inversion efficiency determined via simulations of the Bloch equations (as per Okell et al\(\text{a}\)), assuming laminar flow with average velocity 30 cm/s.
Figure 1. (A) Schematic sequence diagram. Note that the timing of the first global inversion pulse is constrained by the (vessel-encoded) pseudocontinuous arterial spin labeling ((VE)PCASL) pulse train; (B) Simulated longitudinal magnetization at the start of the echo planar imaging (EPI) readout for postlabeling delay (PLD) = 1 second and optimum $T_1 (T_{1,\text{opt}}) = 390$ ms. Tissues at $T_{1,\text{opt}}$ and 2$T_{1,\text{opt}}$ are nulled perfectly but those with longer $T_1$ values are also largely suppressed; (C) A Time-of-flight (TOF) axial slice through the neck showing a typical labeling plane. The four main brain-feeding arteries are circled in color: red = right internal carotid artery (RICA), green = left internal carotid artery (LICA), blue = right vertebral artery (RVA), and magenta = left vertebral artery (LVA). For VEPCASL, left–right encodings contrast vessels aligned with line A versus those at line B, anterior–posterior encodings contrast lines C and D and diagonal encodings contrast lines E and F. Note that F is shown twice due to the periodic nature of the encoding function.

These calibration images allowed the PCASL and VEPCASL data to be corrected for the uneven spatial sensitivity profile of the head coil and facilitated calibration of CBF in absolute units (see ‘Processing’ section). A $T_1$-weighted structural image was also acquired for registration and tissue segmentation.

Processing

A schematic of the processing stages is shown in Figure 2. The PCASL and VEPCASL raw images were motion corrected using the head coil calibration image as a reference, before averaging across repeats. A pairwise control minus tag subtraction was then performed on the PCASL data to generate a perfusion image at each PLD. The separation of signals arising from each feeding artery in the VEPCASL data was performed using a maximum a posteriori (MAP) solution (method BT) to the general Bayesian framework with two vessels per class. This approach can account for rigid subject motion between the planning TOF and VEPCASL acquisitions. For the purposes of the SNR comparison, this processing was repeated with a matrix inversion (MI) approach (see TOF and VEPCASL acquisitions).

The calibration images were time averaged before dividing the head coil image by the body coil image to give an estimate of the receive coil sensitivity map. This map was used to correct the perfusion and head coil calibration images to prevent bias in the final quantitative parameter maps.

Signal calibration was performed using cerebrospinal fluid (CSF) as a reference (similar to MacIntosh et al. First, a standard (MNI152) space ventricle mask was nonlinearly registered to the subject’s structural image, followed by linear registration to the ASL calibration image and slight erosion to prevent partial volume effects. The mean CSF signal within the ventricles was calculated and corrected for the $T_1$ and $T_2^*$ of CSF at the TR and TE used, to determine the equilibrium magnetization, $M_0,\text{CSF}$. This value was corrected for the $T_2^*$ and relative proton density of blood, the density of brain tissue (to allow CBF quantification in units of mL/100 g per minute), and the inversion efficiency of the PCASL pulse train (see Table 1), to obtain an estimate of the effective equilibrium magnetization of blood, $M_{b,\text{eq}}$. Note that the appropriate $T_2^*$ value used to correct $M_{b,\text{eq}}$ depends on whether the labeled water still resides in the vascular compartment, or whether it has exchanged into tissue. In practice, these values do not yield a significantly different result at the short TE used for this experiment. The PCASL and VEPCASL perfusion images were divided through by the effective $M_{b,\text{eq}}$ value to complete the calibration.

A nonlinear fit to the general ASL kinetic model was performed for all voxels within a brain mask using a variational Bayes approach, accounting for the differences in acquisition time across the slices. To minimize the TE, flow crushers were not used in these experiments. As a result, the macrovascular component of the signal, which describes blood that is passing through but not contributing to perfusion in that voxel, was modeled as part of the analysis, preventing bias in the resulting CBF estimates. For the VEPCASL data, fitting was performed for each feeding artery separately. This analysis produces maps of absolute CBF and BAT and their associated uncertainty in the form of a variance value in each voxel for each parameter. To obtain a single BAT image from VEPCASL data to simplify subsequent analyses, the ‘weighted BAT’ was calculated in each voxel by summing the BAT from each feeding artery weighted by the CBF fraction contributed by that artery.

Segmentation of white matter, GM, and CSF was performed using the structural image. The resulting GM partial volume estimate was transformed into the space of the ASL data before being thresholded at 0.5 to generate a GM mask for use in subsequent analyses.

Statistics

To determine whether there was any systematic bias in the total CBF estimates derived from VEPCASL compared with those from PCASL, a linear regression was performed on each subject for all voxels within a whole brain mask. Due to the relatively high and variable uncertainty on both
CBF estimates, standard linear regression tools, which minimize the sum of squared differences between two variables, are not appropriate. We therefore chose to minimize a modified version of the $w^2$ function, defined as:

$$w^2 = \sum_{\text{voxels}} \frac{(f_{\text{VEPCASL}} - (m_{\text{PCASL}} + c))^2}{s^2_{\text{VEPCASL}} + m^2 s^2_{\text{PCASL}}}$$

where $f$ and $s$ are the total CBF estimate and its uncertainty, respectively, derived from PCASL or VEPCASL data, and $m$ and $c$ are the fitted slope and intercept of the line of best fit, respectively. The numerator represents the square of the difference between the observed and expected VEPCASL CBF estimate, and the denominator is the square of the uncertainty in this difference. If the two CBF estimates are equivalent, then we expect $m \approx 1$ and $c \approx 0$.

**Figure 2.** Overview of the processing performed to obtain quantitative cerebral blood flow (CBF), CBF uncertainty and bolus arrival time (BAT) maps from the vessel-encoded (VE) and standard pseudocontinuous arterial spin labeling (PCASL) data. The VEPCASL data give rise to one map per feeding artery, but these are shown together here for brevity. Partial volume estimates (PVEs) derived from the structural image were used to generate a gray matter (GM) mask used in subsequent analyses (see Results). Time-series data are represented with three dots. Various FMRIB Software Library (FSL) tools were used for brain extraction (BET), linear (FLIRT) and non-linear (FNIRT) registration, motion correction (MCFLIRT), segmentation (FAST) and non-linear model fitting of ASL data (BASIL).
Comparison of the SNR of each technique was performed using perfusion images, considering each VEPCASL vascular territory image separately and averaging over all repeats and PLDs. The mean perfusion signal was calculated within the GM mask, and divided by the standard deviation of the noise in a background region of interest. Since each vascular territory only covers a portion of the brain, the mean signal was only calculated in those GM voxels where the feeding artery under consideration was the dominant supplier (i.e., contributed the highest mean signal of all the feeding arteries). To ensure a fair comparison, the PCASL SNR was calculated using an identical mask for each vascular territory. Finally, a separate comparison was performed in which the VEPCASL data were first summed across all feeding arteries before the SNR was calculated within all GM voxels.

RESULTS

Examples of results from the simulations are shown in Figure 3A. As expected, when the BATs of the two arterial components feeding the simulated voxel are equal, the PCASL perfusion signal (total) has the same shape as the two VEPCASL signals (components 1 and 2), resulting in an accurate estimation of CBF. However, when there is a difference in the BAT between the two components, an accurate CBF estimate can no longer be extracted from the PCASL data. For VEPCASL, the two components are fitted separately, so the total CBF estimate is unaffected and remains accurate.

A summary of the simulation results is shown in Figure 3B. In the high SNR regime, PCASL systematically underestimated the CBF when the difference in arrival time between the two arterial feeders was greater than ~0.25 second. The CBF error was greater when the delayed component contributed a larger amount to the total perfusion: errors up to 37% were found to occur over the range of parameters tested here. In contrast, VEPCASL produced accurate CBF estimates over the entire range of parameters tested here when the SNR was high. The standard deviation in the total estimated CBF increases when one arterial component is considerably delayed because this component experiences a greater degree of $T_1$ decay, lowering the SNR. In addition, when the delay is considerable, many of the simulated data points occur before the delayed blood has arrived, reducing the average perfusion signal and therefore increasing the error in the CBF estimate.

Similar trends were seen in the more realistic ‘low’ SNR regime. The systematic underestimation of CBF was the same for PCASL, although the spread of results is greater due to the higher noise level. Vessel-encoded pseudocontinuous ASL produced reasonable accurate CBF estimates for small differences in the BAT of the two arterial components, although when blood from one artery was delayed by more than ~0.6 second, there was an underestimation of the total CBF. However, the mean errors were considerably smaller than those for PCASL and do not appear to have a strong dependence on the CBF ratio contributed by the two arterial components.

Example perfusion images at each PLD are shown in Figure 4 for both PCASL and VEPCASL in the same subject. In this subject, the right anterior cerebral artery territory is supplied by both the RICA and the LICA. In the highlighted voxel, it can be seen that blood from the RICA is somewhat delayed relative to blood from the LICA, causing PCASL to underestimate the CBF here. However, in these healthy volunteers there were few such voxels showing significant differences in the BAT: for voxels within the brain masks only 2.0% had significant ($P < 0.01$) perfusion from more than one artery and BAT differences greater than 0.5 second. This value decreases to 0.3% for BAT differences greater than 1 second.

Figure 5A shows example VEPCASL and PCASL CBF maps in each subject, highlighting the good image quality obtained in all cases and the qualitative similarity between the two methods. An example of the correlation analysis performed in one subject is shown in Figure 5B, showing the high degree of correlation between the CBF estimates of the two methods and a line of best fit that is very close to the ideal line of equality. In voxels fed by multiple arteries with a BAT difference of greater than 0.5 second it can be seen that there is a tendency for PCASL to underestimate the CBF, as expected from the simulations above. These voxels are therefore excluded from the correlation analysis.

A comparison of the SNR between PCASL and VEPCASL perfusion images is shown in Figure 6. When MAP processing...
was used, the SNR of VEPCASL was equivalent to PCASL in territories supplied mainly by one artery (ICAs), but lower in territories with mostly mixed supply (VAs). In addition, perfusion maps resulting from the MI processing had lower SNR than those obtained with MAP processing.

When the perfusion signals from all feeding arteries were summed, somewhat counterintuitively the SNR of VEPCASL decreased to about half that of PCASL. However, this effect did not appear to propagate through to the total CBF estimates: there was no significant difference in the standard deviation of the total CBF within GM, averaged across subjects, between the two methods (29.2 mL/100 g per minute for PCASL versus 29.5 mL/100 g per minute for VEPCASL, \( P = 0.57 \)).

**DISCUSSION**

In this study, we have shown that VEPCASL is a viable alternative to PCASL for CBF quantification, but with the added benefit of vessel-selective information: simulations showed that VEPCASL can produce more accurate CBF estimates in regions with mixed supply and experimentally the two methods gave identical CBF estimates with comparable SNR in the same scan time.

Figure 3 shows that considerable errors can arise in standard ASL acquisitions when a voxel is fed by multiple arteries with different BATs, as might be the case in patients with collateral flow. Vessel-encoded pseudocontinuous ASL does not have this systematic underestimation since both boluses are accurately modeled. However, in a realistic SNR regime both methods begin to underestimate the CBF when the BAT of one feeding artery is delayed. The correlation between the two methods appears to be strong (Figure 5B), with lines of best fit having gradients close to one (Figure 5C). However, in the minority of voxels with very low perfusion, the underestimation of CBF by PCASL predicted in simulations was apparent. The small deviations from equality in other voxels could arise from minor registration errors as well as from the noise in the data. These fits also have very small intercepts (<10^-6 mL/100 g per minute) which could, in part, be due to a number of voxels within the brain mask having zero, or very little, perfusion (e.g., in the ventricles or at the edges of the brain).

The SNR of VEPCASL with MAP processing was found to be equal to that of PCASL in voxels supplied by a single artery (within the ICA territories), as was expected from the ideal encoding matrix (Equation 1). In the VA territories, the SNR of VEPCASL was a little lower than that of PCASL. This might be expected, since the two VAs fuse to form the basilar artery that supplies the two posterior cerebral artery territories. Thus, many of the voxels fed by one VA have significant contributions from the other VA, decreasing the mean signal from each and therefore the SNR. Due to nonideal vascular geometry in some subjects, the actual encoding matrix deviated from the ideal case, lowering the SNR obtained with an MI approach. However, much of this is regained...
with the Bayesian MAP technique, which considers only a subset of the encoding matrix at a time, helping to boost the SNR.24 However, when the perfusion signals from each artery are summed, the SNR of VEPCASL decreases to about half that of PCASL. This is because when the VEPCASL images are summed, the total ‘true’ perfusion signal is also summed, thereby giving the same total signal as the PCASL data. However, the noise present in each VEPCASL perfusion image is approximately equal to that in the PCASL perfusion image. Thus, for four feeding arteries the noise variance of the summed image is four times that of the individual VEPCASL perfusion images, and thus the SNR is halved. Therefore, a simple summation of the raw VEPCASL perfusion signals is detrimental to image quality.

Interestingly, this effect does not appear to propagate through to the total CBF estimates in the same way. The standard deviation of the total CBF in GM was not significantly different for VEPCASL and PCASL. Clearly, this measure encompasses CBF variations due to partial volume effects and natural variability. However, if there was a considerable difference in the uncertainty of the total CBF, then it would be expected that the standard deviation would be higher for VEPCASL. The similarity in the standard deviation of both techniques may be attributable to the kinetic model fitting procedure. Arterial components that do not contribute to perfusion are effectively suppressed by the zero-mean CBF prior. Therefore, since most voxels are only supplied by one artery, the uncertainty in the total CBF is approximately equal to the uncertainty in the dominant arterial component, which is comparable to that of PCASL.

Given these results, it is expected that the VEPCASL technique would be particularly useful for CBF quantification in patients with stenosis or occlusion of the proximal brain-feeding arteries. The ability of VEPCASL to separate out the signals arising from each feeding artery should allow more accurate CBF quantification in regions of mixed supply, which may arise due to collateral flow.

Figure 5. Comparison of cerebral blood flow (CBF) estimates from vessel-encoded (VE) and standard pseudocontinuous arterial spin labeling (PCASL): (A) Central slice of the CBF map for each subject in this study (in units of mL/100 g per minute) with VEPCASL images shown as separate components (in color) as well as summed across all feeding arteries, to aid comparison; (B) Correlation between the two methods for one subject for all voxels within a brain mask with the ideal equality line and line of best fit overlaid (note that PCASL tends to underestimate the CBF in voxels supplied by multiple arteries whose bolus arrival time (BAT) differences are greater than 0.5 second, plotted separately here); (C) Gradient of the line of best fit for each subject. Intercept values are too small to be shown here (< 10^-6 mL/100 g per minute).
could cause problems when analyzing magnitude images since inverted blood flowing in will add to, rather than subtract from, the magnitude of the total measured signal, leading to a negative perfusion signal. For the maximum value of $T_{1,opt}$ used here (500 ms) white matter, with $T_1$ approximately equal to 1 second at 3 T, will be close to this problematic region for some PLDs. However, this value of $T_{1,opt}$ has previously been used successfully for ASL experiments, probably because we are primarily interested in the perfusion of GM, which has a longer $T_1$. In addition, since $T_1$ recovery continues during the readout, inverted tissue magnetization will become positive in later slices. Simulations similar to those in Figure 1B reveal that for the timings used in this study inverted tissue magnetization is only present within the first slice, with all other slices containing only positive tissue magnetization.

In the simulations, it was assumed that the PCASL data were always fitted using a single vascular component model. Fitting two components could have resulted in improved CBF estimates. However, as can be seen in Figures 3A and 4B, the summed signal from two components is difficult to distinguish from a single component, particularly in the presence of noise. In addition, the number of arteries contributing to the perfusion in a given voxel would not be known a priori, so the practical implementation would be difficult.

Although it has been shown that VEPCASL can produce more accurate estimates of CBF in regions of mixed supply, this is only the case when each arterial source has been separately encoded at the labeling plane. For the encoding scheme used in this study, this will allow more accurate CBF quantification in the presence of primary collateral flow around the circle of Willis. However, in voxels supplied by multiple arterial branches distal to the circle of Willis (e.g., two branches of the right middle cerebral artery), the different boluses would not be distinguished.

Finally, the fitting procedure used the simplest version of the general kinetic model. The incorporation of dispersion information, either using estimates from angiographic data or by fitting to the data directly, might help improve the accuracy of CBF quantification. Additionally, more complex kinetic models could be used that account explicitly for microvascular and tissue compartments and the finite permeability of the capillary bed.

To conclude, we have shown in this study that VEPCASL produces the same CBF estimates as standard PCASL with comparable SNR, but with the addition of vessel-selective information. Simulations showed that this would improve CBF estimates in regions supplied by multiple arteries, such as those partially fed by collateral flow. The only significant disadvantages of this method are increased complexity in the acquisition set-up and image processing, along with the potential for increased sensitivity to subject motion.

DISCLOSURE/CONFLICT OF INTEREST
MAC and TWÖ are authors of a pending US patent licensed to Siemens Healthcare (Erlangen, Germany) relating to the MAP processing technique used in this study.

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