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Determining the Optimal Postlabeling Delay for Arterial Spin Labeling Using Subject-Specific Estimates of Blood Velocity in the Carotid Artery

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Abstract

Background: Arterial spin labeling with 3D acquisition requires determining a single postlabeling delay (PLD) value. PLD affects the signal-to-noise ratio (SNR) per unit time as well as quantitative cerebral blood flow (CBF) values due to its bearing on the presence of a vascular signal.

Purpose: To search for an optimal PLD for pseudocontinuous arterial spin labeling (pCASL) using patient-specific carotid artery blood velocity measurements.

Study Type: Prospective.

Subjects: A control group of 11 volunteers with no known pathology. Corroboration was through a separate group of six volunteers and a noncontrol group of five sickle cell disease (SCD) patients.

Field Strength/Sequence: Pseudocontinuous arterial spin labeling with 3D nonsegmented echo planar imaging acquisition at 3T.

Assessment: A perfusion-based measure was determined over a range of PLDs for each of 11 volunteers. A third-order polynomial was used to find the optimal PLD where the defined measure was maximum. This was plotted against the corresponding carotid artery velocity to determine a relationship between the perfusion measure and velocity. Corroboration was done using a group of six volunteers and a noncontrol group of five patients with SCD. PLD was determined from the carotid artery velocity and derived relationship and compared with optimal PLD obtained from measured perfusion over a range of PLD values. Error between the perfusion measure at predicted and measured optimal PLD was determined.

Statistical Tests: Chi-squared goodness of fit; Pearson correlation; Bland–Altman.

Results: Carotid artery velocity was 63.8 ± 6.6 cm/s ($53.1 < v < 72.3$ cm/s) while optimal PLD was 1374 ± 226.5 msec ($1102 < \text{PLD} < 1787$ msec) across the 11 volunteers. PLD as a function of carotid velocity was determined to be $\text{PLD} = -31.94 \cdot v + 3410$ msec (Pearson correlation -0.93). In six volunteers, mean error between the perfusion measure at predicted and measured optimal

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PLD was 1.35%. Pearson correlation between the perfusion measure at the predicted PLD and the measure obtained experimentally was $r = 0.96$ ($P < 0.001$). Bland–Altman revealed a slight bias of 1.3%. For the test case of five SCD patients, the mean error was 1.3%.

Data Conclusion: Carotid artery velocity was used to determine optimal PLD for pCASL with 3D acquisition. The derived relationship was used to predict optimal PLD and the associated perfusion measure, which was found to be accurate when compared with its measured counterpart.

Level of Evidence: 2

Technical Efficacy Stage: 1

Arterial spin labeling (ASL)¹ provides noninvasive measurements of cerebral blood flow (CBF) by using labeled blood as an endogenous contrast agent. In addition, repetitive measurements of cerebral perfusion can be performed without the use of a contrast bolus injection, which is useful for evaluating temporal changes. Measurement of cerebral perfusion can provide unique information not achievable with other magnetic resonance imaging (MRI) contrasts in a number of clinical situations, eg, differentiation of tumor recurrence from radiation necrosis.

Both qualitative and quantitative ASL pose limitations in clinical use. Qualitative evaluation of ASL images has been hampered by differences in transit time delay, which can result in a vascular signal confounding tissue perfusion.^{2–4} Use of bipolar crusher gradients can remove the vascular signal but results in lower-quality perfusion maps due to loss of signal. This can impact the appearance of vascular pathologies such as slow flow states associated with infarction or high flow states associated with arteriovenous malformations. Quantitative MRI is hindered by inaccuracies in measurement of fully relaxed tissue signal, efficiency of the labeling sequence, T_1 differences between blood and tissue, as well as transit delay between the tagged blood in arteries and its arrival in tissue. Accurate determination of gray matter (GM) perfusion requires a postlabeling delay (PLD) sufficiently long to allow all tagged blood to move from the arteries into the tissue, but not so long as to suffer signal-to-noise ratio (SNR) loss from T_1 decay. Strategies for reducing transit delay include minimizing the distance between the tagging and imaging planes but is successful only if the imaging section is thin. Volumetric imaging of the brain still experiences substantial transit delays. Multiple PLD using a Look–Locker acquisition after a single ASL preparation can be used to determine inflow dynamics and remove the macrovascular component of the ASL signal.^{5–7} Alternatively, Hadamard encoding of the labeling bolus can also be employed with images acquired after different temporal tagging and control encoding of the bolus.⁸ Images can then be processed to derive CBF maps with different transit delays.

Pseudocontinuous arterial spin labeling (pCASL) with centric encoded nonsegmented 3D acquisition provides higher SNR^{9–12} and improves CBF quantification as the PLD is consistent throughout the image (defined by the end of labeling to the $k_z = 0$ acquisition). PLD is typically set to longer values in the absence of a priori knowledge. For example, a recommended value for adults is 1800 msec. However, since the ASL signal decays with time constant T_1 after labeling, a conservative choice for PLD can prove expensive in terms of SNR.¹³ (Typically, ASL is an SNR-starved application.) Therefore, determining an optimal PLD is advantageous. PLD has a dependency on the physiological state of an

individual.¹⁴⁻¹⁷ Therefore, a patient-specific method for determining the optimal PLD is desired. Liu et al¹⁶ showed that CBF and blood transit times were compromised by aging and that females had shorter arteriole transit times than males. Blood velocities in carotid arteries are typically higher in females than males and decreases with age.^{18,19} We therefore hypothesized that blood velocity in the carotid artery had a bearing on the transit time and could be used as a surrogate for determining optimal PLD in an expedient manner. In this work, our purpose was to establish a relationship between blood velocity in the carotid artery as measured using phase contrast velocity mapping and the optimal PLD. The method might be easily adapted for clinical use with only a marginal increase in scan time.

Materials and Methods

Perfusion Signal

In the absence of strong magnetization transfer effects, the relationship between the CASL or pCASL signal and tissue perfusion, transit time, and efficiency of tagging can be given by²⁰:

$$\Delta M = 2M_t \cdot \alpha \cdot \beta \cdot T_1 \cdot f \cdot e^{-\delta/T_{1a}} \cdot \left[e^{-\frac{\max(w-\delta,0)}{T_1}} - e^{-\frac{\max(\tau+w-\delta,0)}{T_1}} \right] / \lambda \quad (1)$$

In the above equation, M_t refers to the magnetization of completely relaxed tissue, f is the perfusion rate, α is the tagging efficiency of the sequence, β refers to the loss of signal if vascular crushing is employed, λ is the tissue to blood partition coefficient of water, δ is the transit time, τ is the labeling duration, T_{1a} and T_1 are the longitudinal relaxation times for arterial blood and tissue, respectively, and w is the PLD.

Perfusion Measure

The SNR efficiency measure, $SNR_{eff} = \Delta M / \sqrt{T_{scan}}$ has been used previously²¹ for optimization of labeling parameters. For a single voxel, the measure is maximized when $w = \delta$. For a 3D volume, voxels exhibit a range of transit times.

Considering a range of transit times (δ_i), SNR_{eff} is plotted in Fig. 1 as a function of w . Assumed relevant parameters were $T_{1a} = 1660$ msec, $T_1 = 1500$ msec, $\tau = 1650$ msec, $T_{acq} = 850$ msec, $T_{shot} = \min$.

First, a simpler case of three voxels with different transit times ($\delta_i = 400, 1200, 2000$) msec is considered. For individual transit times, the value of SNR_{eff} is maximum when PLD is at the corresponding transit time. When the cumulative signal from the three voxels is calculated, the single PLD where the value is maximum (dashed line) provides a value shorter than the longest transit delay. Generalizing the calculation for a range of transit delays between 400 msec and 2000 msec shows a similar result (Fig. 1, integral value). The PLD determined from SNR_{eff} then provides a vascular signal for a large range of voxels (with transit times to the right of the dashed line in Fig. 1).

Modified Perfusion Measure

For our case of nonsegmented 3D acquisition, a single w needs to be determined based on a measure of the global perfusion signal. A modified function, $SNR_w = e^{w/T_1} \times SNR_{eff}$ provides an accurate measure for determining optimal PLD. This is seen from Fig. 2 for the same range of transit delays used above. Parameters used for the simulation were the same as used for SNR_{eff} . For the case of three transit delays, the cumulative measure for SNR_w provides optimal delay at the longest transit time, $\delta = 2000$ msec. For a full range of transit delays between 400 msec and 2000 msec, the optimal PLD again corresponds well with the longest delay, thereby reducing any vascular contribution to the perfusion signal. All constant parameters were the same for both simulations (SNR_{eff} and SNR_w).

Scanning

All volunteers and patients were scanned under an Institutional Review Board (IRB)-approved protocol after obtaining informed consent. Eleven volunteers (6 M, 5F; age: 42 ± 12.9 years; 24 age 63 years) were scanned on a 3T Philips Achieva TX scanner (Best, Netherlands) using an 8-channel head coil.

In addition, six volunteers (2 M, 4F; age: 40.8 ± 14.3 years; 23 age 57 years) were used to corroborate the relationship between carotid velocity and optimal PLD.

Furthermore, five participants with sickle cell disease (SCD) were enrolled under this IRB-approved protocol. A quarter of SCD patients experience stroke by age of 45 years, at least in part due to the development of vascular stenosis and occlusions as a manifestation of SCD vasculopathy.²² Therefore, SCD patients were deemed appropriate to verify if the relationship extended to a noncontrol group susceptible to cerebrovascular disease and compromised CBF. Demographic and relevant data for the five patients are provided in Table 1.

Velocity Measurement

Velocity in the common carotid artery was determined using phase contrast (PC) imaging. The following scan parameters were used: field of view (FOV) = 23 cm, resolution = 1 mm^2 , repetition time / echo time (TR/TE) = 20/6.3 msec, maximum velocity = 100 cm/s, flow compensation, $\theta = 15^\circ$, number of signal averages (NSA) = 2, scan time: 37 sec. A single slice was placed perpendicular to the carotid arteries. Regions of interest (ROIs) were drawn in the left and right carotid arteries.

ASL Measurement

The pCASL sequence with nonsegmented 3D echo planar imaging (EPI) acquisition had the following scan parameters: pCASL: label duration (τ) = 1.65 sec, PLD (w) = 600–2000 msec (2200 msec for SCD patients) in steps of 200 msec; FOV = 24×20 cm, resolution $3 \times 3 \times 4 \text{ mm}^3$, EPI TR/TE = 22/11 msec, centric k_z encoding, SENSE (y) = 2.5, 32 slices, spectral-spatial excitation pulse $\theta = 25^\circ$ with optimal flip angle train for reduced blurring,^{11,23} 10 dynamic pairs, scan time: ~1 min to 1 min 30 sec. Two background suppression adiabatic inversion pulses were used so that GM and cerebrospinal fluid tissue suppression was approximately equal for all delay times.

GM Imaging

A 3D MPRAGE sequence provided higher resolution images for GM segmentation. The following parameters were used: FOV = 24 cm, axial orientation, SENSE (y, z) = 2, $\theta = 12^\circ$, resolution = 1 mm³, scan time: 4 min.

Analysis

All images were transferred offline and processed using MatLab code (MathWorks, Natick, MA). Optimal PLD was determined using the following steps:

1. Acquire pCASL images at values of PLD $\in [600, 800, \dots, 2000]$ msec.
2. Register all ASL images to the first acquired image using the Statistical Parametric Mapping tool (SPM-12, Wellcome Trust Center for Neuroimaging, London, UK).
3. Register 3D MPRAGE images to ASL images and generate a GM mask.
Calculate defined function SNR_w for all δM in the entire GM for each PLD $\in [600, 800, \dots, 2000]$ msec. Exclude voxels with signal greater than one standard deviation above mean.
4. Plot SNR_w vs. PLD and fit a third-order polynomial for a smooth fit.
5. Ascertain PLD for which SNR_w is maximum.
6. Correlate optimal PLD to PC velocity.
7. All curve fitting was checked for statistical significance for χ^2 goodness of fit (SNR_w vs. PLD) or Pearson correlation (PLD vs. PC velocity).

In six noncontrol volunteers, the derived relationship was used to predict the optimal delay time post-PC velocity mapping. pCASL images were acquired at the predicted optimal PLD. CBF measure (SNR_w) at this predicted PLD was corroborated against maximum SNR_w obtained by plotting SNR_w vs. PLD. Error between SNR_w at predicted optimal PLD and calculated optimal SNR_w from measured SNR_w vs. PLD was recorded. In addition, Pearson correlation was determined between the two measures. Bland–Altman analysis was performed by plotting the difference against the mean of the values and was used to determine bias and limits of agreement.

In the five SCD patients, error between the two SNR_w measures defined above was determined.

Results

Determination Study

A third-order polynomial provided excellent fit (χ^2 fit; not significantly different with $P < 0.01$) for SNR_w vs. PLD in all cases. Mean optimal delay for the 11 volunteers was 1374 ± 226.5 msec (1102 PLD 1787 msec). Mean carotid velocity was 63.8 ± 6.6 cm/s (53.1 ± 72.3 cm/s). Figure 3 shows an example plot of SNR_w vs. PLD in two volunteers. The optimal PLD was 1603 msec and 1551 msec, respectively.

Figure 4 shows the ASL images obtained in an individual, corresponding to optimal PLD = 1603 msec, for a range of delay times. While ASL images obtained at PLD < 1.6 sec show increased vascular signal, images with PLD > 1.6 sec exhibit lower perfusion signal. Figure 5 shows segmented GM ASL images for every fifth of the 32 slices obtained in a volunteer. Optimal PLD plotted against maximum carotid artery velocity for 11 volunteers is shown in Fig. 6. Pearson correlation (r) for a linear fit was -0.93 . Optimal delay as a function of velocity can be calculated using:

$$PLD = -31.94 \times v + 3410 \text{ msec}$$

Prediction Studies

For the six volunteers used in the corroboration study, predicted PLD resulted in mean perfusion measure reduction by 1.35% compared with the maximum. Pearson correlation (Fig. 7a) showed a significant relationship between the two measurements ($r = 0.98$, $P < 0.001$). Bland–Altman analysis (Fig. 7b) provided a bias of 1.33% with the CBF measure being lower at the predicted PLD when compared with measured maximum CBF measure. 95% limits of agreement were -0.048 to 0.09 (mean of optimal CBF measure over six subjects = 1.57).

In the five sickle cell patients, predicted optimal PLD resulted in mean perfusion measure reduction by 1.33% compared with the maximum (0.05% error 2.1%). Mean optimal PLD was 1538 ± 208 msec. Figure 8 shows CBF maps obtained in an SCD patient with an old external (cortical) watershed infarct at the border zone of the right anterior and middle cerebral artery territories. Maps obtained at the optimal delay (Fig. 8b) are compared with maps obtained at PLDs ~ 200 msec shorter (Fig. 8a) and 200 msec longer (Fig. 8c) than the optimal PLD. CBF maps for a patient with preserved patency of the right posterior cerebral artery, multiple intracranial stenosis and occlusions, development of Moyamoya collateralization, and severe internal (deep) watershed infarcts are shown in Fig. 9. Stenosis and collateral flow result in varying delays to different vascular territories, so that there is no unique optimal delay for the entirety of the brain. Vascular signal persists at much longer PLDs (>2200 msec), while tagged spins washout from other regions of the brain. Nevertheless, images obtained at the predicted optimal delay show lower global vascular signal than at other shorter and longer PLDs.

Discussion

The relationship derived here is not restricted by duration of a clinically feasible PLD but reflects the optimal delay based on the perfusion measure. In the case of SCD patients with compromised vasculature, longer delay times can still be suboptimal since tagged spins from territories with shorter transit times undergo relaxation in addition to gradual washout from the capillary bed. In such a case, the CBF measure provides the best compromise between two conflicting processes.

The function SNR_w is truly bimodal, but given the unknown inflection point, a unimodal third-order polynomial provides an approximation. Given that the mean reduction in peak

SNR_w is 0.76% for a ± 100 msec difference from estimated optimal PLD, such an approximation works well. Nevertheless, sampling the delay time at closer intervals could have improved estimation of optimal PLD by allowing for a bimodal model.

On the other hand, prescribing a recommended PLD of 1800 msec¹³ results in a CBF SNR loss of 11.8% (maximum 48%) in volunteers and 3.9% (maximum 11.4%) across the five SCD patients.

A practical technique for determining the optimal PLD can provide CBF maps with the highest SNR/time. Multiple PLD using Look–Locker acquisition^{5–7} or Hadamard-based techniques⁸ show lower sensitivity to perfusion per unit acquisition time of the time series when compared with an image acquired with a single optimal time delay. In addition, such techniques may not be feasible for nonsegmented 3D acquisition with full brain coverage. Another technique employed use of multiple PLDs with lower resolution images to determine transit times and therefore the optimal PLD.²¹ The total time required for such a prescan (prior to a higher resolution ASL scan) was ~7 minutes. One assumption was that spatial variation in transit times has inherently low spatial resolution since neighboring voxels typically share arterial supply.

Labeling efficiency and flow velocity were assumed to be constant for a subject during the duration of each study. There was better correlation between maximum of the velocities in the two carotids and optimal PLD. This is related to velocity measurements being more accurate (and higher) for ROIs placed perpendicular to the vessel. 3D PC imaging or two separate single slice PC acquisitions could be used to mitigate this problem at the expense of increased scan time. PC velocity measured in this work was the averaged velocity over the entire cardiac cycle and could show some variation based on heart rate. However, PC-based velocity mapping is more likely to suffer from inaccuracies arising from ROI placement, concomitant gradient correction based on slice positioning,²⁴ residual eddy currents,²⁵ and correction for gradient nonlinearity.²⁶ Therefore, the relationship between velocity and optimal PLD could differ across scanners. Velocity gradient over the length of the carotid arteries would also result in errors. Consistent slice positioning away from carotid bifurcation (to avoid turbulent flow-related errors) was done to reduce this error.

A more accurate determination of transit time could be done using finite element analysis of a geometric model of the vascular tree obtained from anatomical MR images.²⁷ As a zeroth-order approximation, flow velocity in the external carotids has been used, since determining velocities in the larger arteries can be done more accurately by avoiding partial volume effects. In addition, the vertebral artery blood velocity was not considered. The carotid artery accounts for about 72% of CBF to the brain, while only 28% can be attributed to vertebral artery supply.²⁸ In addition, measurement error due to partial volume effect would be higher in vertebral arteries due to their smaller cross-sectional areas. Since the impetus of our work was to provide a quick technique to estimate PLD on the fly, carotid artery velocity served as a proxy for total CBF.

White matter (WM) CBF was not considered in the calculation of PLD since WM ASL signal is not reliable due to poor SNR and heterogeneous transit time.²⁹ One work showed

that 70% of WM voxels showed a significant signal after 10 minutes of scanning, while 150 averages (and a considerably longer scan time) were needed to detect signal in deep WM.³⁰

Dependent and independent factors such as vessel diameter and resistance, blood viscosity, among other parameters, could likely influence transit delay and were not independently considered in this study. Collateral flow in the carotid artery as well as increased vessel tortuosity with aging can affect velocity determination, and therefore the relationship between carotid artery blood velocity and optimal PLD. In addition, transit times increase with carotid occlusion³¹ and can confound determination of the optimal transit delay. However, limited application of our technique in SCD patients, two of whom had Moyamoya disease, provided CBF maps with reduced vascular signal compared with maps obtained at other PLDs. Furthermore, the CBF maps of the vascular territories corresponding to the distribution of the normal feeding vessels appeared to be absent of arterial signal. Therefore, the presence of arterial signal in the CBF maps accurately indicates the presence of delayed circulation.

The relationship between carotid blood velocity and PLD was established based on scanning 11 volunteers on a single scanner. Corroboration was done in a limited number of patients susceptible to cerebrovascular disease. The relationship obtained may not be reflective of the entire patient population with cerebrovascular diseases. In addition, volunteers were not controlled for caffeine use and their physiological state was assumed constant during the duration of each study (~25 min).

In conclusion, a relationship between carotid blood flow velocity (determined by PC imaging) and optimal PLD for pCASL was derived in this work. To our knowledge, this allows for the most time-efficient way (adding less than a minute to total scan time) to determine optimal PLD on a per-subject per-scan basis and is particularly suitable for 3D ASL of the entire brain.

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FIGURE 1:

Plot illustrates $\text{SNR}_{\text{eff}} = M / T_{\text{scan}}$ for several different transit times (δ). The measure for three different transit times ($\delta = 400, 1200, 2000$ msec) shows an inflection at $\delta = 400$ msec resulting in a suboptimal PLD which would result in a vascular signal. For a range of transit times $\delta \in [400, 2000]$ msec, a similar behavior is seen where inflection point is much lower than 1000 msec and would be suboptimal.

FIGURE 2:

$SNR_w = \Delta M \times e^{\frac{w}{T_1}} / \sqrt{T_{scan}}$ is illustrated for the same conditions as in Fig. 1. For three different transit times as well as for an entire range of transit times, the inflection point occurs at the longest transit time, and therefore provides the optimal PLD.

FIGURE 3: SNR_w measured in GM as a function of PLD time for two volunteers. Optimal PLD was determined to be 1603 msec (top) and 1551 msec (bottom) for the two volunteers, respectively.

FIGURE 4:
GM ASL maps obtained with different delay times for the volunteer with optimal delay of 1603 msec. Window/level is the same for all images. Scan time: 2:30.

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FIGURE 6:

Plot shows the optimal PLD as a function of velocity estimated by the two methods. The function fits given by equation: $PLD (msec) = A \cdot v + B$ where $A = -31.94$, $B = 3410$ and v is velocity as determined by PC imaging; Pearson $r = -0.93$ ($P < 0.001$).

FIGURE 7:

Agreement between perfusion measure at predicted optimal PLD and at measured optimal PLD obtained in a noncontrol group of six subjects. Pearson correlation (a) between the two was $r = 0.98$. Bland–Altman analysis (b) showed a bias of 1.33% higher values at measured optimal PLD. The 95% limits of agreement is shown in the figure, while the mean was 1.57.

FIGURE 8:

CBF maps for a SCD patient (spaced five slices apart) with a previous vaso-occlusive infarct. (a) PLD = 1400 msec, (b) optimal PLD = 1573 msec, and (c) PLD = 1800 msec. Red arrow indicates area of the infarct. Window/level is the same for all CBF images. Last row (d) shows corresponding FLAIR images.

FIGURE 9:

CBF maps for SCD patient (spaced five slices apart) with severe Moyamoya disease and parieto-occipital lobe infarction. (a) PLD = 1400 msec, (b) Optimal PLD = 1603 msec, and (c) PLD = 1800 msec. Various areas of vascular signal are seen due to occluded vessels. Red arrows indicate areas where less vascular signal is seen at CBF corresponding to optimal PLD, while yellow arrows indicate areas where slightly higher vascular signal can be seen at the optimal PLD when compared with the longer PLD CBF maps. Window/level is the same for all CBF images. Last row (d) shows corresponding FLAIR images.

TABLE 1.

Characteristics of Sickle Cell Disease Patients

Gender	Age	Parenchymal disease (FLAIR)		Vascular disease	
		External (cortical) watershed	Internal (deep) watershed	Occlusion/stenosis	Collateralization
Female	51	Right (R) frontal	R Mild, L Severe	B ICA	EC-IC COW
Male	19	None	None (2 non-specific foci)	None	None
Male	37	None	R Mild, L moderate	L ICA, L MCA, R ACA	EC-IC Moyamoya
Male	28	None	R Severe, L Severe	B ICA, B MCA, B ACA, L PCA	Moyamoya
Male	32	R Frontal	None	None	None

EC: external carotid; ICA: internal carotid artery; COW: Circle of Willis; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery.