The value of a shorter-delay arterial spin labeling protocol for detecting cerebrovascular impairment

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Background: The aim of this study was to determine the relationship between blood oxygen level dependent (BOLD) cerebrovascular reactivity (CVR) and cerebral blood flow (CBF) obtained from arterial spin labeling (ASL) using different post labeling delays (PLD).

Methods: Forty-two patients with steno-occlusive diseases and impaired CVR were divided into two groups, one scanned with a 1.5-second (1.5-s) and the other with a 2.5-second (2.5-s) PLD ASL protocol. For all patients, a region of interest (ROI) was drawn around the CVR impairment. This affected ROI was then left-right flipped across the brain midline to obtain the control ROI. For both groups, the difference in grey matter CVR between affected and control ROI was first tested to confirm significance. The average grey matter CBF of affected and control ROIs were then compared. The same analysis method was used to compare affected and control hemispheres.

Results: In both groups of 1.5-s and 2.5-s PLD, CVR values in the affected ROI (−0.049±0.055 and −0.042±0.074 %/mmHg, respectively) were significantly lower compared to that in the control ROI (0.152±0.054 and 0.152±0.053 %/mmHg, respectively, P<0.0001). In the group with the 1.5-s PLD, CBF in the affected ROI (37.62±11.37 mL/100 g/min) was significantly lower compared to CBF in the control ROI (44.13±11.58 mL/100 g/min, P<0.05). However, in the group with the 2.5-s PLD, no significant differences could be seen between CBF in the affected ROI (40.50±14.82 mL/100 g/min) and CBF in the control ROI (39.68±12.49 mL/100 g/min, P=0.73). In the hemisphere-based analysis, CBF was significantly lower in the affected side than in the control side for the group with the 1.5-s PLD (P<0.05) when CVR was impaired (P<0.0001), but not for the group with the 2.5-s PLD (P=0.49).

Conclusions: In conclusion, our study reveals and highlights the value of a shorter-PLD ASL protocol, which is able to reflect CVR impairment. At the same time, we offer a better understanding of the relationship between BOLD CVR and CBF obtained from ASL.

Keywords: Arterial spin labeling (ASL); blood oxygen level dependent cerebrovascular reactivity (BOLD CVR); post labeling delay (PLD)

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Introduction

In the past few years, there has been a widespread application of arterial spin labeling (ASL) in the assessment of neurological and psychiatric disorders (1). However, using ASL in steno-occlusive disease assessment is far more challenging due to very long arterial transit times (ATT) observed in these patients. While ATT is well defined for both young and aging participants (2), it can vary considerably with disease state (3). Accordingly, efforts have been made to prolong post-labeling delay (PLD) or apply multi-PLD to improve the measurement of cerebral blood flow (CBF) (4). Since T1-weighted magnetic resonance imaging (MRI) for blood and grey matter is similar, as long as the PLD is longer than the longest transit time, the ASL signal becomes insensitive to variations in the arterial arrival time (5,6). Therefore, with a longer delay, ASL measurements have the potential to take into account the CBF from collaterals with long ATT. However, we suggest that differentiating between well-developed (short ATT) and stagnant collateral vessels (long ATT) cannot be achieved unless a dual PLD is applied (7-9). Using a shorter PLD, the CBF of stagnant collateral vessels may be underestimated, but this measure may be more sensitive for detecting potential ischemic areas by comparison with healthy areas because stagnant collateral vessel flow will be missed.

Cerebrovascular reactivity (CVR) measures the sensitivity of the vasculature to a vasodilatory challenge such as CO_2. CVR measures may serve to guide treatment and predict outcomes (10,11), with impairment of CVR in steno-occlusive patients indicating a high risk of stroke (12,13). The several types of vasoactive stimuli for measuring CVR have been discussed in detail elsewhere (14). Some studies indicate that there is significant relationship between baseline ASL values and the acetazolamide (ACZ)-iodine-123-N-isopropyl-p-iodoamphetamine (IMP) value acquired with single-photon emission computed tomography (SPECT) with a 2.0-s PLD (7,15). In this case the baseline CBF value measured by ASL has a significant relationship with the CVR value obtained from SPECT imaging. Blood oxygen level dependent (BOLD) MRI is a primary form of functional MRI (16). Although the potential of BOLD MRI for evaluating CVR has been demonstrated in previous literature (17-19), to the best of our knowledge, the relationship between BOLD CVR and baseline CBF values obtained from ASL has not been previously investigated. However, it is not uncommon to observe lower signal intensities in ASL maps of the hemisphere where BOLD CVR is impaired compared to the contralateral side using a 1.5-s PLD ASL protocol. With a longer delay, there is enough time for the spins to perfuse the CVR impaired tissue, and as a result, the CBF values increase, but the ability of ASL to detect potential ischemic areas corresponding to areas of impaired CVR may be decreased. Therefore, in this study, as well as investigating the relationship between BOLD CVR and CBF values measured with ASL, we also examined the influence of different PLDs in the relationship between ASL CBF and BOLD CVR. Our hypothesis was that because short PLD ASL protocols discriminate against stagnant collateral vessels, and because CVR derived from step stimuli also are reduced for regions with slow responses, then their ability to detect such impaired regions should agree for short PLD ASL but not for long PLD ASL. We tested this hypothesis in patients with BOLD CVR maps that showed unilateral impairment, where one hemisphere was more severely impaired than the other hemisphere.

Methods

Subject recruitment and assessment

This study was conducted at the Toronto Western Hospital (TWH). Patients were referred from neurosurgery or stroke prevention clinics and enrolled in ongoing CVR and ASL studies. All studies were approved by the Research Ethics Board (REB) at the University Health Network and all subjects provided their informed consent. Following REB approval, images from patients at the TWH between January 2011 and July 2017 were retrospectively screened by an experienced neuroradiologist (DJM) using the following inclusion criteria: (I) BOLD CVR maps show unilateral impairment, where one hemisphere is more severely impaired than the other hemisphere; (II) a 1.5-s or 2.5-s PLD ASL protocol, as well as a BOLD CVR sequence were performed during the same session. Patients with motion artifacts on BOLD or ASL images were excluded from the analysis. Forty-two patients with steno-occlusive diseases met those inclusion and exclusion criteria (*Table 1*). Patients were then assigned into two groups based on the ASL protocol applied, namely, one group with 1.5-s PLD (age range/mean: 25–83; 56 years) and the other group with 2.5-s PLD (age range/mean: 32–74; 50 years). There is no age difference between these two groups (one-way ANOVA, P>0.05). Patient demographic and diagnoses are listed in *Tables 2,3*.

Table 1 Patient grouping

Group	Male	Female	Age range/mean (years)	Moyamoya disease/syndrome	Stenosis
1.5-second PLD group	8	13	25–83/55	15	6
2.5-second PLD group	9	12	32–74/51	14	7

PLD, post labeling delay.

Table 2 Patient characteristics for the long PLD ASL group

Case No.	Gender	Age, years	Diagnosis	Angiographic findings
1	Female	50	Moyamoya disease	Left ICA bifurcation stenosis
2	Female	48	Moyamoya syndrome	Right ICA bifurcation stenosis, right MCA occlusion
3	Male	36	Moyamoya disease	Left ICA bifurcation occlusion
4	Male	32	Moyamoya disease	Bilateral ICA bifurcation stenosis
5	Male	48	Moyamoya disease	Right MCA occlusion
6	Female	38	Moyamoya syndrome	Left MCA occlusion
7	Female	51	Moyamoya disease	Right intracranial ICA and MCA stenosis
8	Female	44	Moyamoya disease	Left MCA stenosis
9	Female	45	Moyamoya disease	Bilateral MCA stenosis
10	Female	35	Moyamoya syndrome	Right ICA bifurcation stenosis
11	Male	70	Stenosis	Left MCA stenosis
12	Male	58	Moyamoya disease	Left MCA occlusion
13	Male	45	Occlusion and stenosis of bilateral carotid artery	Right MCA occlusion
14	Male	50	Moyamoya-like	Bilateral ICA bifurcation stenosis
15	Male	57	Stenosis	Right MCA stenosis
16	Female	74	Moyamoya disease	Right MCA occlusion
17	Female	51	Moyamoya disease	Left MCA occlusion
18	Male	62	Stenosis	Left MCA occlusion
19	Female	54	Ischemic	Right MCA stenosis
20	Male	65	Stenosis	Bilateral intracranial ICA stenosis
21	Female	52	Stenosis	Right ICA and ACA stenosis, right MCA occlusion

ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PLD, post labeling delay; ASL, arterial spin labeling.

MRI data acquisition

All of the MRI scans were performed on a 3.0T scanner (Signa HDX platform, GE Healthcare, Milwaukee, Wisconsin, USA) at TWH using an 8-channel phased array head coil. T1-weighted anatomical images of the entire brain were acquired using a three-dimensional spoiled gradient echo pulse sequence [1.0 mm thick, matrix 256×256, field of view (FOV) 22 cm, flip angle 12, echo time (TE) 3.06 ms, repetition time (TR) 7.88 ms]. BOLD MR CVR data were acquired for the entire brain using a T2*-weighted echo-planar gradient-echo sequence (TR 2,000 or 2,400 ms, TE 30 ms, flip angle 85° or 70°, slice thickness 5.0 or 3.5 mm, no gap, matrix 64×64, 255 temporal frames) during manipulation of arterial CO_2. ASL MR data were acquired for the entire brain with 3D pseudo-continuous ASL sequence provided by GE (46 axial slices of 4 mm;

Table 3 Patient characteristics for the short PLD ASL group

Case No.	Gender	Age, years	Diagnosis	Angiographic findings
1	Male	55	Moyamoya disease	Stenosis of the left ICA bifurcation, the proximal ACA and MCA
2	Female	38	Moyamoya syndrome	Bilateral ICA bifurcation stenosis
3	Female	45	Moyamoya disease	Right MCA occlusion
4	Male	63	Moyamoya disease	Bilateral MCA occlusion at origin
5	Male	62	Moyamoya disease	Bilateral intracranial ICA stenosis
6	Female	62	Moyamoya disease	Left ICA bifurcation stenosis, left MCA occlusion
7	Female	79	Stenosis	Right ICA stenosis at the origin
8	Male	80	Stenosis	Intracranial left ICA stenosis
9	Female	57	Stenosis	Left MCA occlusion, right intracranial ICA, MCA, and ACA stenosis
10	Female	26	Query moyamoya	Left MCA occlusion
11	Female	73	Stenosis	Left intracranial ICA occlusion
12	Female	48	Moyamoya disease	Right ICA occlusion
13	Female	49	Moyamoya disease	Bilateral ICA bifurcation occlusion
14	Female	43	Moyamoya disease	Bilateral intracranial ICA stenosis
15	Female	83	Stenosis	Right intracranial ICA stenosis
16	Male	48	Moyamoya disease	Left ICA bifurcation occlusion
17	Female	39	Moyamoya disease	Bilateral proximal MCA and basilar artery occlusion
18	Female	57	Moyamoya disease	Bilateral intracranial ICA stenosis
19	Male	25	Moyamoya disease	Bilateral intracranial ICA stenosis
20	Male	80	Moyamoya syndrome	Left intracranial ICA occlusion
21	Male	64	Stenosis	Right ICA from origin and left ICA stenosis

ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PLD, post labeling delay; ASL, arterial spin labeling.

FOV =220 mm; acquisition matrix =128×128, 8 spiral arms in each 3D partition; TE =9.8 ms; PLD/TR =1,525/4,718 ms or PLD/TR =2,525/5,413; flip angle 155°; acquisition time =4 minutes 17 seconds). No injection was required.

Vasodilatory stimulus (gas manipulation, end-tidal PCO₂ and PO₂ manipulation)

In order to manipulate arterial CO_2, we used an automated gas blender that adjusts the flow and gas composition to a sequential gas delivery breathing circuit (RespirAct™, Thornhill Research Inc., Toronto, Canada) as previously described (20,21). This system enables independent control of the end-tidal partial pressure of carbon dioxide ($PetCO_2$) and end-tidal partial pressure of oxygen ($PetO_2$) in cooperative patients unaffected by breathing pattern and minute ventilation. The stimulus sequence protocol used in this study was as follows: $PetCO_2$ 40 mmHg baseline for 60 s, a hypercapnic step change to a $PetCO_2$ of 50 mmHg for 90 s, a return to baseline for 90 s, and a second hypercapnic step to for 120 s with a final return to baseline. All steps were implemented while maintaining normoxia ($PetO_2$ ~110 mmHg). Previous work describes the $PetCO_2$ and $PetO_2$ sequences used during the analysis of BOLD MRI CVR in more detail (14,22).

Image processing

The acquired BOLD MRI, $PetCO_2$ and ASL data were imported into AFNI (23) software for analysis. BOLD images were slice time-corrected, and volume-registered. $PetCO_2$ was time-shifted to the point of maximum

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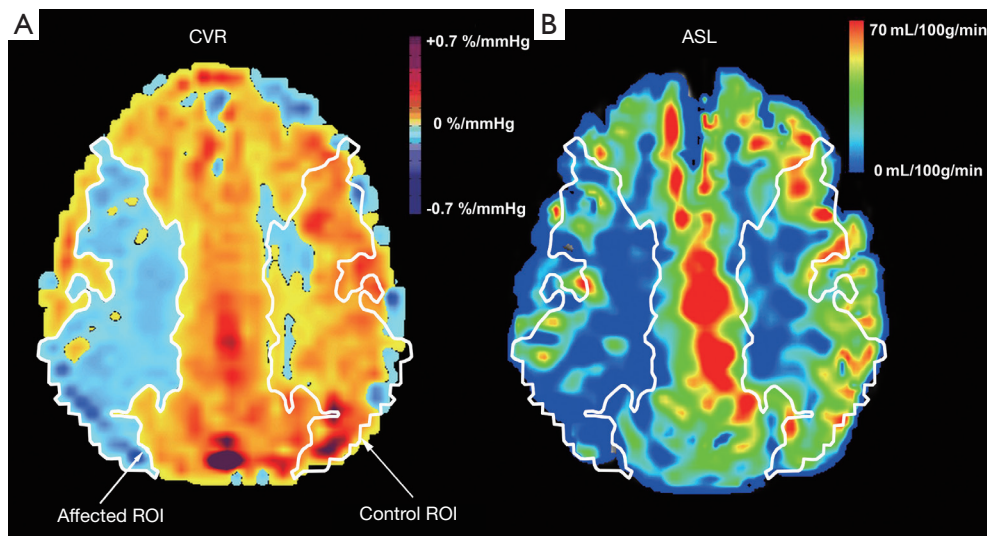Zhuang et al. The value of a shorter-delay ASL protocol

Figure 1 The region of interest (ROI) of cerebrovascular reactivity (CVR) (A) and arterial spin labeling (ASL) (B) maps for a representative subject; an 83-year-old female patient with ICA stenosis. A ROI was drawn (white line) tracing the impairment of CVR on one hemisphere, and then left/right flipped to the other hemisphere using the x-axis in the maps as a midline. The patient's ROI in the CVR maps were then used as a mask for each subject's ASL maps.

correlation with the whole brain average BOLD signal using MATLAB software. A voxel by voxel linear regression of the BOLD signal time series against the $PetCO_2$ data was then performed and the slope of the line of best fit was taken as the CVR measurement. CVR is therefore the change in BOLD MRI signal in response to a change in $PetCO_2$, and expressed as %/mmHg. The quantification of CBF was available as a GE product (8).

Data analysis

Patients with unilateral CVR impairment were first identified by DJM. Using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College, London, UK), their T1-weighted anatomical images were normalized into Montreal Neurological Institute (MNI) space and segmented into cerebrospinal fluid, grey matter and white matter. Using this data, CVR and ASL grey matter masks were generated and transformed into MNI standard space.

A region of interest (ROI) was drawn around the region of CVR impairment, which was then left/right flipped across the brain midline to obtain the corresponding control ROI (*Figure 1*). CVR and CBF values for the impaired ROIs were compared to their respective values in the control ROIs, using a Wilcoxon matched-pairs signed ranks test,

and results were considered significant if the P value was less than 0.05.

In patients with long ATT collateral flow and a relatively short PLD, the image acquisition of the ASL sequence might occur before the spin tag arrives in the ROI. Therefore, a hemisphere-based analysis was also performed to validate our results. The same statistical test as above was used in this analysis.

Results

Results from the different analysis method were shown in (*Table 4*). CVR in the affected ROI was −0.049±0.055 %BOLD/mmHg for the 1.5-s PLD group, and −0.042±0.074 %BOLD/mmHg for the 2.5-s group. Those values were significantly lower compared to CVR in the control ROI, with 0.152±0.054 %BOLD/mmHg for the 1.5-s PLD group and 0.152±0.053 %BOLD/mmHg for the 2.5-s PLD group (P<0.0001, *Figure 2A,B*).

In the group with the 1.5-s PLD, CBF in the affected ROI (37.62±11.37 mL/100 g/min) was significantly lower compared to CBF in the control ROI (44.13±11.58 mL/100 g/min, P<0.05, *Figure 2C*). However, in the group with the 2.5-s PLD, no significant differences could be seen between the CBF in the affected ROI (40.50±14.82 mL/100 g/min) and the CBF in the control ROI

Table 4 Results from different analysis methods

Analysis methods	Control side (mean ± SD)	Impaired side (mean ± SD)	P value (paired t-test)
ROI-based analysis			
BOLD CVR of 1.5-second PLD group (%/mmHg)	0.152±0.054	−0.049±0.055	<0.0001
BOLD CVR of 2.5-second PLD group (%/mmHg)	0.152±0.053	−0.042±0.074	<0.0001
CBF of 1.5-second PLD group (mL/100 g/min)	44.13±11.58	37.62±11.37	<0.05
CBF of 2.5-second PLD group (mL/100 g/min)	39.68±12.49	40.50±14.82	0.73
Hemisphere-based analysis			
BOLD CVR of 1.5-second PLD group (%/mmHg)	0.211±0.060	0.130±0.058	<0.0001
BOLD CVR of 2.5-second PLD group (%/mmHg)	0.269±0.066	0.179±0.068	<0.0001
CBF of 1.5-second PLD group (mL/100 g/min)	48.27±6.28	45.55±7.06	<0.05
CBF of 2.5-second PLD group (mL/100 g/min)	43.10±8.58	42.58±8.89	0.49

ROI, region of interest; BOLD, blood oxygen dependent; CVR, cerebrovascular reactivity; CBF, cerebral blood flow; PLD, post labeling delay; SD, standard deviation.
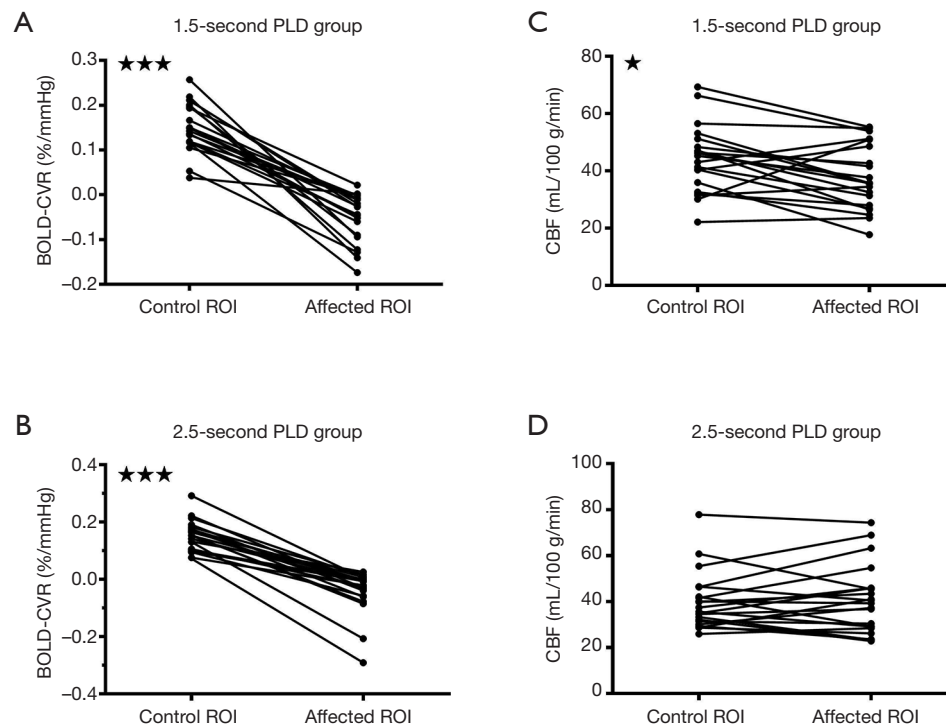
Figure 2 Figures showing the different post-labeling delays (PLDs) and their effects on cerebral blood flow (CBF) when blood oxygen level dependent cerebrovascular reactivity (BOLD CVR) was impaired, according to the region of interest (ROI)-based analysis. When BOLD CVR values were significantly decreased in the affected ROI compared with the control ROI (A,B), CBF values were significantly correspondingly decreased for the 1.5-s PLD arterial spin labeling (ASL) protocol (C). However, such a difference was not observed for the 2.5-s PLD ASL protocol (D). *, P<0.05; ***, P<0.0001.

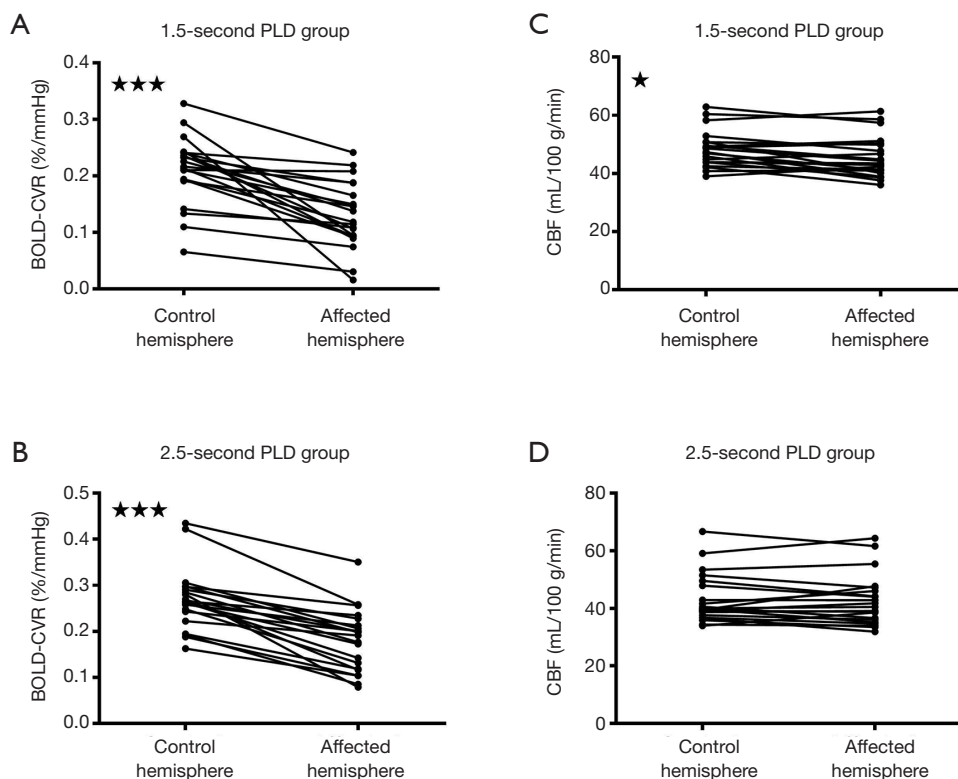**Figure 3** Figures showing different post-labeling delays (PLDs) and their effects on cerebral blood flow (CBF) when blood oxygen level dependent cerebrovascular reactivity (BOLD CVR) was impaired, according to the hemisphere-based analysis. When BOLD CVR values were significantly decreased (A,B), CBF values were significantly correspondingly decreased for the 1.5-s PLD arterial spin labeling (ASL) protocol (C), although less pronounced compared to the region of interest (ROI) analysis. Such a difference was not observed for the 2.5-s PLD ASL protocol (D). *, $P<0.05$; ***, $P<0.0001$.

(39.68±12.49 mL/100 g/min, P=0.49) (*Figure 2D*).

Similar results were observed in the hemisphere-based analysis. In the hemisphere-based analysis, CVR in the affected hemisphere was 0.130±0.058 %BOLD/mmHg for the 1.5-s PLD group and 0.179±0.068 %BOLD/mmHg for the 2.5-s group. Those values were significantly lower compared to the CVR in the control hemisphere, with 0.211±0.060 %BOLD/mmHg for the 1.5-s PLD group and 0.269±0.066 %BOLD/mmHg for the 2.5-s PLD group P<0.0001 (*Figure 3A,B*). In the group with the 1.5-s PLD, CBF in the affected hemisphere (45.55±7.06 mL/100 g/min) was significantly lower compared to CBF in the control hemisphere (48.27±6.28 mL/100 g/min, P<0.05) (*Figure 3C*). However, in the group with the 2.5-s PLD, no significant differences could be seen between the CBF in the affected hemisphere (42.58±8.89 mL/100 g/min) and the CBF in the control hemisphere (43.10±8.58 mL/100 g/min, P=0.49) (*Figure 3D*).

Discussion

Our results demonstrate that a 1.5-s PLD ASL protocol is able to show decreased CBF when BOLD CVR is impaired in support of our hypothesis, whereas the 2.5-s PLD ASL protocol is not. Nevertheless, it must be acknowledged that the relationship between regional BOLD CVR and baseline CBF is complex. The stages of cerebral hemodynamic impairment described by Powers *et al.* and Derdeyn *et al.* (24-26) suggest that CBF may be maintained until vessels exhaust their vasodilatory reserve capacity even though there may be slight decreases in CBF through the autoregulatory range. However, our results showed that with a longer PLD, the difference of CBF values acquired by ASL between the hemisphere with impaired BOLD CVR and the other hemisphere could not be observed, whereas with a shorter PLD, CBF values were significantly different.
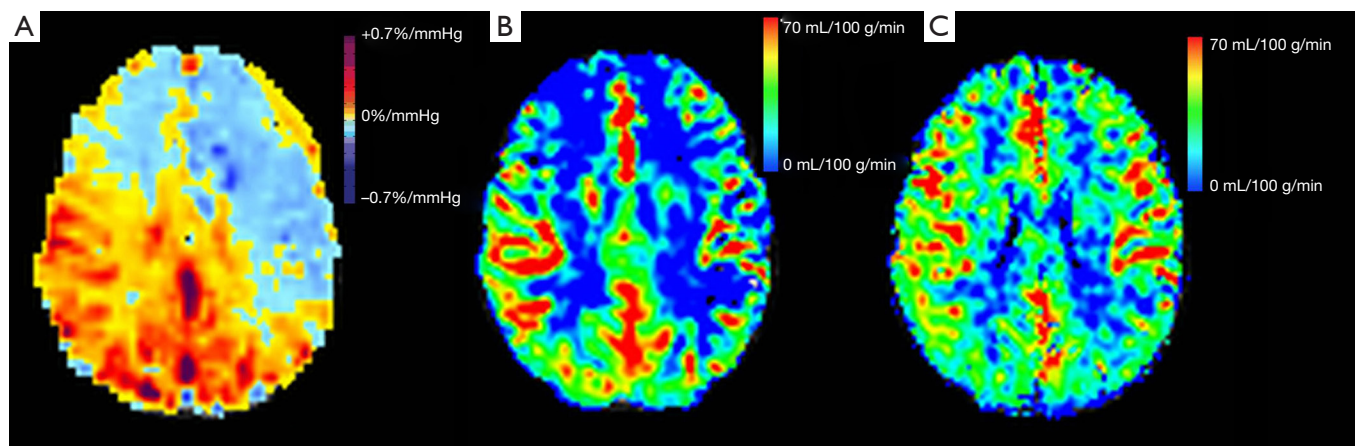
Figure 4 Figures showing cerebrovascular reactivity (CVR) (A), arterial spin labeling (ASL) with a shorter 1.5-s post-labeling delay (PLD) (B) and ASL with a longer PLD (C) for a representative subject. When the CVR was more severely impaired on the left hemisphere (A), then for the 1.5-s PLD ASL protocol, a larger area with blue color signifying lower perfusion was observed on the corresponding left side (B). However, a longer 2.5-s PLD allowed for more spins to reach the tissue, and as depicted, there was an improved perfusion in both hemispheres (C). A discrepancy in perfusion between the two hemispheres was not observed.

In *Figure 4*, a patient with both 1.5-s and 2.5-s PLD ASL protocols is shown as an example. CVR was more severely impaired in the left hemisphere (*Figure 4A*) and the 1.5-s PLD ASL protocol correspondingly showed a larger area with low signal intensity (blue) on the left side (*Figure 4B*). In contrast, a longer PLD ASL protocol allowed for more spins to perfuse the tissue, resulting in an improvement of perfusion in both hemispheres (*Figure 4C*), so that the discrepancy in perfusion between hemispheres could not be observed. However, the serpiginous high signal intensity does indicate collateral blood flow (9), which means that although CVR is impaired, CBF is maintained by slowly responding collateral pathways (27,28). Because the BOLD CVR measured by a step stimulus is reduced for slowly responding regions, it is therefore capable of detecting regions where collateral pathways are still able to maintain CBF as measured with the 2.5-s PLD ASL protocol but are slow to respond. Thus, BOLD CVR using a step stimulus enables earlier detection of potential ischemic areas compared with 2.5-s PLD ASL protocol.

Our results highlight the benefit of using an ASL sequence with a short PLD. It is well known that a shorter delay results in an underestimation of the CBF due to arterial transit time artifacts (ATA) (29), so many studies try to minimize this bias (28,30,31) using longer PLD or multiple PLD ASL sequences. Not only do such ASL sequences increase scan time, but they are also not readily available on clinical scanners (8). On the other hand, we show in this study that a shorter-PLD ASL protocol is valuable since it has the potential to detect areas with a risk of ischemia that correspond to reduced CVR. In our study, we found that when CVR was decreased, the short-PLD ASL also showed hemodynamic insufficiency. Even though in the short PLD group, the CBF may be underestimated, it may serve to predict CVR impairment. Another study also tried to use ASL perfusion MRI to assess CVR (8). It compared the CBF values obtained through dual-PLD ASL protocol with CVR obtained through 123I-IMP SPECT with ACZ loading, and showed that dual PLD methods could be used to assess CVR. It indicated that in the dual-PLD methods, if CBF was improved with 2.5-s PLD compared with 1.5-s PLD, CVR would be maintained due to streaming collateral pathways, which meant only when CBF was decreased with both long and short PLD, would the CVR be impaired. However, this did not follow the stages of cerebral hemodynamic deficiency. CBF may be maintained even though CVR is impaired in the autoregulative stage, even though a slight decrease of CBF could be observed in this stage (26). Moreover, when CBF was obtained with a longer PLD, the ATA was minimized and the CBF value was more reliable. Nevertheless, it should be accepted that though short PLD ASL protocol may be sensitive in detecting CVR impairment, its specificity may be relatively low, since decreased CBF with short PLD may be due to extensive and functional collaterals, where CVR is maintained. Further study with
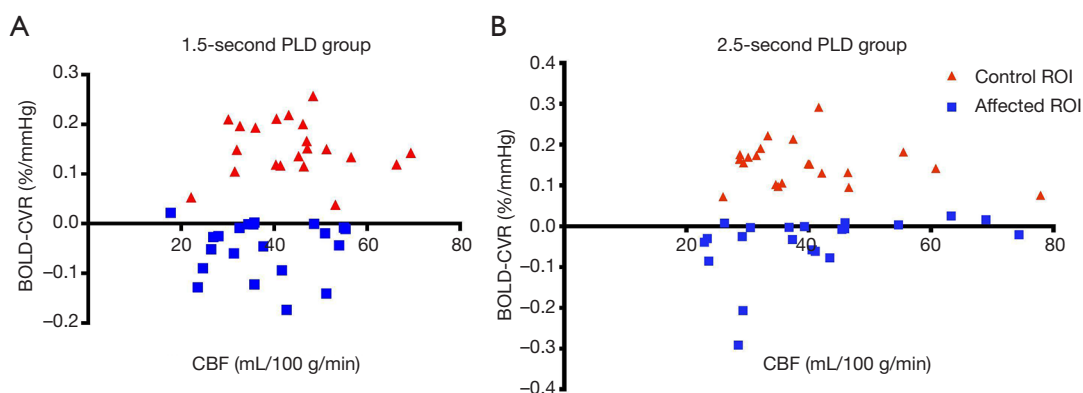
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Figure 5 Relationship between blood oxygen level dependent cerebrovascular reactivity (BOLD CVR) and CBF in the 1.5-s post-labeling delay (PLD) group (A) and the 2.5-s PLD group (B). Both groups included 21 subjects.

larger patient number may be needed to know the exact sensitivity and specificity, in which patient with normal CVR should be included.

The underlying mechanism for short PLD ASL to reflect impaired CVR may be explained as follows. First, in patients with steno-occlusive disease, when CVR is exhausted (24-26), their CBF may decrease, which will be presented with either short or long PLD ASL protocol. Second, the presence of collaterals does not necessarily mean that they are functional. Their adequacy can be assessed by BOLD CVR (32). Meanwhile, in patients with impaired CVR and relatively maintained true CBF, CBF may be decreased with short PLD due to stagnant collaterals (8,9). As such, short PLD ASL protocol may serve to discriminate against stagnant collateral vessels and show similar results to CVR.

It should be emphasized that in this study, we used patients' relatively unaffected hemisphere or ROI as presented in the CVR maps as a control and see if CBF acquired by short or long PLD ASL protocol was decreased in the affected hemisphere or ROI compared to the control hemisphere or ROI. The reason for us to do this are as follows. Using the contralateral hemisphere or ROI as a control will help us to get rid of the effects caused by age, since age difference contributes to a difference in CBF between the two groups. Second, it's hard to decide whether CBF is decreased or not since a single PLD ASL protocol could not make accurate CBF estimation due to ATA, multi-PLD ASL sequences are used for better and true CBF estimation (28,30). By using the contralateral relative unaffected hemisphere or ROI as a control, we are able to decide whether CBF acquired by single PLD ASL sequence is decreased or not.

This study also demonstrates that an ASL protocols with different PLDs lead to different conclusions. For example, in contrast to other studies showing a linear relationship between CBF using a 2-s PLD ASL protocol and CVR using SPECT (7,15), our results do not show such a relationship (*Figure 5*).

Of further interest, we found that with a 2.5-s PLD ASL protocol, in both ROI and hemisphere-based analysis, the CBF values on the affected side were higher than the control side in 10/21 patients. By contrast, with the 1.5-s PLD ASL protocol, only 5/21 and 6/21 patients showed higher CBF in the affected side than the control side (ROI and hemisphere-based analysis respectively). This finding suggests that with a longer PLD, there is a trend to overestimate CBF. Another study also showed that there is a tendency for ASL sequence to overestimate CBF, because the presence of tagged blood in arterial vessels destined to perfuse tissue in more distal regions may contaminate the ASL signal (33).

Limitations

Our study had limitations. First, this is a retrospective study. We only applied both short and long-PLD ASL to one patient. However, applying both techniques to the same patient group will help to accurately determine short or long PLD ASL's ability. Second, we use the patients' relatively unaffected hemisphere or ROI as a control, however, it's better to include patients with normal CVR and see if CBF acquired with short or long PLD ASL is normal or not.

Conclusions

In conclusion, our study demonstrates the value of a shorter-PLD ASL protocol, which is able to reflect CVR impairment. These findings also offer a better understanding of the relationship between BOLD CVR and CBF obtained from ASL.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-148). The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was designed in line with the guidelines outlined in the Declaration of Helsinki and approved by the Research Ethics Board (REB) at the University Health Network in Toronto. After a complete description of the study was provided to each participant, informed written consent was obtained from each participant before the study.

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