RESEARCH ARTICLE

# Arterial Spin Labeling-Based MRI Estimation of Penumbral Tissue in Acute Ischemic Stroke

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**Background:** Arterial spin labeling (ASL) has shown potential for the assessment of penumbral tissue in patients with acute ischemic stroke (AIS). The postlabeling delay (PLD) parameter is sensitive to arterial transit delays and influences cerebral blood flow measurements.
**Purpose:** To assess the impact of ASL acquisition at different PLDs for penumbral tissue quantification and to compare their performance regarding assisting patient selection for endovascular treatment with dynamic susceptibility contrast MRI (DSC-MRI) as the reference method.
**Study Type:** Retrospective.
**Population:** A total of 53 patients (59.98 ± 12.60 years, 32% women) with AIS caused by internal carotid or middle cerebral artery occlusion.
**Field Strength/Sequence:** A 3-T, three-dimensional pseudo-continuous ASL with fast-spin echo readout.
**Assessment:** Hypoperfusion volume was measured using DSC-MRI and ASL with PLDs of 1.500 msec and 2.500 msec, respectively. Eligibility for endovascular treatment was retrospectively determined according to the imaging criteria of the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke trial (DEFUSE 3).
**Statistical Tests:** Kruskal–Wallis tests, Bland–Altman plots, Cohen's kappa, and receiver operating characteristic analyses were used. The threshold for statistical significance was set at $P < 0.05$.
**Results:** Hypoperfusion volume for ASL with a PLD of 1.500 msec was significantly larger than that for DSC-MRI, while the hypoperfusion volume for a PLD of 2.500 msec was not significantly different from that of DSC-MRI ($P = 0.435$). Bland–Altman plots showed that the mean volumetric error between the hypoperfusion volume measured by DSC-MRI and ASL with PLDs of 1.500/2.500 msec was −107.0 mL vs. 4.49 mL. Cohen's kappa was 0.679 vs. 0.773 for DSC-MRI and ASL, respectively, with a PLD of 1.500/2.500 msec. The sensitivity and specificity for ASL with a PLD of 1.500/2.500 msec in

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.28364

Received Apr 10, 2022, Accepted for publication Jul 1, 2022.

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Grant Support: This work was supported by the National Natural Science Foundation of China (81825012, 81730048, and 82151309 to X.L., 81625011 and 21921004 to X. Z., and 81901708 to J.H.L.).

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identifying patients eligible for treatment were 89.74% vs. 97.44% and 92.86% vs. 64.29%, respectively.
**Data Conclusion:** In AIS, PLDs for ASL acquisition may have a considerable impact on the quantification of the hypoperfusion volume.
**Evidence Level:** 3
**Technical Efficacy:** Stage 2

J. MAGN. RESON. IMAGING 2023;57:1241–1247.

Penumbral tissue quantification using imaging is critical for effective treatment decision making in patients with acute ischemic stroke (AIS).[1] Computed tomography (CT)-based assessment of perfusion, dynamic susceptibility contrast MRI (DSC-MRI), and diffusion-weighted imaging (DWI) have been widely implemented in numerous studies to quantify penumbral tissue using the critical hypoperfusion–ischemic core mismatch paradigm.[2–8] Arterial spin labeling (ASL), a noninvasive perfusion imaging technique that does not require contrast agent administration, has shown feasibility in the qualitative assessment of the perfusion–core mismatch.[9,10]

Although ASL has shown promising results in stroke imaging, it has not been routinely applied in clinical scenarios. Challenges may arise from the fact that the critically hypoperfused tissue is usually overestimated using ASL under the currently available techniques.[11–14] Several parameters exist may affect the measurement of hypoperfusion in ASL.[15] Some studies have tested the influence of different thresholds on measuring hypoperfusion.[12,13] However, the influence of the postlabeling delay (PLD) during ASL acquisition, a key parameter in cerebral blood flow (CBF) quantification, has not been investigated.

In the present study, we aimed to assess the impact of ASL acquisition with two different PLDs for penumbral tissue quantification and to compare their performance with respect to patient selection for endovascular treatment using DSC-MRI as the reference method.

## Materials and Methods

This study was approved by the institutional review boards of the participating institutions. Written informed consent was obtained from all patients. For the purpose of this research, we retrospectively analyzed the data from a prospective multicenter study recruiting AIS patients from January 2019 to December 2020 (The MR-based STroke mechAnism and future Risk Score, MR-STARS study; http://www.clinicaltrials.gov. Unique identifier: NCT02580097).

The inclusion criteria were as follows: 1) age > 18 years, 2) AIS caused by internal carotid artery or middle cerebral artery M1–M2 segment occlusion, 3) ASL and DSC-MRI acquisition within one scanning session, and 4) time last known from being healthy to symptom onset below 24 hours. The exclusion criteria were 1) previous lesions greater than one-third of the downstream territory defined as encephalomalacia extending beyond one-third region of the internal carotid artery or middle cerebral artery territory; 2) insufficient imaging quality, which was defined as images with severe artifacts from motion or three-dimensional (3D) spiral readout, background suppression, and severe signal loss; and 3) failure of postprocessing for DSC-MRI.

### MRI Protocol

All MRI studies were performed using a 3-T scanner (Discovery 750; GE Healthcare, Milwaukee, WI, USA) with a 32/8-channel head coil. The MR protocol included a routine head scan including T1-weighted imaging (T1WI), T2-weighted imaging, T2-weighted fluid-attenuated inversion recovery, DWI and time-of-flight MR angiography, as well as 3D pseudo-continuous ASL (pCASL) and DSC-MRI. Fast spin-echo T1WI had the following parameters: repetition time (TR) = 1.750 msec, echo time (TE) = 24 msec, field of view = 24 cm, slice thickness = 5.0 mm, number of slices = 20. DWI with echo-planar readout had the following parameters: TR = 6.800 msec, TE = 90 msec, field of view = 24 cm, slice thickness = 5.0 mm, *b*-values = 0 and 1.000 sec/mm$^2$, number of slices = 20. The pCASL sequence with fast-spin echo readout had the following parameters: TR = 4.590 msec (PLD = 1.500 msec) or 5.285 msec (PLD = 2.5000 msec), labeling duration = 1.500 msec, TE = 10.5 msec, field of view = 24 cm, 512 sampling points on eight spirals, spatial resolution = 3.64 mm, slice thickness = 4.0 mm, number of slices = 36, background suppressed, scan time = 4 minutes. The DSC-MRI sequence had the following parameters: TR = 1.200 msec, TE = 16.7 msec, slice thickness = 5 mm, echo train length = 1, scan time = 1 minute; gadolinium contrast agent (Gadodiamide Injection, GE Healthcare, Co., Cork, Ireland) was used (dosage = 0.2 mL/kg; flow rate = 4 mL/sec).

### Imaging Postprocessing

Penumbral tissue quantification by DSC-MRI was conducted using commercially available software (NeuBrainCare, Version 1.0, Neusoft Medical Systems Co. Ltd, Shenyang, Liaoning, China), functionally similar to the rapid processing of perfusion and diffusion (RAPID) software (iSchemaView, Inc., Menlo Park, CA, USA).[16] Using the multistream 3D convolution network described in a previous study, the software applied an automatic method for arterial input function (AIF) estimation. Using the singular-value decomposition method, the response curve of each pixel to the AIF was calculated for each sample. Perfusion maps were then collectively obtained. Specifically, the time to the maximum of the tissue residue function ($T_{max}$) was calculated as the time to peak of the response curves.[17]

First, the ischemic core was identified based on DWI and apparent diffusion coefficient (ADC) maps as regions with ADC < $620 \times 10^{-6}$ mm$^2$/sec. Second, the volume of critical hypoperfusion was measured by $T_{max}$ > 6 seconds. The mismatch volume and mismatch ratio were then calculated based on the perfusion–

diffusion mismatch paradigm, which was defined as the ground truth of penumbral tissue assessment in this study.[6]

The ASL imaging preprocessing included imaging co-registration, spatial normalization to Montreal Neurological Institute coordinates, and spatial smoothing using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Then, the CBF map, ADC map, and T1-weighted images were inputted in a Matlab-based program (MathWorks, Natick, MA, USA) developed by our team. Hypoperfusion on ASL at different PLDs applied the same segmentation workflow. Based on previous studies, the segmentation method was modified as a combination of a seed growing scheme and a threshold-based scheme.[11–13] A hypoperfusion mask was outputted in three steps: 1) region 1: seed selection as voxels with ADC < $620 \times 10^{-6}$ $mm^2$/sec, and growth halt when the voxel CBF value and surrounding voxel CBF exceed 4 mL/100 g/min, and then multiply the region <60% CBF of each pixel in the corresponding contralateral side region; 2) region 2: seed selection as voxels <50% contralateral side CBF, and growth is halted when voxel CBF value and surrounding voxel CBF exceed 4 mL/100 g/min, and then multiply the region <60% CBF of each pixel in the corresponding contralateral side region; and 3) combine regions 1 and 2 (illustration is provided in Supplemental Fig. S1). The parameter 4 mL/100 g/min was determined by the CBF standard deviation of penumbra tissue according to a prior study.[18] The 60% was adapted from a previous threshold.[11]

The mismatch volume was obtained by hypoperfusion of ASL at 1.500/2.500 msec PLD minus the ischemic core. The mismatch ratio was obtained by hypoperfusion on ASL at 1.500/2.500 msec/ischemic core.

**TABLE 1. Patient Demographics**

| | **Patients $n = 53$** |
|---|---|
| Age, mean (SD), years | 59.98 (12.60) |
| Male, *n* (%) | 36 (68) |
| NIHSS, median (IQR) | 9 (6–14) |
| Event-to-MRI time, median (IQR), hours | 12.17 (5.97–21.43) |
| DWI lesion volume, mean (SD), mL | 28.09 (39.35) |
| Risk factors | |
| Hypertension, *n* (%) | 33 (62) |
| Lipid disorders, *n* (%) | 20 (38) |
| Diabetes, *n* (%) | 18 (34) |
| Coronary heart disease, *n* (%) | 5 (9) |
| Smoking, *n* (%) | 21 (40) |

NIHSS = National Institutes of Health Stroke Scale; SD = standard deviation; IQR = interquartile range.

### Imaging Criteria for Endovascular Treatment

The eligibility for endovascular treatment was retrospectively determined according to the imaging criteria for hypoperfusion and ischemic core mismatch profile in the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial. The imaging criteria were as follows: 1) ischemic core < 70 mL, 2) mismatch volume greater than 15 mL, and 3) mismatch ratio > 1.8.[6]

### Statistical Analysis

All quantitative data are expressed as mean ± standard deviation (SD). Normality tests were performed using the Kolmogorov–Smirnov test. Leaner Pearson correlations and Bland–Altman plots were used to depict the correlation and agreement of quantitative measures obtained from ASL and DSC-MRI. Cohen's kappa was calculated to evaluate the agreement of assisting patient selection based on the DEFUSE 3 imaging criteria between ASL at each PLD and DSC-MRI.[6] A receiver operating characteristic (ROC) curve was constructed to evaluate the performance of ASL at different PLDs in assisting patient selection. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported. All statistical analyses were performed using SPSS (version 20.0; IBM Corporation, Armonk, NY, USA). The threshold for statistical significance was set at $P < 0.05$.

## Results

Ultimately, 57 patients were identified. Three of these patients were excluded due to postprocessing failure of the DSC-MRI. One patient was excluded because of the presence of a large older lesion in the affected territory. The mean age ± SD of the included 53 patients was 59.98 ± 12.60 years, and there were 36 men. The patient characteristics are listed in Table 1.

The mean infarct core volume was 28.09 ± 39.35 mL based on ADC. The mean hypoperfusion volume was 205.38 ± 102.25 mL on ASL with a PLD of 1.500 msec, 93.88 ± 63.93 mL on ASL with a PLD of 2.500 msec, and 98.38 ± 74.65 mL on $T_{max}$ > 6 seconds from DSC-MRI. There was no significant difference between the hypoperfusion volume on ASL with a PLD of 2.500 msec and $T_{max}$ > 6 seconds ($P = 0.435$), while a significant difference was observed between the hypoperfusion volume on ASL with a PLD of 1.500 msec and $T_{max}$ > 6 seconds (Fig. 1a,b).

Because the data were not normally distributed, the cubic root of the volume was plotted (Fig. 1c). The hypoperfusion volume on ASL with a PLD of 1.500 msec was correlated with the volume of $T_{max}$ > 6 seconds ($r = 0.627$), and the hypoperfusion volume on ASL with a PLD of 2.500 msec was also moderately correlated with the volume of $T_{max}$ > 6 seconds ($r = 0.641$). The Bland–Altman plots showed that the mean volumetric difference between the hypoperfusion volume measured by $T_{max}$ > 6 seconds and 1.500/2.500 msec ASL was −107.0 mL vs. 4.49 mL (Fig. 1d,e).

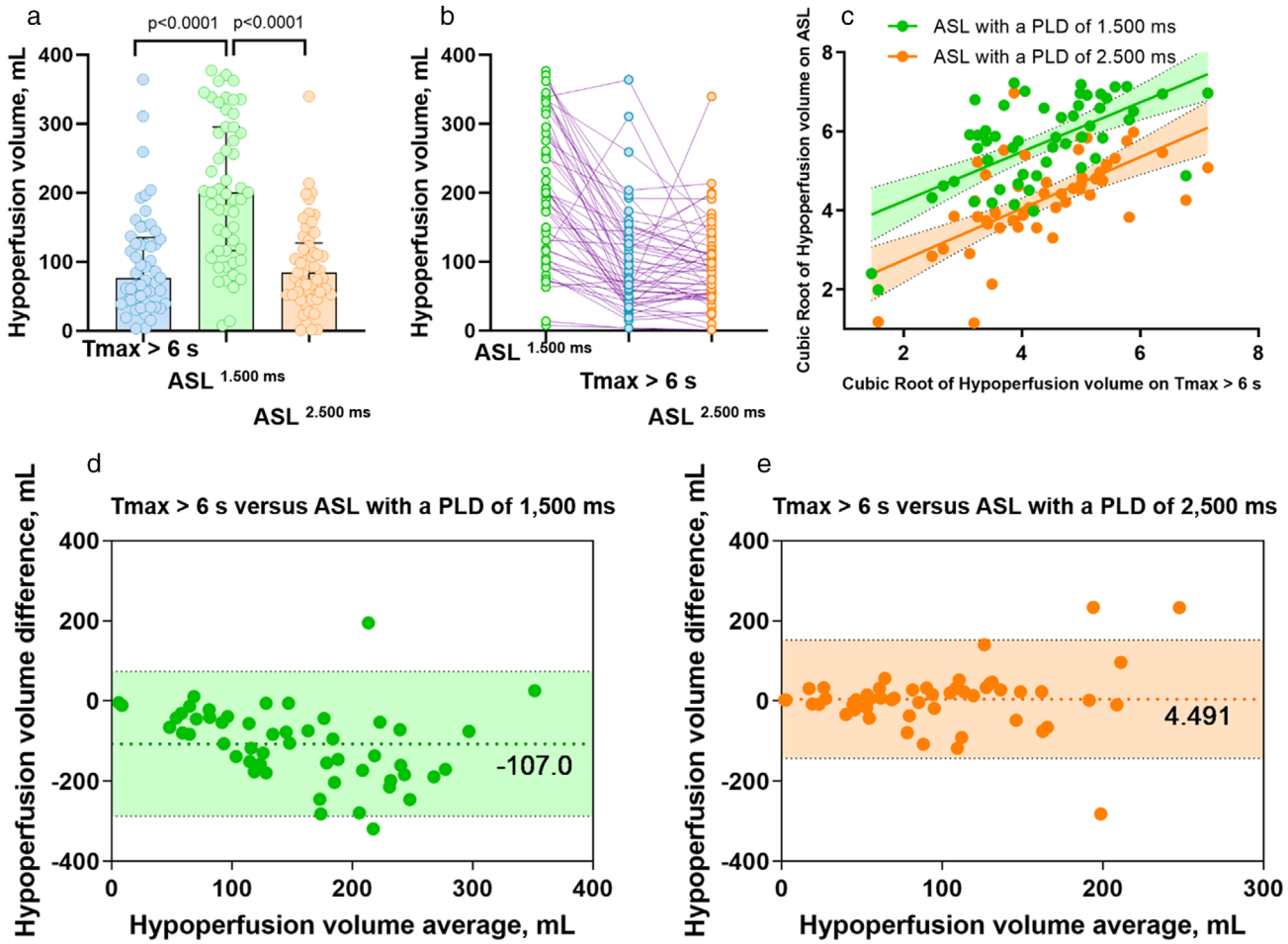


**FIGURE 1: Plot of hypoperfusion volume of different measurements (a). Aligned dot plots of hypoperfusion volume on pseudo-continuous arterial spin labeling (ASL) with postlabeling delays (PLDs) of 1.500/2.500 msec and time to maximum of the residue function ($T_{max}$) > 6 seconds (b). Correlation of hypoperfusion volume on ASL with PLDs of 1.500/2.500 msec and $T_{max}$ > 6 seconds (c). Bland–Altman plots for hypoperfusion volume on ASL with PLDs of 1.500/2.500 msec and $T_{max}$ > 6 seconds (d,e).**

In assisting the selection of patients meeting the imaging criteria for endovascular treatment according to the DEFUSE 3 trial, 39 cases were selected based on DSC-MRI, 43 cases were selected based on ASL with a PLD of 1.500 msec, and 36 cases were selected based on ASL with a PLD of 2.500 msec. Referring to DSC-MRI as the reference method, Cohen's kappa was 0.679 (95% confidence interval [CI]: 0.446–0.913) for DSC-MRI and ASL with a PLD of 1.500 msec and 0.773 (95% CI: 0.586–0.960) for DSC-MRI and ASL with a PLD of 2.500 msec, which indicated substantial agreement.

The sensitivity, specificity, PPV, and NPV for ASL with a PLD of 2.500 msec for identifying patients eligible for treatment were 89.74%, 92.86%, 97.2%, and 76.5%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value for ASL with a PLD of 1.500 ms for identifying patients eligible for treatment were 97.44%, 64.29%, 88.4%, and 90.0%, respectively. A representative case of a 78-year-old man with acute right middle cerebral artery occlusion is shown in Fig. 2. Additional case illustrations are provided in the Supplemental Figs. S2–S5.

## Discussion

In this study, we investigated the impact of two PLDs on penumbral tissue quantification using ASL. Hypoperfusion measured by ASL with a longer PLD (2500 msec vs. 1500 msec) was more similar to hypoperfusion regions using $T_{max}$ > 6 seconds based on DSC-MRI. Related to the imaging criteria of DEFUSE 3, ASL with a PLD of 2.500 msec rather than 1.500 msec showed substantial agreement with DSC-MRI for assisting patient selection in receiving endovascular treatment. The diagnostic performance of ASL with a PLD of 2.500 msec was also better than that of 1.500 msec with a high specificity in assisting patient selection. A PLD of 2.500 msec may be preferable over 1.500 msec for the estimation of penumbral tissue in the hypoperfusion–core mismatch paradigm.

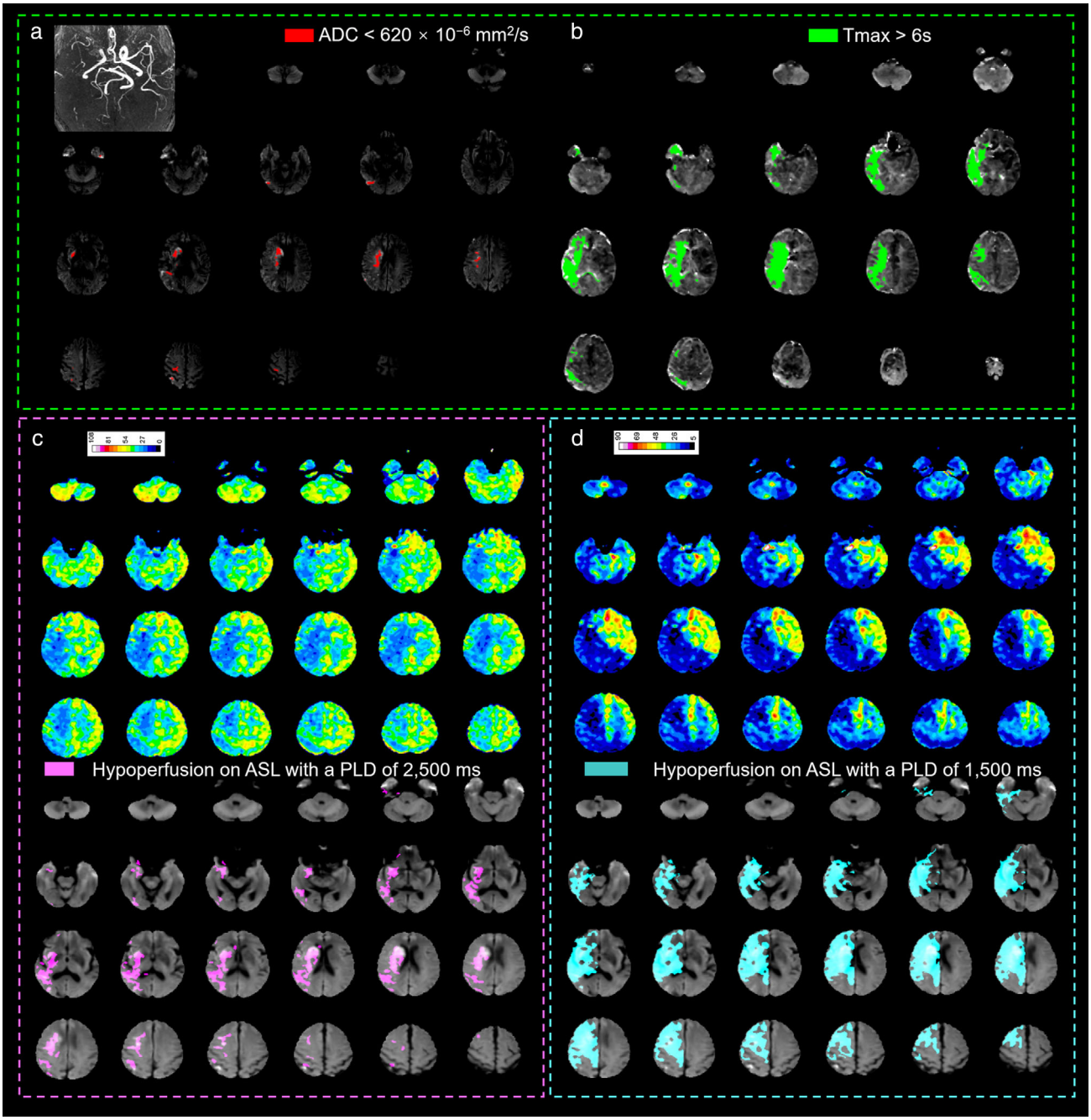


**FIGURE 2: A representative case of a 78-year-old man with acute right middle cerebral artery occlusion shows multiple acute infarctions in the corresponding blood supply territory (a). The infarct core volume was 8.92 mL (a). The volume of hypoperfusion on time to maximum of the residue function ($T_{max}$) > 6 seconds (b), arterial spin labeling (ASL) with a postlabeling delay (PLD) of 2.500 msec (c), and ASL with a PLD of 1.500 msec (d) were measured as 123.79 mL, 93.04 mL, and 338.19 mL, respectively. Hypoperfusion mask in purple on ASL with a PLD of 2.500 msec (c) shows good agreement in location and extent with the region with $T_{max}$ > 6 seconds in green (b).**

Penumbral tissue quantification by ASL has gained great interest in the imaging community because of its noninvasive and absolute CBF quantifiable features.[19] The quantification of CBF makes ASL a valuable methodology for detecting important pathological changes.[20] There are experimental reference CBF thresholds to define key features in AIS: core < 8 mL/100 g/min, penumbra < 20 mL/100 g/min, and benign oligemia < 50 mL/100 g/min.[21] Absolute CBF measures promote ASL as a promising tool for confirming the status of ischemic tissues.[20] A previous study has indicated that an absolute CBF threshold of 20 mL/100 g/min, which was very similar to the experimental reference, might be able to define the penumbra.[12] However, overestimation of ASL in defining the penumbra was reported, and further clinical studies using this threshold have not reported.[19,20,22] One major reason for this might be that CBF did not reach its

peak in patients with large vessel occlusion (LVO). Blood flow is delayed and atrial transit time is prolonged in the downstream of the stenotic or occlusive artery.[23,24] The volume of hypoperfusion for longer PLD indicates a territory with more severely delayed blood flow.[25–27] The previously proposed thresholds to define the penumbra were derived from the CBF map using ASL with a PLD of 2.000 msec.[12,14,20] As shown in our study, in terms of $T_{max}$ > 6 seconds, the PLD of 2.500 msec shows better agreements in volume, which may indicate that a longer PLD could be helpful to reduce the possibility of overestimation and provides a more accurate measurement of penumbral tissue in AIS due to LVO. A multidelay ASL technique has also been reported to generate delay-corrected CBF maps; thus, it might be useful in the hemodynamic evaluation of AIS.[28] Nevertheless, multidelay ASL requires additional post-processing and a longer scanning time, along with increasing accuracy from applying more PLDs.[29] A single long-delay ASL might be more practical in clinical scenarios to ensure imaging quality for subsequent hypoperfusion measurements.

In patient eligibility for treatment analysis, ASL with a PLD of 2.500 msec showed substantial agreement with DSC-MRI and showed high sensitivity and specificity for identifying patients eligible for endovascular treatment. These results may reinforce the clinical value of a long PLD for ASL in AIS. In AIS clinical guidelines, the use of CT perfusion or DSC-MRI to evaluate the penumbra is recommended.[1] However, there are no recommendations for evaluating the penumbra when the patients are not eligible for CT perfusion or DSC-MRI, such as those with advanced stage of chronic kidney disease, refusal to provide consent for contrast-based perfusion imaging, especially for children and pregnant women, or those who are allergic to contrast agents.[30] Therefore, although CT perfusion or DSC-MRI is excellent approaches for estimating penumbra and hemodynamic status in AIS, they are not perfect. Rather than substituting CT perfusion or DSC-MRI, ASL can be an important complement in these circumstances. In addition, although ASL requires a slightly longer scanning time of approximately 3–5 minutes, it is free of high-pressure syringes and venipuncture preparations, which may provide a more fluent and convenient emergency pathway for AIS patients in imaging sessions.

### Limitations

First, only PLDs of 1.500 msec and 2.500 msec were analyzed in our study. Frequently used PLDs of 1.800 msec and 2.000 msec were not acquired and their performance in penumbra assessment was not analyzed. Similarly, although less frequently applied, other time delays (eg 1.600 and 2.400 msec) were also not acquired either. Because a longer PLD in 3-T MRI subsequently reduces the signal-to-noise ratio, it remains unreliable for CBF quantification and thus hypoperfusion segmentation based on absolute CBF value threshold in clinical scenarios.[26] In addition, hypoperfusion on ASL can represent any hemodynamic state, such as benign oligemia, penumbra, and ischemic core. Owing to an insufficient signal-to-noise ratio, it is impossible to distinguish between these hemodynamic states using the current thresholding method. Second, different ASL techniques and MRI scanners may have affected the clinical translation of the present findings. Nonetheless, we believe that the findings of this study may support the use of longer PLDs. Third, the study sample size was small; therefore, the methods proposed by our study still need further validation for clinical acceptance and reproducibility. Finally, patient selection for treatment depends on many parameters in addition to imaging.[1] The efficiency of long PLDs for ASL in actual clinical decision-making for AIS still needs to be further evaluated.

### Conclusion

In AIS, the PLD used during ASL acquisition may have a considerable impact on the quantification of the hypoperfusion volume.

## References


1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early Management of Patients with Acute Ischemic Stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-e110.
2. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015; 372:1009-1018.
3. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015; 372:1019-1030.
4. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever Thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285-2295.
5. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372:11-20.
6. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378: 708-718.
7. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11-21.
8. Campbell BCV, Majoie CBLM, Albers GW, et al. Penumbral imaging and functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: A meta-analysis of individual patient-level data. Lancet Neurol 2019;18:46-55.
9. Zaharchuk G, El Mogy IS, Fischbein NJ, Albers GW. Comparison of arterial spin labeling and bolus perfusion-weighted imaging for detecting mismatch in acute stroke. Stroke 2012;43:1843-1848.
10. Bokkers RPH, Hernandez DA, Merino JG, et al. Whole-brain arterial spin labeling perfusion MRI in patients with acute stroke. Stroke 2012; 43:1290-1294.
11. Hernandez DA, Bokkers RPH, Mirasol RV, et al. Pseudocontinuous arterial spin labeling quantifies relative cerebral blood flow in acute stroke. Stroke 2012;43:753-758.

12. Niibo T, Ohta H, Yonenaga K, Ikushima I, Miyata S, Takeshima H. Arterial spin-labeled perfusion imaging to predict mismatch in acute ischemic stroke. Stroke 2013;44:2601-2603.

13. Bivard A, Krishnamurthy V, Stanwell P, et al. Arterial spin labeling versus bolus-tracking perfusion in hyperacute stroke. Stroke 2014;45:127-133.

14. Wang K, Shou Q, Ma SJ, et al. Deep learning detection of penumbral tissue on arterial spin labeling in stroke. Stroke 2020;51:489-497.

15. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med 2015;73:102-116.

16. Straka M, Albers GW, Bammer R. Real-time diffusion-perfusion mismatch analysis in acute stroke. J Magn Reson Imaging 2010;32:1024-1037.

17. Fan S, Bian Y, Wang E, et al. An automatic estimation of arterial input function based on multi-stream 3D CNN. Front Neuroinform 2019;13:1-11.

18. Murphy BD, Fox AJ, Lee DH, et al. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. Stroke 2006;37:1771-1777.

19. Zaharchuk G. Arterial spin-labeled perfusion imaging in acute ischemic stroke. Stroke 2014;45:1202-1207.

20. Nael K, Meshksar A, Liebeskind DS, Coull BM, Krupinski EA, Villablanca JP. Quantitative analysis of hypoperfusion in acute stroke. Stroke 2013;44:3090-3096.

21. Yuh WTC, Alexander MD, Ueda T, et al. Revisiting current Golden rules in managing acute ischemic stroke: Evaluation of new strategies to further improve treatment selection and outcome. Am J Roentgenol 2017;208:32-41.

22. Chalet L, Boutelier T, Christen T, et al. Clinical imaging of the penumbra in ischemic stroke: From the concept to the era of mechanical thrombectomy. Front Cardiovasc Med 2022;9:1-17.

23. Bang OY, Goyal M, Liebeskind DS. Collateral circulation in ischemic stroke: Assessment tools and therapeutic strategies. Stroke 2015;46:3302-3309.

24. Lyu J, Zhang S, Wang X, et al. FLAIR vessel hyperintensities predict functional outcomes in patients with acute ischemic stroke treated with medical therapy. Eur Radiol 2022; in press. https://doi.org/10.1007/s00330-022-08661-2.

25. Lyu J, Ma N, Liebeskind DS, et al. Arterial spin labeling magnetic resonance imaging estimation of antegrade and collateral flow in unilateral middle cerebral artery stenosis. Stroke 2016;47:428-433.

26. Lyu J, Ma N, Tian C, et al. Perfusion and plaque evaluation to predict recurrent stroke in symptomatic middle cerebral artery stenosis. Stroke Vasc Neurol 2019;4:129-134.

27. Lou X, Ma X, Liebeskind DS, et al. Collateral perfusion using arterial spin labeling in symptomatic versus asymptomatic middle cerebral artery stenosis. J Cereb Blood Flow Metab 2019;39:108-117.

28. Wang DJJ, Alger JR, Qiao JX, et al. Multi-delay multi-parametric arterial spin-labeled perfusion MRI in acute ischemic stroke — Comparison with dynamic susceptibility contrast enhanced perfusion imaging. NeuroImage Clin 2013;3:1-7.

29. Lou X, Yu S, Scalzo F, et al. Multi-delay ASL can identify leptomeningeal collateral perfusion in endovascular therapy of ischemic stroke. Oncotarget 2017;8:2437-2443.

30. Mehdi A, Taliercio JJ, Nakhoul G. Contrast media in patients with kidney disease: An update. Cleve Clin J Med 2020;87:683-694.