Clinical Benefits of Multiple Post-Labeling Delay Pseudo-Continuous Arterial Spin Labeling (Multi-PLD PCASL) in Pediatric Patients with Moyamoya Disease

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Introduction

Moyamoya disease, which frequently occurs in Asian countries including Japan, causes stenosis or obstruction in the circle of Willis and results in a number of new small blood vessels forming around the stenotic or obstructed arteries. The incidence peaks in two age groups: childhood and adulthood. It is roughly classified into either stenotic type or hemorrhagic type, depending on the onset condition. It is known that revascularization is effective in ischemic moyamoya disease, which is common in young patients, and that receiving treatment before the condition becomes serious leads to a better prognosis. The disease received the name “moyamoya” at Tohoku University in 1969 [1, 2]. The word, which means “puff of cigarette smoke” in Japanese, was chosen because this is what the newly generated cerebral blood vessels look like on cerebral angiography. This name is currently used worldwide. Our hospital conducts research on moyamoya disease as a related institute of Tohoku University, and is one of the representative facilities for studying pediatric moyamoya disease in Japan. We are working on safer and more effective treatments using a perioperative management method such as postoperative cerebral blood flow evaluation [3–5].

In the treatment of pediatric patients with moyamoya disease, examining cerebral blood flow dynamics plays an important role in determining the treatment strategy. Although several methods exist, measurement by $^{15}$O-H$_2$O PET is said to be the most reliable. However, in actual clinical practice, dual-table autoradiography (DT-ARG) by single photon emission computed tomography (SPECT) is popular and widely used because it is a simple and reliable method that requires less capital investment [6]. In our hospital, although we use DT-ARG for long-term follow-up, we do not apply it to younger patients because it requires arterial blood sampling during the examination, which is rather invasive. In recent years, 3T MRI has become widespread and noninvasive quantification of cerebral blood flow is routinely available with arterial spin labeling (ASL), which provides regional cerebral blood flow (rCBF). However, it has been reported that cerebral blood flow measured by ASL changes significantly depending on age and sex [8]. Buxton proposed a more robust ASL methodology to assess blood flow differences in individuals. The rCBF map is calculated from PCASL data obtained with multiple post-labeling delays (PLDs) in a process called multi-PLD pseudo-continuous ASL (multi-PLD PCASL) [9]. Furthermore, by observing perfusion-weighted imaging (PWI) with different PLDs performed with this method, it is also possible to see pseudo hemodynamics. The method is highly advantageous, especially for children: It is noninvasive and can be repeatedly performed because it involves no radiation exposure or contrast media. We used a Siemens Healthineers prototype multi-PLD PCASL sequence following the ASL study group recommendations [10], in

1 Comparison of multi-TI PASL and DT-ARG
ROIs were taken from four regions in each hemisphere of three moyamoya patients (24 ROIs).
which a Buxton model fit was also implemented. 3T MR is generally advantageous for ASL, which requires a higher signal-to-noise ratio (SNR). Therefore, prior to clinical application, we optimized the protocol for our 1.5T MAGNETOM Aera. We also tried to reduce the scan time to make it suitable for pediatric examinations. In this paper, we present two clinical cases for which multi-PLD ASL was useful, and a case which requires attention.

Materials and methods
The local institutional review board approved all study protocols, and written informed consent was obtained from healthy volunteers and from the parents of patients with moyamoya disease. We optimized the protocol with five healthy volunteers (aged between 25 and 43 years).

Protocol optimization and validation
A MAGNETOM Aera 1.5T and a 20-channel head/neck coil were used for this study. As the ASL signal from blood flow is acquired during T1 relaxation of magnetization labeled by inversion pulse, it is strongly influenced by the T1 value of blood and the PLD, which is the time between the labeling inversion pulse and data acquisition. In order to determine an acceptable PLD range at 1.5T, the rCBF of healthy volunteers was evaluated with single-PLD PCASL by changing the PLD from 1600 to 3200 ms with a step of 200 ms (labeling duration 1500 ms). The rCBF obtained with each PLD was compared in each brain region, and the upper PLD limit at 1.5T was decided. A small PLD step was set for the accuracy of rCBF estimation regarding the upper limit of the PLD. In terms of TGSE segments, which form the data-acquisition part of ASL, we investigated three, two, and one segment(s) in order to reduce scan time.

Concerning the accuracy of rCBF by ASL, we found a good correlation between DT-ARG and multi-TI PASL, which was used on the same moyamoya patients (n = 3) in our previous study (Fig. 1). In this study, due to the difficulty of collecting DT-ARG and ASL data from the same patient, we evaluated rCBF correlations between the previous multi-TI PASL and the new multi-PLD PCASL protocol on healthy volunteers.

Results
Protocol optimization
Figure 2 shows that the obtained rCBF was almost equivalent up to a PLD of 2800 ms, but decreased markedly at 2800 ms and above. As a result, we recognized that the upper limit of PLD was 2800 ms at 1.5T.

![Graph showing relCBF depending on PLD by single-PLD PCASL (healthy adult volunteer)](image-url)

SNR of perfusion-weighted imaging decreased markedly (not shown in Figure) at a PLD of > 2800 ms (PLD) and affected relCBF. The reliable relCBF will be provided with a PLD of less than 2800 ms.
Strong correlation was found between multi-TI PASL and multi-PLD PCASL (Fig. 3). In addition, strong correlation in rCBF was found between the TGSE segments numbering one to three (Fig. 4A). Although a higher number of segments should theoretically provide a higher spatial resolution due to less T2 blurring, we could not see any major differences in one, two, or three segments (Fig. 4B). Since pediatric examinations need minimal scan times in order to avoid the possibility of patient motion during the examination, we chose to use one segment, which provided a scan time of 2 min 52 sec. Table 1 shows the detailed parameters, which are within the recommendation of the white paper [9] (TE x turbo factor < 300 ms, ESP x EPI factor < 15 ms). We were also able to observe pseudo cerebral hemodynamics by continuously showing PWI with multi-PLD.

**Table 1.** Detailed parameters within recommendation of white paper [9].

<table>
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<tr>
<th>Parameter</th>
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<tr>
<td>TE x turbo factor</td>
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<tr>
<td>ESP x EPI factor</td>
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**Fig. 3.** Comparison of PASL (3 segments; 8 min) and PCASL (3 segments; 8 min).

ROIs were taken from four regions in each hemisphere of four healthy volunteers (32 ROIs).

**Fig. 4A.** Comparison of PCASL (3 segments), PCASL (2 segments), and PCASL (1 segment).

ROIs were taken from four regions in each hemisphere of five healthy volunteers (40 ROIs).

**Fig. 4B.** Comparison of PCASL 3, 2, and 1 segment(s).
All moyamoya patients in our hospital are examined with this optimized protocol. Below, we present three clinical cases.

Case 1
This is a postoperative follow-up case of a 10-year-old boy who underwent left direct and indirect revascularization in April 2016. As shown in the PWI, it was confirmed that the left reconstructed vessel was depicted later than the contralateral side (Figs. 5A, B). MRA performed on the same day showed narrowing at the left internal carotid artery from the end to the left A1-M1 and also at the right A1 (Fig. 5C). This result was consistent with the result observed in PWI. On the other hand, single-PLD ASL with a PLD of 1800 ms showed an erroneous result that suggested the CBF was high (Fig. 5D).

<table>
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<tr>
<th>TR</th>
<th>TE</th>
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<tr>
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Table 1: Multi-Ti PCASL parameters, TA 2 min 52 sec.

5A Moyamoya disease in a 10-year-old boy
Revascularization by left STC, single-PCASL PWI.
**5B** PWI signal intensity (SI) by multi-TI PCASL
The BAT in the left hemisphere extended. This result was consistent with the MRA showing narrowing at Lt. carotids – A1, M1, and Rt. A1.

**5C** Moyamoya disease in a 10-year-old boy
Revascularization by left STC, MRA-MIP.

**5D** Comparison of SPECT and ASL.
Case 2
This is the case of a two-year-old boy who was too young for perfusion quantification by SPECT. He was diagnosed with moyamoya disease due to the onset of cerebral infarction at 10 months. Revascularization on the right side, opposite to the infarction, was quickly performed and postoperative follow-up was initiated (Fig. 6A). In April 2018, MRA and an rCBF map suggested a decrease in blood flow in the left hemisphere. However, no change was observed in the qualitative SPECT and follow-up observation was continued. A re-examination using MR after two months showed further progression at the same lesion in MRA and on the rCBF map from ASL. The qualitative SPECT again failed to detect the decrease in blood flow (Figs. 6B–D). Based on these results, a neurosurgeon decided to perform left vascular reconstruction. Although the postoperative course was good and the child was discharged, he was hospitalized again for examination in August 2018 because right upper and lower limb cataplexy was observed several times when he cried at home. Even then, no changes were found in qualitative SPECT. MRA showed stenosis at both sides of the PCA and the left reconstructed vessel. An rCBF map revealed a perfusion defect caused by the stenosis (Figs. 6E–G).
Comparison of SPECT and ASL.

Comparison of SPECT and ASL.
Moyamoya disease in a two-year-old boy
Revascularization by both STC, MRA-MIP.

Comparison of SPECT and ASL.
Case 3
This is a postoperative follow-up case of a 16-year-old female who underwent left-direct and indirect revascularization in March 2016. The perfusion delay was clearly visible in the PLD vs. PWI signal curve (Figs. 7A–C) at the left hemisphere where revascularization was done. On the other hand, in the left MCA and PCA dominant region, the PWI signal in the vessel was high for a long period of PLD, from 1600 to 3000 ms (Fig. 7D), resulting in high rCBF even with Buxton model analysis. As a result, the rCBF map differed a great deal between quantitative SPECT (Fig. 7E) and the multi-PCASL method (Fig. 7F).

Discussion
The upper limit of PLD obtained in this study at 1.5T was 2800 ms. It is thought that at a PLD of 2800 ms or longer, rCBF estimation might fail (Fig. 2) because the T1 value at 1.5T is shorter than at 3T and the difference between the tagged signal and the control signal becomes smaller. We reduced the scan time to less than three minutes, as desired for pediatric examinations. The rCBF also showed strong correlation with the conventional protocol, so it can be considered a sufficiently useful condition for clinical practice.

Case 1 clearly showed the decrease in PWI signal and the prolongation of bolus arrival time in the dominant region of narrowing vessels, which was also recognized in MRA. The progression of vascular lesions in moyamoya disease does not occur symmetrically. In addition, every revascularization procedure results in the hemodynamics of the brain becoming more complicated. Therefore, PWI over time allows us to easily obtain valuable information on current hemodynamics. In this case, rCBF by single-PLD PCASL showed incorrect results that suggested the CBF was high in the left hemisphere (Fig. 5D). This was caused by the stagnated blood flow in the revascularized vessels. On the other hand, since multi-PLD PCASL takes bolus arrival time into account (Fig. 5D), it showed the same result as SPECT, even in a patient with very slow blood flow. This indicates the usefulness of this method.

In Case 2, there was no change in qualitative SPECT, and ASL showed lesion progression. In fact, based on the ASL results, we canceled a scheduled SPECT study with pharmacologic challenge, and a neurosurgeon decided on revascularization. In infancy, the immature brain is actively developing and needs a relatively high blood flow, so moyamoya disease onset in infancy carries a high risk [10]. Unlike SPECT, which requires a radioactive tracer, ASL can be easily carried out whenever necessary. It is very convenient and its application is clinically valuable.

Case 3, on the other hand, showed a mismatch in the results between SPECT and ASL. In patients with slow blood flow maintaining signals in vessels at PLD above the upper limit of field strength, we have to be careful because there is a possibility that multi-PLD ASL will produce incorrect results. Generally, in patients with moyamoya disease, bolus arrival time is slower than in healthy subjects. Therefore, in order to make an accurate diagnosis, it is very important to not only investigate the rCBF map but also the PWI time series in terms of bolus arrival time.
Moyamoya disease in a 16-year-old female
Revascularization by left STC, single-PCASL PWI.

Moyamoya disease in a 16-year-old female
Revascularization by left STC, MRA-MIP.
PWI signal intensity (SI) by multi-TI PCASL.

Multi-PLD PCASL PWI.

DT-ARG.
Comparison of SPECT and ASL
Long-stagnating blood flow cannot be evaluated correctly.

Conclusion
Moyamoya disease requires follow-up for a long period of time, and ASL can be a suitable examination for this disease. The multi-PLD PCASL is significant as a screening tool because it provides information on whole-brain perfusion distribution in a 3D rCBF map as well as information on pseudo hemodynamics by PWI time series and bolus arrival time, respectively. Brain perfusion examination by MRI is especially significant for pediatric patients because it can be performed easily, is repeatable and noninvasive with no need for arterial blood sampling, and enables us to quickly decide on a procedure. In this paper, we presented clinical cases in which perfusion evaluation by multi-PCASL was useful for pediatric patients with moyamoya disease who had unusual blood flow caused by stenosis or revascularization. We also presented a case that showed incorrect results caused by very slow blood flow compared with the upper limit of PLD.

Therefore, when viewing the results of multi-PLD PCASL, it is necessary to consider them carefully and in conjunction with clinical symptoms and findings from PWI and other modalities. We aim to continue our work on finding the best way to provide information that will improve diagnosis and clinical decisions for pediatric patients.

Acknowledgments
The authors wish to thank Dr. Josef Pfeuffer, Siemens Healthcare, Erlangen, for providing the 3D ASL prototype sequence.

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