ORIGINAL

Evaluation of the Ischemic Penumbra and Prognosis in acute Cerebral Infarction Using Cerebral Blood Flow and Delay Time Derived from Multi-delay pCASL Imaging

Mihoko Sasahara[1], Moriaki Yamanaka[1], Tomoki Matsushita[1], Takashi Abe[1], Maki Otomo[1], Yuki Yamamoto[2], Nobuaki Yamamoto[2], Yasuhisa Kanematsu[3], Yuishin Izumi[2], Yasushi Takagi[3], Mitsuharu Miyoshi[4], and Masafumi Harada[1]

[1]Department of Radiology, Tokushima University, Tokushima, Japan, [2]Department of Neurology, Tokushima University, Tokushima, Japan, [3]Department of Neurosurgery, Tokushima University, Tokushima, Japan, [4]GE Healthcare Japan

Abstract : Purpose : The purpose of this study was to evaluate the ischemic penumbra and prognosis in acute cerebral infarction using cerebral blood flow (CBF) and delay time (DT) derived from multi-delay pseudo-continuous arterial spin-labeling (pCASL) imaging and to estimate the possible use of such indices to predict prognosis. Method : Our subjects comprised 25 patients who were diagnosed with cerebral infarction in our stroke center between September 2017 and December 2018 and underwent pCASL perfusion MRI. The time from onset to MRI was 0.6 to 20 h (mean, 6 h) and was less than 4.5 h in 16 patients. Twelve patients received conservative treatment, three were treated with tPA, and the remaining 10 patients underwent invasive treatment (e.g., thrombectomy). They were subdivided by recanalization : 18 patients were non-recanalized and 7 were recanalized. We evaluated the mean cerebral blood flow (CBF) and mean arterial transit DT at the infarct core and penumbra and the infarct size at the initial and follow-up examinations and calculated the infarct enlargement ratio (ER) from the initial and final infarct sizes. We also assessed clinical prognosis by using the initial and final NIHSS scores. We investigated the relationship among the ASL, ER, and NIHSS parameters and determined predictors of infarct enlargement using logistic analysis. Result : The degree of the CBF decrease was related to the size of the initial infarct lesion (CBF at core : $r=-0.4060$, $p=0.044$; CBF at penumbra : $r=-0.4970$, $p=0.012$) and initial NIHSS ($r=-0.451$, $p=0.024$; CBF at penumbra : $r=-0.491$, $p=0.013$). Because no parameters were correlated with the ER in all patients. Specifically in the non-recanalization group, the DT at the penumbra was positively correlated with the ER ($r=-0.496$, $p=0.034$). Moreover, by logistic regression analysis, the DT at the penumbra was the only independent predictor of infarct enlargement in all patients ($p=0.047$) and in non-recanalization patients ($p=0.036$). Conclusion : The only parameter predicting the ER was the mean DT at the penumbra, and the tendency was affected by recanalization status. DT obtained by multi-delay ASL may become a prognostic index of acute cerebral infarction. J. Med. Invest. 71 : 286-292, August, 2024

Keywords **:** *Ischemic Penumbra, Cerebral Infarction, Cerebral Blood Flow, Delay Time, pCASL*

INTRODUCTION

In patients with acute cerebral infarction, magnetic resonance diffusion and perfusion imaging has higher sensitivity for the identification of the ischemic core and can potentially estimate the volume of salvageable ischemic tissue (1). Magnetic resonance imaging (MRI) has the potential to differentiate unsalvageable from salvageable tissue ; the latter is called the ischemic penumbra. Tissue with hypoperfusion that is severe enough to eventually result in cell death can be identified with perfusion-weighted MRI (PWI) (1).

Arterial spin-labeling (ASL), which is based on the use of a freely diffusible tracer and no need for contrast agents, is a non-invasive magnetic resonance perfusion approach for the measurement of cerebral blood alterations that functions via the magnetic labeling of the inflowing water proton spins in the arterial blood proximal to the tissue of interest. (2, 3) As a recently developed ASL technique, background suppressed three-dimensional pseudo-continuous arterial spin-labeling (3D pCASL) offers an improved signal-to-noise ratio (SNR) and reduced susceptibility to transit time variability compared with standard 2D pCASL (4). Several recent studies have evaluated the clinical utility of 3D pCASL with multiple post-labeling delays (PLDs) in acute ischemic stroke (5-7). The quantitative value of cerebral blood flow (CBF) with ASL is affected by the radiofrequency pulse application time and the time from application to measurement. The absolute CBF value and the time taken for the labeled blood to reach the tissue, called the arterial transit delay time (DT), can be calculated from ASL images when data with multiple PLDs have been acquired.

Compared with ASL with a single delay, 3D pCASL with multiple PLDs may provide improved visualization of collateral flow in acute stroke via dynamic image series. This modality could be used for the quantitative assessment of collateral perfusion using CBF and DT parameters, which can be a new CBF parameter reflecting blood flow velocity, and a prolonged DT may identify collateral perfusion. (8-11) Collateral tissue perfusion is an important determinant of tissue outcome in acute stroke (12) because it sustains tissue viability prior to reperfusion and maintains blood flow in the longer term (13). Patients with extensive collateral vessels have better clinical outcomes (8, 13-15), and collateral vessel status may be used to select patients who are likely to benefit from recanalization therapies (15, 16).

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Address correspondence and reprint requests to Mihoko Sasahara, Department of Radiology, Tokushima University, Tokushima, Japan and Fax : +81-88-633-7468. E-mail : k.mihoko.928@gmail.com

In this study, the ischemic penumbra was defined by the enlargement area between the final infarct area and the initial hyperintense area on diffusion-weighted imaging (DWI). Then, the CBF and DT values derived from multi-delay pCASL imaging in the ischemic penumbra were compared to the enlargement extent between the initial ischemic core and the final infarct region. Our aim was to evaluate the correlation between the perfusion parameters in the ischemic penumbra and the enlargement extent from the initial ischemic core in acute cerebral infarction and to assess whether CBF or DT could be a prognostic parameter for infarct enlargement after the acute infarction onset.

METHODS

Patients

Our study population comprised 25 patients who were diagnosed with cerebral infarction in our stroke center between September 2017 and December 2018. The inclusion criteria were as follows : patients who had been diagnosed with cerebral infarction in the anterior circulation area ; patients who underwent DWI and pCASL perfusion MRI in the initial examination at diagnosis ; patients who underwent follow-up MRI and fluid-attenuated inversion recovery (FLAIR) imaging ; patients who received no therapy for cerebral infarction before the initial examination ; and patients without serious underlying conditions.

Of the 25 patients, the types of cerebral infarction were cardiogenic in 15 patients, atheromatous in 8, paradoxical in 1, and aortoid in 1.

They were divided into groups based on whether the recanalization was successful or not : 18 patients were non-recanalized and 7 were recanalized.

This study was approved by the institutional review board and ethics committee of Tokushima University Hospital. Informed consent was obtained via the opt-in method.

MRI protocol

The imaging date were obtained using a 3.0-T MRI scanner (Discovery 750 ; GE Healthcare, Milwaukee, WI) equipped with an eight-channel phased-array head coil provided by the manufacturer. The scanning parameters for DWI were as follows : repetition time (TR)/echo time (TE), 10,000/71.8 ms ; field of view (FOV), 28×28 cm^2 ; matrix, 128×128 ; b values, 0, 1,000 s/mm^2 ; and slice thickness/gap, 5/1 mm.

The scanning parameters for FLAIR were as follows : TR, 8000-10000 ms ; inversion time, 2000-2500 ms ; effective TE, 105-120 ms ; matrix size, 256×192 to 320×224 ; FOV, 210-220 mm ; slice thickness, 5-6 mm with 1-1.5 mm interslice gaps ; and 19-20 slices per patient.

We performed 3D pCASL imaging with three PLD times with the following parameters according to previous reports (17, 18) : FSE spiral readout ; TR, 6015 ms ; TE, 11.2 ms ; FOV, 240 $\times$ 240 mm^2 ; slice thickness, 4 mm ; data sampling, 6 spirals $\times$ 600 sampling points ; image matrix, 128×128 ; number of slices, 36 ; three different PLD times of 1.00 s, 1.57 s, and 2.46 s ; and effective label durations of 0.57 s, 0.89 s, and 2.04 s, respectively. The shortest DT was chosen to be 1.00 s to allow sufficient time for the T2 preparation module to be completed. The longest DT was 2.460 s to obtain a compromise between the range of coverage and signal-to-noise. The other delay times were chosen to have approximately equal intervals. By setting the labeling duration to exponential, in consideration of the signal degradation due to the difference in PLDs, the SNR of the image at each PLD was nearly equal and the SNR of the corrected image was kept high. CBF maps were generated using the software on the GE Healthcare scanner console computer with the method proposed by Wang *et al*. (19).

Transit flow time maps were generated by three different PLD times and CBF maps after correction by the transit flow time according to the formula of Dai *et al*. (17, 18). The reproducibility of the technique was then evaluated.

All MRI findings were evaluated by two board-certified radiologists, and the presented data represent a final consensus.

Date acquisition and MRI analysis

The severity of the patients' symptoms and the degree of improvement were evaluated using the National Institutes of Health Stroke Scale (NIHSS). We assessed the NIHSS at the time of the initial examination (initial NIHSS) and when the symptoms were fixed (final NIHSS). Fixed of symptoms is defined as the acute treatment is completed and the patient is discharged or transferred to another hospital. The mean ± standard deviation time of assess the final NHISS from initial NHISS was 20.2 ± 8.6 days (range, 11-42 days)

The improvement in prognosis was evaluated by calculating the difference between the initial and final NIHSS scores (ΔNIHSS).

For all patients, we assessed DWI, FLAIR, and ASL from the MRI at the time of the initial examination and the FLAIR image at the follow-up MRI. The fixed onset of symptoms is defined as the completion of acute treatment and the patient's discharge or transfer to another hospital. The mean ± standard deviation time to assess the final NIHSS score from the initial NIHSS score was 20.2 ± 8.6 days (range, 11-42 days).

The DWI high signal on MRI in the acute phase represents the area that will become infarcted if there is no reperfusion. Often, there is no signal change in FLAIR on the initial MRI. Therefore, the size of the high-intensity area on DWI at the initial MRI was defined as the initial size.

Conversely, at the time of the follow-up MRI, the DWI high signal had decreased following the course of treatment and the passage of days. Thus, the size of the high-intensity area on FLAIR at the follow-up examination was defined as the final size. The maximum area of each was measured and the enlargement ratio (ER) was calculated as final size − initial size/final size. We also scored the degree of expansion from the ER as an enlargement score : 0, ER $\leq$ 20% ; 1, ER 20%-50% ; and 2, ER $\geq$ 50%.

The high-intensity area on DWI was defined as the ischemic core. The area of differentiation in the final infarct size on FLAIR at the follow-up examination from the initial infarct size on DWI at the initial examination was defined as the ischemic penumbra.

We evaluated the mean CBF and arterial transit DT at the infarct core and penumbra. It is written as follows : CBF-core, cerebral blood flow at the core ; DT-core, arterial delay time at the core ; CBF-penumbra, cerebral blood flow at the penumbra ; DT-penumbra, arterial delay time at the penumbra

The sizes of the areas with reduced CBF (CBF size) and prolonged DT (DT size) were also measured.

All regions of interest (ROIs) were drawn by a board-certificated physician (diagnostic radiology). The ROI was manually drawn around the high-intensity area. The infarct size was evaluated at the slice that showed the largest extent of the lesion. CBF and DT was evaluated at three locations in the target area and averaged. Images of the other MRI sequences were available as anatomical references at the time of ROI placement. The ROIs were drawn as large as possible while avoiding the inclusion of other structures.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. Because the data were not

normally distributed, Spearman correlation coefficient analysis was used to assess the relationship among the parameters of ASL, infarct size, ER, and NIHSS.

The Kruskal-Wallis test was applied to analyze the relationship between ASL parameters and the enlargement score. Logistic regression analysis was also performed to assess the predictive ability of parameters of ASL for infarct enlargement. All tests were two-sided and the 95% confidence interval was obtained for each parameter. A p value of less than 0.05 was considered to indicate a statistically significant difference. IBM SPSS Statistics 23 (IBM Japan, Ltd., Tokyo, Japan) was used for the statistical analysis.

RESULTS

Patient characteristics

The mean ± standard deviation time of initial MRI from onset was 5.9 ± 6.1 h (range, 0.6 to 20 h ; <4.5 h in 16 patients). The NIHSS scores were 10 ± 8 (range, 3-31) at the initial assessment and 7 ± 7 (range, 0-24) at the final assessment. Twelve patients received conservative treatment, three were treated with tissue-type plasminogen activator (tPA), and the remaining 10 patients received invasive treatment, such as thrombectomy. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Parameter	Data
Gender (n), Male/Female	17 / 8
Age (years) Mean ± SD/range	73.3 ± 11.8 (40-92)
Body weight (Kg) Mean ± SD/range	62.9 ± 17.7 (41-100)
Initial NIHSS Mean ± SD/range	10 ± 8 (range 3-31)
Final NIHSS Mean ± SD/range	7 ± 7 (range 0-24)
Responsible blood vessels	
Anterior Cerebral Artery (ACA)	1 (4%)
Middle Cerebral Artery (MCA)	16 (64%)
Internal Carotid Artery (ICA)	6 (24%)
ACA + MCA	1 (4%)
ICA + MCA	1 (4%)
The types of cerebral infarction	
cardiogenic	15 (60%)
atheromatous	8 (32%)
paradoxical	1 (4%)
aortoid.	1 (4%)
Treatment	
Intravascular thrombectomy	10 (40%)
Recombinant tissue-type plasminogen activator : rt-PA	3 (12%)
Conservative treatment	12 (48%)
Recanalization (+/-)	7 (28%)/18 (72%)
Infarction size (enlargement/no change)	13 (52%)/12 (48%)

NIHSS, National Institutes of Health Stroke Scale ; SD, standard deviation.

Relationship between ASL parameters and infarct size

Initial infarct size was inversely correlated with the CBF at the core (CBF-core) ($r=-0.4060$, $p=0.044$) and the CBF at the penumbra (CBF-penumbra) ($r=-0.4970$, $p=0.012$) in all patients. No ASL parameters were significantly correlated with the ER. In the 18 non-recanalization patients, the ER and DT-penumbra were inversely correlated ($r=-0.496$, $p=0.034$) (Figure 1). In the recanalization group, no ASL parameters were significantly correlated with the ER (Figure 2)(Table 2).

Figure legend

A 55-year-old woman who was diagnosed with cerebral infarction in the right middle cerebral artery (MCA) area. MRI was conducted 4.5 h after onset. CBF at the infarct area is decreased and the DT at the penumbra is slightly prolonged (1651 ms). In this case, conservative treatment was performed without recanalization. Follow-up images obtained 62 h later showed enlargement of the infarct lesion (enlargement ratio [ER]=55%).

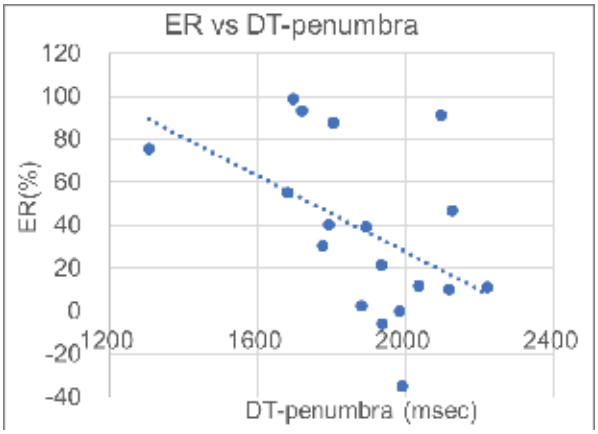


Figure 1. Relationship between the ER and DT-penumbra in non-recanalization patients.
ER, enlargement ratio ; DT-penumbra, arterial delay time at the penumbra.
In the non-recanalization group (n=18), the ER and DT are inversely correlated ($r=-0.496$, $p=0.034$).

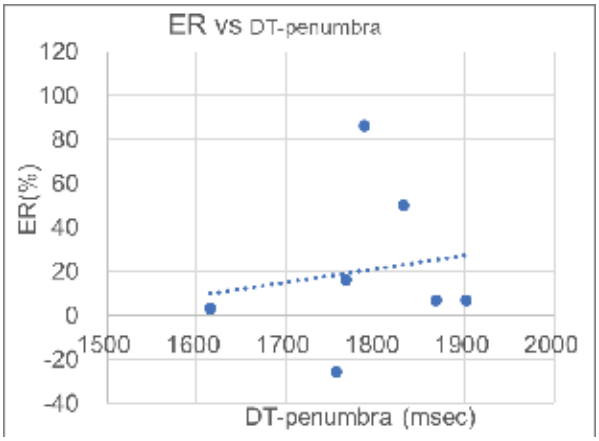


Figure 2. Relationship between the ER and DT-penumbra in recanalization patients.
ER, enlargement ratio ; DT-penumbra, arterial delay time at the penumbra. In the recanalization group (n=7), the ER and DT-penumbra are inversely correlated ($r=0.350$, $p=0.43$).

Table 2. ASL parameters associated with the ER

Parameter	All cases (n=25)	Non-recanalization cases (n=18)	Recanalization cases (n=7)
	r (p-value)	r (p-value)	r (p-value)
CBF-core	0.090 (0.670)	0.247 (0.324)	-0.703(0.078)
DT-core	-0.016 (0.939)	-0.227 (0.322)	0.571(0.180)
CBF-penumbra	0.113 (0.590)	0.051 (0.842)	0.321(0.482)
DT-penumbra	-0.321 (0.118)	0.496(0.034)†	0.357(0.432)
CBF size	-0.028 (0.895)	0.020 (0.938)	0.107(0.819)
DT size	-0.223 (0.284)	-0.285 (0.287)	0.179(0.702)

ER, enlargement ratio ; CBF-core, cerebral blood flow at the core ; DT-core, arterial delay time at the core ; CBF-penumbra, cerebral blood flow at the penumbra ; DT-penumbra, arterial delay time at the penumbra ; CBF size, size of the area with a reduced cerebral blood flow ; DT size, size of the area with a prolonged arterial delay time ; *r*, correlation coefficient.

Logistic regression analysis of the predictive ability of ASL parameters

In the 25 patients, the enlargement scores were as follows : 0, 12 patients ; 1, 5 patients ; and 2, 8 patients. No significant relationship was found between ASL parameters and the enlargement score (Table 3).

Table 3. ASL parameters according to enlargement score in all patients

Enlargement score	0	1	2	p value
number	12	5	8	
CBF-core	10.96±7.24	10.80±6.41	12.31±10.33	0.098
DT-core	1523.67±323.70	1560.20±163.85	1537.25±176.51	0.971
CBF-penumbra	13.65±7.51	15.23±8.21	14.85±10.25	0.991
DT-penumbra	1922.36±157.54	1904.20±125.46	1740.22±204.82	0.097

Data are presented as mean ± standard deviation. The p value is based on a comparison of the ASL parameters according to the enlargement score (Kruskal-Wallis test).
CBF-core, cerebral blood flow at the core ; DT-core, arterial delay time at the core ; CBF-penumbra, cerebral blood flow at the penumbra ; DT-penumbra, arterial delay time at the penumbra.

In the 18 non-recanalization patients, the enlargement scores were as follows : 0, 7 patients ; 1, 5 patients ; and 2, 6 patients. The DT at the penumbra (DT-penumbra) was significantly different according to the enlargement score (p=0.031) (Table 4). In polytomous logistic regression analysis, DT-penumbra was identified as the only independent predictor of the enlargement score (DT-penumbra, p=0.036 ; CBF-core, p=0.953).

Relationship between ASL parameters and prognostic factors

In all 25 patients, the initial NIHSS was inversely correlated with the CBF-core ($r=-0.451$, p=0.024) and CBF-penumbra ($r=-0.491$, p=0.013) and the final NIHSS was positive correlated with CBF size ($r=0.411$, p=0.041). No ASL parameters were significantly correlated with the ΔNIHSS (Table 5).

In the 18 non-recanalization patients, the final NIHSS was positively correlated with CBF size ($r=0.497$, p=0.036) and the ΔNIHSS was inversely correlated with CBF size ($r=-0.520$, p=0.027). The ΔNIHSS was also inversely correlated with DT size ($r=-0.496$, p=0.036) (Table 6).

Table 4. ASL parameters according to enlargement score in non-recanalization patients

Enlargement score	0	1	2	P value
number	7	5	6	
CBF-core	11.86±7.08	10.80±6.41	14.92±10.73	0.821
DT-core	1658.21±190.85	1560.20±163.85	1523.83±189.48	0.570
CBF-penumbra	15.45±6.34	15.23±8.21	16.89±10.69	0.833
DT-penumbra	2022.93±105.56	1904.20±125.46	1716.75±231.53	0.031

Data are presented as mean ± standard deviation. The p value is based on a comparison of the ASL parameters according to the enlargement score (Kruskal-Wallis test).
CBF-core, cerebral blood flow at the core, DT-core, arterial delay time at the core ; CBF-penumbra, cerebral blood flow at the penumbra ; DT-penumbra, arterial delay time at the penumbra.

Table 5. ASL parameters associated with NIHSS score in all patients

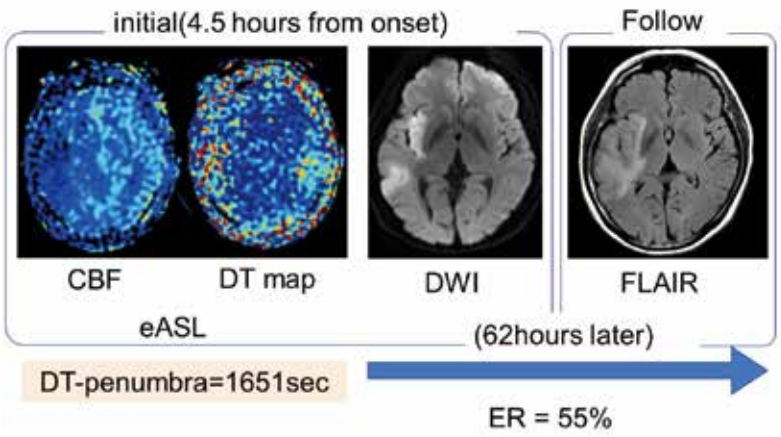
Parameter	Initial NIHSS	Final NIHSS	ΔNIHSS
	r (p-value)	r (p-value)	r (p-value)
CBF-core	-0.451 (0.024)	-0.352 (0.084)	0.012 (0.954)
DT-core	-0.254 (0.220)	-0.182 (0.383)	0.129 (0.540)
CBF-penumbra	-0.491 (0.013)	-0.279 (0.177)	-0.029 (0.889)
DT-penumbra	-0.035 (0.069)	0.112 (0.593)	-0.043 (0.837)
CBF size	-0.212(0.309)	0.411 (0.041)	-0.223 (0.289)
DT size	-0.236 (0.259)	0.386 (0.067)	-0.237 (0.264)

NIHSS, National Institutes of Health Stroke Scale ; CBF-core, cerebral blood flow at the core ; DT-core, arterial delay time at the core ; CBF-penumbra, cerebral blood flow at the penumbra ; DT-penumbra, arterial delay time at the penumbra ; CBF size, size of the area with a reduced cerebral blood flow ; DT size, size of the area with a prolonged arterial delay time.

Table 6. ASL parameters associated with NIHSS score in non-recanalization patients

Parameter	Initial NIHSS	Final NIHSS	ΔNIHSS
	r (p-value)	r (p-value)	r (p-value)
CBF-core	-0.377 (0.123)	-0.234 (0.309)	0.164 (0.514)
DT-core	-0.115 (0.649)	-0.226 (0.368)	0.311 (0.209)
CBF-penumbra	-0.281 (0.259)	-0.114 (0.653)	-0.163 (0.517)
DT-penumbra	-0.155 (0.540)	0.346 (0.160)	-0.032 (0.899)
CBF size	-0.210(0.403)	0.497 (0.036)	-0.520 (0.027)
DT size	-0.227 (0.364)	0.464 (0.053)	-0.496 (0.036)

NIHSS, National Institutes of Health Stroke Scale ; CBF-core, cerebral blood flow at the core ; DT-core, arterial delay time at the core ; CBF-penumbra, cerebral blood flow at the penumbra ; DT-penumbra, arterial delay time at the penumbra ; CBF size, size of the area with a reduced cerebral blood flow ; DT size, size of the area with a prolonged arterial delay time.



Case Presentation
Figure 3. Non-recanalization patient (55-year-old woman).
CBF, cerebral blood flow ; DT, arterial delay time ; DWI, diffusion-weighted image ; FLAIR, fluid-attenuated inversion recovery ; ER, enlargement ratio ; DT-penumbra, arterial delay time at the penumbra.

DISCUSSION

"Late-arriving flow appears in ASL images, representing collateral flow (20, 21), which has been associated with better clinical outcomes (22). ASL can noninvasively provide information on the origin and distal function of collateral flow comparable to that obtained with conventional angiography (23, 24)."

we focused on DT, which is another parameter that can be quantitatively evaluated by ASL. DT refers to the time taken for the labeled blood to reach the tissue. DT is considered a parameter for correcting CBF, and it also reflects the late-arriving flow and might be useful for assessing collateral flow (25, 26).

Several studies have suggested a relationship between a prolonged DT and collateral tract formation (27, 28). However, to the best of our knowledge, no studies have examined the relationship between the quantitative evaluation of DT and enlargement of infarct lesions in acute stroke.

In the non-recanalization group, which was considered to represent the natural course of cerebral infarction without the effect of an intervention, the DT at the penumbra was longer and the ER was smaller and, in logistic analysis, the DT at the penumbra was the only independent predictor of the enlargement score both in all patients and in non-recanalization patients. This indicated that a longer DT causes minimal enlargement of the infarct, which may reflect the existence and extent of collateral flow in the ischemic region.

On the other hand, in the recanalization group, the infarct size was not enlarged, even with a low DT, probably due to tissue salvage from a successful reperfusion intervention. In addition, the DT in the penumbra was the only factor predicting the extent of its expansion.

Several researchers have examined the relationship between MRI findings and ischemic regions and their prognosis prediction. The ischemic penumbra has been assessed with PWI to identify its outer edge (29) and DWI has been used to identify its inner edge. A DWI-PWI mismatch has become a widely used biomarker for estimating the ischemic penumbra. Because the penumbral concept is based on CBF assessment, quantitative evaluation of CBF might be useful for evaluating the extent of infarct lesions (30, 31). Butcher *et al*. reported that the acute CBF was 10% lower in infarcted regions relative to salvaged regions (32). However, they also showed that CBF values in salvaged regions were not significantly different between patients with and without reperfusion. This reflected the relatively smaller difference in CBF between infarcted and salvaged regions. Thus, tissue with a lower CBF was at higher risk of infarction, but CBF alone did not predict the response to reperfusion (32, 33). Overall, although PWI and the CBF calculated from this modality have been suggested to be useful, they cannot be said to be definitive indicators.

In many studies, perfusion imaging can be conducted using dynamic susceptibility contrast (DSC)-MRI. DSC-MRI is considered the gold-standard perfusion method for assessing CBF in acute ischemia (34-36). Several studies have compared ASL perfusion to DSC (6, 37, 38). These studies had largely concordant findings, suggesting that ASL could be used in place of DSC without any change in the interpretation or subsequent clinical management. Chalela *et al*. demonstrated the feasibility of using ASL in acute cerebral infarction patients, found the expected CBF decreases in the affected regions, and showed that CBF deficits were correlated with the NIHSS (24). In our study, a lower CBF was correlated with a larger size of the infarct lesion and with a higher NIHSS at the time of visit. On the other hand, CBF was not an indicator associated with infarct enlargement.

For predicting infarct enlargement and neurological prognosis, CBF is not a sufficient indicator and evaluation of collateral flow is required. As an index related to the infarct enlargement and neurological prognosis that is obtained by evaluating collateral flow, the Tmax (the time to the maximum residue function obtained by deconvolution) has been used in recent studies (39-41). Olivot *et al*. suggested that a Tmax threshold > 4 s most closely predicted the final infarct volume in patients who did not undergo reperfusion and that a threshold in the range of 4 to 6 s provided the best early estimate of the critically hypoperfused area (39). Tmax has also been found to correlate with CBF (40, 41).

Huang *et al*. suggested that ASL-CBF lesion volume was significantly correlated with lesion volume for a Tmax > 5 s. However, ASL perfusion may overestimate the perfusion defect, and a lesion volume of a Tmax > 5 s was closer to the estimated mean final infarct size than the mean lesion volume on ASL (42). Marks *et al*. suggested that collateral flow is correlated with the median volume of the tissue at a Tmax > 6 s. They also revealed that patients with poor reperfusion showed a trend toward greater infarct growth if they had poor collaterals versus good

collaterals (43).

Recently, the hypoperfusion intensity ratio (HIR ; volume ratio of brain tissue with [Tmax > 10 s/Tmax > 6 s]) has been considered to be a useful indicator of infarct enlargement and prognosis. A lower HIR suggests more favorable collaterals and predicts a good functional outcome (44, 45). Thus, DT may be a similar indicator to Tmax that includes information concerning collateral flow and may become a useful marker of infarct enlargement and prognosis without the need for contrast-enhancing pharmaceuticals. We believe that the evaluation of collateral flow by DT should be compared to Tmax and HIR as a means of predicting the prognosis of cerebral infarction but, in this study, contrast-enhanced MRI was not performed, and a direct comparison between the two methods could not be conducted. Accordingly, further studies are required.

Several limitations should be mentioned. First, this study is a single-center retrospective study and, based on our aims, we included patients who underwent both an initial ASL-MRI and a follow-up brain MRI ; thus, the limited sample size might not be sufficiently powered to reveal definitive conclusions. Second, the choice of the precise time parameters, including PLD and delayed filling time, was also empirical because no standards exist. Third, we did not investigate the consistency of the CBF score and collateral grading on conventional angiography or other collateral grading approaches.

Despite these limitations, we believe that our study is the first to reveal that quantitative assessment of DT at the penumbra might be a prognostic parameter of acute cerebral infarction enlargement. Furthermore, by evaluating the presence or absence of DT prolongation, it may be possible to obtain information on whether recanalization treatment is necessary. DT is easily calculated by ASL and it may be a very useful clinical parameter.

CONCLUSION

Of all perfusion parameters, the only prognostic parameter for ER was the DT at the penumbra, and the tendency depended on the performance or not of recanalization. DT obtained by multi-delay ASL may become a prognostic index of acute cerebral infarction.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

The authors declare no conflicts of interest.

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