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Distinctive Patterns of Three-Dimensional Arterial Spin-Labeled Perfusion Magnetic Resonance Imaging in Subtypes of Acute Ischemic Stroke

Naoto Kohno, MD,*† Kazunori Okada, MD, PhD,‡ Shingo Yamagata, MD, PhD,§ Hiroyuki Takayoshi, MD,† and Shuhei Yamaguchi, MD, PhD†

Background: Ischemic penumbra in acute ischemic stroke (AIS) can be evaluated using arterial spin-labeled (ASL) perfusion magnetic resonance imaging (MRI). We used three-dimensional ASL-MRI to examine patients with different stroke subtypes and the clinical utility of the method within 24 hours of AIS onset. *Subjects and Methods:* The 55 male and 48 female patients (mean age, 79.0 years) underwent diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery imaging, magnetic resonance angiography, and pulsed continuous ASL perfusion imaging to determine stroke subtype, hypoperfused ASL area, and neurological deficit severity (National Institutes of Health Stroke Scale). Arterial transit artifacts, indicative of occlusive regions or collateral flow, and other stroke indices were compared. *Results:* ASL hypoperfusion was detected in 3 of 9 patients with transient ischemic attack (TIA), 2 of 27 patients with lacunar infarction (LI), 19 of 31 patients with atherothrombotic infarction (AT), and 30 of 36 patients with cardiogenic embolic infarction (CE). ASL abnormalities were significantly less frequent in LI than in AT and CE, and more frequent in CE than in TIA. ASL abnormalities were more prevalent in patients with medium-to-large DWI-assessed lesions than in those with small lesions on DWI. Patients with medium-sized lesions following AT and CE had a high frequency of diffusion–perfusion mismatch. In 4 of the 5 patients who underwent intravenous thrombolytic therapy, ASL hypoperfusion and diffusion–perfusion mismatch were improved and the occluded arteries were recanalized. *Conclusions:* ASL perfusion studies may provide useful clinical information allowing diffusion–perfusion mismatch detection and treatment selection in AIS patients, depending on stroke subtype. **Key Words:** Magnetic resonance imaging (MRI)—diffusion-weighted imaging (DWI)—arterial spin labeling (ASL)—arterial transit artifact (ATA)—cerebral infarction—acute ischemic stroke.

Introduction

Arterial spin labeling (ASL) is a noninvasive magnetic resonance imaging (MRI) technique used to quantitatively assess brain perfusion in humans. ASL-MRI is associated with minimal risk and expense compared to imaging methods using exogenous tracers.[1] It has been applied to elucidate the mechanism underlying ischemic penumbra, defined as a perfusion–diffusion mismatch in patients with acute ischemic stroke (AIS).[2,3] Recent studies have used ASL to assess reperfusion in thrombolytic therapies and hemorrhagic transformation.[4-7] However, few studies have investigated the clinical advantages of ASL in various types of AIS. Thus, in the present work we

From the *Department of Internal Medicine, Seto Inland Sea Hospital, Imabari, Japan; †Department of Neurology, Faculty of Medicine, Shimane University, Matsue, Japan; ‡Ohda Silver Clinic, Ohda, Japan; and §Department of Internal Medicine, Ohda Municipal Hospital, Ohda, Japan.

Received November 3, 2015; revision received February 26, 2016; accepted March 17, 2016.

Address correspondence to Naoto Kohno, MD, Department of Internal Medicine, Seto Inland Sea Hospital, Kitahorai-cho 2-4-9, Imabari 794-0028, Japan. E-mail: kohnonaoto@gmail.com, nkohno@ikirukai.or.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.03.035

investigated the clinical utility of ASL for evaluating AIS and its medical treatment in a group of serially enrolled patients with AIS who were admitted to a municipal hospital in Japan within 24 hours after stroke onset. In addition, following routine MRI and pulsed continuous ASL imaging, the presence of arterial transit artifacts (ATAs) was determined in this group of patients.

Subjects and Methods

Subjects

The 103 consecutively enrolled AIS patients (55 men and 48 women, mean age 79.0 years; range: 48-100 years) were admitted to Ohda Municipal Hospital between April 2011 and March 2013, where they were examined using a prescribed protocol that included emergent MRI procedures. Informed consent was provided by the patients and/or their families. The NINCDS-III[8] criteria were used to classify the patients by stroke subtype: transient ischemic attack (TIA), lacunar infarction (LI), cerebral atherothrombotic infarction (AT), and cardiogenic embolic infarction (CE). The severity of impairment in activities of daily living was assessed using the modified Rankin Scale. Neurological deficits were scored by the National Institutes of Health Stroke Scale (NIHSS).

MRI Procedures

All patients underwent an emergent MRI (1.5 Tesla; GE HDxt, version 23; GE Medical Systems, Milwaukee, WI) examination, including diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery imaging, magnetic resonance angiography (MRA), and pulsed continuous ASL perfusion imaging. ASL images were obtained using three-dimensional (3D) fast spin echo acquisition with pulsed continuous ASL under the following conditions: TR = 4546 ms, TE = 10.5 ms, slice thickness = 4 mm, and fixed postlabel delay = 1525 ms. The imaging time was 4 minutes 33 seconds for ASL and 15 minutes for all MRI procedures.

Imaging Analysis

Images were interpreted qualitatively in random order by 2 expert neurologists (N.K. and K.O.) blinded to the patients' data. DWI lesions were classified according to size as small (lesion diameter ≤1.5 cm), medium, and large (encompassing the entire distribution area of the anterior cerebral artery [ACA], middle cerebral artery [MCA], posterior cerebral artery [PCA], superior cerebellar artery [SCA], or posterior inferior cerebellar artery [PICA]). MRA abnormalities were defined as stenosis greater than 50% or occlusion of the major infarct-related brain vessel. ASL findings were classified according to hypoperfusion size as none (no abnormal findings), focal (hypo- or hyperperfusion less extensive than diffuse), and diffuse (hypo- or hyperperfusion encompassing the entire distribution area of the ACA, MCA, PCA, SCA, or PICA) (Figs 1-3). The presence of perfusion deficits and diffusion–perfusion mismatches (DPM), defined as a perfusion/diffusion volume (PDV) ratio greater than 1.2 according to the Desmoteplase in Acute Ischemic Stroke study criteria,[9] were also assessed. The presence of an ATA, seen as a bright intraluminal area[10] on ASL images, was also determined.

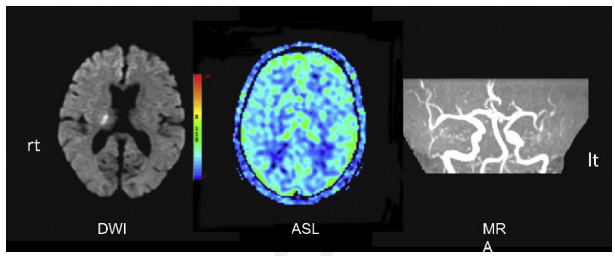

Figure 1. *Magnetic resonance imaging of a 76-year-old woman with a lacunar stroke. DWI showed a small hyperintense lesion in the rt. The ASL image revealed no hypoperfusion and MRA showed no abnormalities. Abbreviations: ASL, arterial spin labeling; DWI, diffusion-weighted imaging; lt, left thalamus; MRA, magnetic resonance angiography; rt, right thalamus.*

Statistical Analysis

Interobserver agreement regarding ASL abnormality patterns was assessed using kappa (κ) statistics. A κ value greater than .6 was defined as good agreement, whereas a κ value greater than .8 was defined as excellent agreement. The frequency of positive ASL findings in each stroke group was compared using the χ^2 test and the column proportion test followed by a Z test for post hoc analysis. SPSS for Windows software (version 22; SPSS Inc., Chicago, IL) was used for all analyses. Two-sided *P* values < .05 were considered to indicate statistical significance.

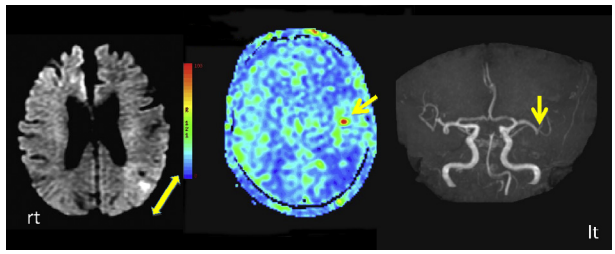

Figure 2. *Magnetic resonance imaging of an 80-year-old man with an atherothrombotic infarction. Diffusion-weighted imaging showed a medium-sized hyperintense lesion in the left MCA-PCA watershed territory. Arterial spin labeling showed a focal hypoperfusion in the left MCA-PCA watershed territory and an arterial transit artifact (arrow). Magnetic resonance angiography revealed occlusion of the M2 segment of the left MCA (arrow). Abbreviations: lt, left thalamus; MCA, middle cerebral artery; PCA, posterior cerebral artery; rt, right thalamus.*

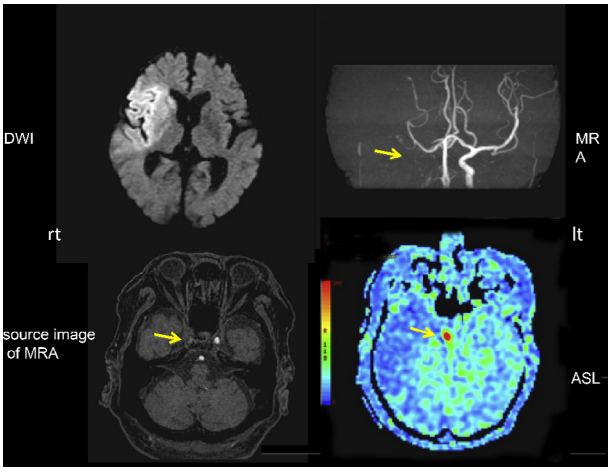

Figure 3. *Magnetic resonance imaging of an 81-year-old man with an embolic stroke. DWI showed a large hyperintense lesion in the right MCA area. MRA showed occlusion of the right ICA (arrow) and the MRA source showed signal loss in the right ICA (arrow). ASL showed diffuse hypoperfusion in the right MCA area and an arterial transit artifact (arrow). A DPM was detected. Abbreviations: ASL, arterial spin labeling; DPM, diffusion–perfusion mismatch; DWI, diffusion-weighted imaging; ICA, internal carotid artery; lt, left thalamus; MCA, middle cerebral artery; MRA, magnetic resonance angiography; rt, right thalamus.*

Results

The average time between symptom onset and image acquisition was 4.7 hours (standard deviation [SD] = 5.5 hours). Table 1 lists the admission data of the patients. Agreement between readers for DWI and ATA was perfect (κ = 1.0), and agreement regarding an ASL abnormality was excellent (κ = .96; 95% confidence interval = .92-1.00).

Data on the occurrence of DWI, MRA, ASL, ATA, and DPM are shown in Table 2. The PDV ratio, based on the DWI images, was significantly lower in the TIA group than in the other groups (all $P < .05$). ASL and MRA positivity was significantly lower in the LI group than in the AT and CE groups ($Ps < .05$). Hypoperfusion was seen in all patients in the AT and CE groups, except for 2 AT patients, in whom a hyperperfusion pattern was detected. ATAs without ASL abnormality were identified in 14 patients. The occurrence of ATA was significantly lower in the LI group than in the AT and CE groups ($Ps < .05$). The total ASL and ATA abnormality rate for the 103 patients was 68.0% (70/103). DPM positivity was significantly lower in the LI group than in the AT and CE groups.

Table 3 shows the prevalence rates of the different patterns of ASL abnormality for each stroke subtype. The rate of no ASL abnormality was significantly higher, and the rate of a diffuse pattern was significantly lower in the LI group than in the AT and CE groups. The 6 patients with CE and no ASL abnormality were all elderly and had heart failure; however, ATA signs were detected on their ASL images.

Table 1. *Data of the patients on admission*

	TIA	LI	AT	CE
Age (years)	84.8 ± 5.5	73.7 ± 12.6	77.7 ± 11.2	82.7 ± 9.1
Sex (male or female)	3/6	15/12	20/11	17/19
mRS	2.4 ± 1.5	2.9 ± 1.4	3.2 ± 1.3	4.1 ± 1.4
NIHSS	2.3 ± 1.9	7.3 ± 9.0	7.1 ± 7.8	14.3 ± 12.4

Abbreviations: AT, atherothrombotic infarction; CE, cardiogenic embolic infarction; LI, lacunar infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Values are means ± standard deviation.

Table 2. *Stroke subtypes and rates of DWI, MRA, and ASL abnormalities; ATA, and DPM*

	TIA (n = 9) (%)	LI (n = 27) (%)	AT (n = 31) (%)	CE (n = 36) (%)
DWI	33.3	96.3*	93.5*	100*
ASL	33.3	7.4	67.7**	83.3**
MRA	33.3	7.4	74.2**	88.9**
ATA	44.4	11.1	45.2**	80.6**
DPM	33.3	7.4	61.3**	66.7**

Abbreviations: ASL, arterial spin labeling; AT, atherothrombotic infarction; ATA, arterial transit artifact; CE, cardiogenic embolic infarction; DPM, diffusion–perfusion mismatch; DWI, diffusion-weighted imaging; LI, lacunar infarction; MRA, magnetic resonance angiography; TIA, transient ischemic attack.

Comparisons were performed using the raw data.

*$P < .05$ versus TIA; **$P < .05$ versus LI.

Table 3. *Prevalence of ASL abnormality patterns for each stroke subtype*

ASL abnormality pattern	TIA (n = 9) (%)	LI (n = 27) (%)	AT (n = 31) (%)	CE (n = 36) (%)
None	67	93	32	17
Focal	11	7	23	14
Diffuse	22	0	45	69

Abbreviations: ASL, arterial spin labeling; AT, atherothrombotic infarction; CE, cardiogenic embolic infarction; LI, lacunar infarction; TIA, transient ischemic attack.

$P < .0001$ (χ^2 test).

The DWI patterns of the lesions varied from none to large. The results of comparison of lesion size on DWI and ASL abnormality pattern are shown in Table 4. The frequency of a normal ASL image was significantly higher in the group with small lesions than in the groups with medium- and large-sized lesions. Diffuse ASL abnormalities were detected significantly less often in patients with small versus medium- and large-sized abnormalities. Thus, according to these findings, the prevalence of DPM was significantly higher in patients with medium-sized lesions than in patients with small lesions (68.8% versus 21.2%). Table 4 also shows the prevalence of MRA and ATA according to the DWI-determined lesion size. The frequency of MRA and ATA was significantly lower in patients with small lesions than in patients with medium- and large-sized lesions.

Intravenous tissue plasminogen activator (t-PA) therapy was administered to 5 patients according to their clinical indications. The average time from AIS onset to MRI was 91 minutes (SD, 12 minutes) and the average time from AIS onset to initiating thrombolytic therapy was 138 minutes (SD, 7 minutes). Clinical symptom improvement was achieved in all 5 patients. The 5 patients included 4 with DPM (3 AT patients and 1 CE patient). Treatment resulted in improvement of the hypoperfusion, as seen on ASL, and recanalization of the obstructed arteries (Fig 4). In 1 AT patient with a brain stem lesion, there was no change in the ASL abnormalities. The mean NIHSS score of the patients treated with t-PA was 12 on admission and 1 at discharge. The mean NIHSS score of the patients not treated with t-PA was 8.5 on admission and 12.4 at discharge. Thus, the prognosis of patients who received t-PA therapy was significantly better than that of patients who did not receive t-PA therapy.

Discussion

ASL is a new, non–contrast-based MRI method that is sensitive to cerebral perfusion and arterial blood arrival delays. Recently, ASL imaging has been used in many clinical settings, including emergent stroke treatment. In this study, we investigated the clinical utility of ASL imaging. Prior to the clinical introduction of ASL, MRI-based measurement of cerebral perfusion was performed using the dynamic susceptibility contrast (DSC) method, which requires tracer injection. The advantages of ASL versus DSC have been evaluated in several reports.[2,3,11-16] Bokkers et al[12] compared ASL and DSC imaging in 78 AIS patients. ASL detected perfusion deficits in 32 patients but failed to detect them in 7 other patients. The κ scores (inter-rater coincidence rate) for detecting perfusion deficits in that study were .60 for ASL and .64 for DSC; for DPM, the κ scores were .51 for ASL and .71 for DSC using 3 T MRI. Other reports also described generally consistent results in identifying hypoperfused lesions using ASL. It has been argued that ASL perfusion images

Table 4. *Prevalence of ASL abnormality pattern, MRA, and DPM and ATA positivity as a function of lesion size on DWI*

		Lesion size			
		None (n = 9) (%)	Small (n = 33) (%)	Middle (n = 48) (%)	Large (n = 13) (%)
Abnormality pattern	None	78	79	27*	8*
	Focal	0	18	19	0
	Diffuse	22	3	54*	92*
MRA		22	21	79*	100*
DPM		22	21	69	46
ATA		33	12	69*	77*

Abbreviations: ASL, arterial spin labeling; ATA, arterial transit artifact; DPM, diffusion–perfusion mismatch; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography.

Subscript letters mean no significant difference for each proportion.

*$P < .05$ versus the group with small lesions as seen on DWI.

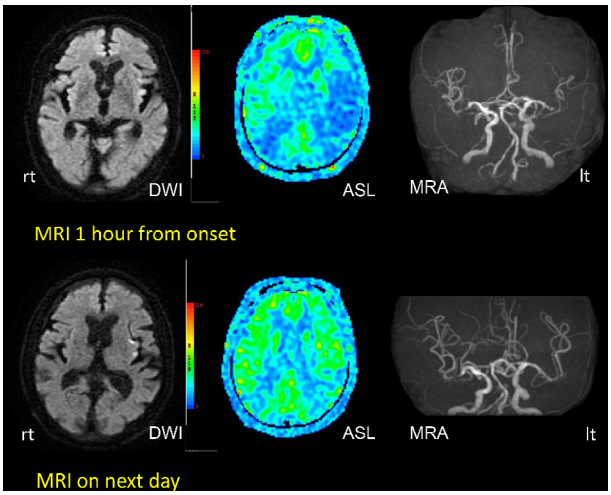

Figure 4. *MRI of an 81-year-old man with an atherothrombotic infarction. On admission, he presented with right hemiparesis, aphasia, and dysarthria. His NIHSS score was 16. DWI 1 hour after onset revealed a medium-sized hyperintense lesion in the left insular lobe. MRA showed severe stenosis in the M2 segment of the left MCA. ASL imaging showed diffuse hypoperfusion in the left MCA area. A diffusion–perfusion mismatch was detected. His neurological symptoms improved the next day and his NIHSS score was 4. DWI showed a medium-sized hyperintense lesion in the left insular lobe. MRA showed improvement of the stenosis in the M2 segment of the left MCA. ASL showed improved hypoperfusion in the left MCA area. Abbreviations: ASL, arterial spin labeling; DWI, diffusion-weighted imaging; lt, left thalamus; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; rt, right thalamus.*

are not clinically reliable because of the inherently low signal-to-noise ratio. However, this and other weaknesses of the method have been overcome with pulsed continuous ASL, which uses background suppression and 3D fast spin echo acquisition to provide robustness against motion and susceptibility artifacts. This method forms the basis of our own MRI system and of those used in more than half of the recently reported studies.

The combined ASL and ATA findings revealed a high abnormality rate (77.5%) in our AIS patients. Zaharchuk et al investigated the ASL findings in a series of patients with TIA and reported that ASL-perfusion-related alterations were more frequently detected than either perfusion-weighted imaging or intracranial MRA abnormalities and were more apparent in the affected hemisphere.[16] They concluded that ASL can aid in the workup and triage of TIA patients, particularly those who cannot undergo a contrast study. Our study had too few TIA patients to confirm their observations, but the ASL patterns in our patients varied from no lesion to a diffuse pattern, depending on the stroke subtype. To the best of our knowledge, ours is the first study to evaluate the relationship between ASL findings and stroke subtype combined with DWI-determined lesion size. The specific features may be explained by the distinct pathophysiological hemodynamic changes that occur in the various stroke subtypes. Thus, patients with LI, who in most cases had small lesions on DWI, had no ASL abnormalities, whereas in patients with AT and CE, who were more likely to have medium- to large-sized lesions, highly diffuse abnormalities were frequently detected. The prevalence of ATA associated with DPM was significantly higher in the AT and CE groups than in the LI group. DPM was most frequently observed in the patient group with medium-sized lesions. These findings may serve as a useful reference in decision making related to acute stroke therapy.

ASL enables noninvasive and repeatable assessment of pre- and post-thrombolytic therapies. In recent studies, it has been used to assess reperfusion following thrombolysis. In the study of Rahmah et al, serial imaging showed an improvement of cerebral blood flow (CBF) after t-PA treatment in 2 patients.[4] Based on their 16 AIS patients who underwent thrombolysis, Griebe et al concluded that ASL perfusion images can provide additional information on the pathophysiology of acute arterial occlusion and its subsequent course.[5] Mirasol et al used ASL and DSC imaging to evaluate the effect of reperfusion and concluded that ASL is a noninvasive and practical alternative to DSC in the assessment of reperfusion in AIS patients.[6] In a series of AIS patients, Yu et al investigated the relationship between postischemic hyperperfusion on ASL and hemorrhagic transformation.[7] They suggested the use of ASL hyperperfusion as an imaging marker of hemorrhagic transformation and recommended that late hyperperfusion should be paid greater attention to prevent deterioration of the patient's clinical course. Five of the patients included in this study underwent thrombolytic therapy. Except for 1 patient with a brain stem lesion, all of the patients showed neurological and hemodynamic improvement associated with recanalization. An improvement in ASL-detected hypoperfusion in these 4 patients supports the usefulness of this technique as an imaging marker of clinical outcome.

In our AIS series, no ASL laterality was seen in the 6 CE patients but ATAs were detected in all of them. The reason for this finding is unclear, but it may be due to reperfusion or delayed cerebral circulation. Earlier reports addressing this same observation recommended the use of a longer postlabel delay time on either conventional ASL or velocity-selective ASL with high field scanners.[3,17,18]

ATA implies delayed flow and manifests as a serpiginous high signal without demonstration of the cortical vessels. ATA detects subtle perfusion alterations that result in prolonged cerebral arterial arrival times, which imply the presence of arterial occlusion or collateral flow.[3,13] Recently, 2 reports compared ATA and the susceptibility vessel sign on T2*-weighted images. Tada et al reported that the sensitivity and accuracy of ATA detection on ASL were significantly higher than the detection of the susceptibility vessel sign using T2*-weighted MRI.[19] Yoo et al reported that the presence of ATA on ASL could provide

an important diagnostic clue allowing for improved detection and localization of arterial occlusive sites in AIS.[20] In our study, the frequency of ATA and MRA was significantly low in LI and high in CE, which indicated that ATA reflects the hemodynamic pathology at the sites of perforator vessel lesions or acute obstruction of a major arterial trunk. Conversely, the lack of ATA development following an AT type stroke can perhaps be attributed to the gradual progressive arterial obstruction in atherothrombotic cerebral infarction.

We assessed qualitative changes in the CBF pattern in AIS patients by means of ASL imaging. In the care of patients with acute stroke, DPM must be identified quickly and treatment started immediately, especially if thrombolytic therapy is indicated. Whereas experts in stroke care can readily determine the appropriate treatment of AIS patients, ASL is a useful tool to guide clinical decision making by nonexpert physicians, such as those working in a local hospital.[11] In their study comparing ASL perfusion-weighted imaging with the DSC method in AIS patients, Niibo et al reported that an ASL threshold of less than 20 mL/100 g/min is a reliable indicator of mismatch and corresponds to a mean transit time threshold of more than 10 seconds.[14]

Our study is preliminary. A more precise assessment of the specific features of the various stroke subtypes requires larger scale studies. However, our results demonstrate the utility of ASL in revealing the pathophysiology underlying the stroke-related hemodynamic state and in guiding decision making for the optimal treatment of AIS patients depending on the stroke subtype.

Acknowledgments: We thank the following physicians in the Department of Internal Medicine of Ohda Municipal Hospital for their participation in this study: Tomoko Hashimoto, Masanori Hashimoto, Fuminori Takeda, and Hiroshi Furuya.

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