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Cerebrovascular Reservoir and Arterial Transit Time Changes Assessed by Acetazolamide-Challenged Multi-Phase Arterial Spin Labeling Perfusion MRI in Chronic Cerebrovascular Steno-Occlusive Disease

만성 뇌혈관 협착폐색증에서 아세타졸아미드 부하 다상 동맥스핀표지 자기공명관류영상으로 평가한 뇌혈류 예비능과 동맥 통과 시간의 변화

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Purpose To explore cerebrovascular reservoir (CVR) and arterial transit time (ATT) changes using acetazolamide-challenged multi-phase arterial spin labeling (MP-ASL) perfusion-weighted MRI in chronic cerebrovascular steno-occlusive disease.

Materials and Methods This retrospective study enrolled patients with chronic steno-occlusion who underwent acetazolamide-challenged MP-ASL between June 2019 and October 2020. Cerebral blood flow, CVR, basal ATT, and ATT changes associated with severe stenosis, total occlusion, and chronic infarction lesions were compared.

Results There were 32 patients (5 with bilateral steno-occlusion) in our study sample. The CVR was significantly reduced during total occlusion compared with severe stenosis (26.2% ± 28.8% vs. 41.4% ± 34.1%, respectively, $p = 0.004$). The ATT changes were not significantly different ($p = 0.717$). The CVR was marginally lower in patients with chronic infarction (29.6% ± 39.1% vs. 38.9% ± 28.7%, respectively, $p = 0.076$). However, the ATT was less shortened in pa-

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tients with chronic infarction (-54 ± 135 vs. -117 ± 128 ms, respectively, p = 0.013).

Conclusion Acetazolamide-challenged MP-ASL provides an MRI-based CVR evaluation tool for chronic steno-occlusive disease.

Index terms Acetazolamide; Cerebrovascular Circulation; Cerebrovascular Disorders; Magnetic Resonance Angiography; Perfusion

INTRODUCTION

The treatment goal of cerebrovascular steno-occlusive disease is to prevent stroke. The current examination for stroke risk mostly depends on the degree of stenosis or poststenotic flow (1, 2). However, collateral flow assessment provides important hemodynamic information to select a treatment plan (3, 4). Cerebrovascular reservoir (or cerebrovascular reactivity; CVR) is defined as a flow response to a given vasoactive stressor (5), and it reflects the net effect of compensatory vasodilation and recruitment of collateral blood flow. It is believed to be a more desirable hemodynamic assessment for chronic steno-occlusive disease (6).

There are several methods to evaluate CVR using various imaging modalities and vasoactive stimuli (5). In particular, arterial spin labeling (ASL) perfusion-weighted MRI uses blood as an endogenous, diffusible tracer; therefore, it is a repeatable method without contrast media administration (7). Furthermore, ASL can provide absolute quantification of cerebral blood flow (CBF). There has been an attempt to use ASL in CVR evaluation with acetazolamide in moyamoya disease, demonstrating excellent diagnostic performance to detect impaired CVR (8). However, ASL has a particular limitation in the quantification of CBF when arterial transit time (ATT) is delayed in chronic steno-occlusive disease, causing underestimation of CBF and delayed ATT artifacts (9). Multiple post-labeling delay (PLD) acquisitions make it possible to improve the quantification of CBF by correction of the ATT. A Hadamard-encoded multi-phase ASL (MP-ASL) can provide transit-time-corrected CBF and ATT maps with reasonable time and signal-to-noise ratio (10). MP-ASL predicts the hypoperfusion area more accurately than standard ASL in moyamoya disease with ^{15}O-water PET as a reference standard (11). However, acetazolamide-challenged MP-ASL has not been rigorously investigated to evaluate CVR.

Therefore, the purpose of this study was to explore the cerebrovascular reservoir and ATT change by acetazolamide-challenged MP-ASL perfusion-weighted MRI in chronic cerebrovascular steno-occlusive disease.

MATERIALS AND METHODS

STUDY POPULATION

The Institutional Review Board approved this single-center, retrospective observational study, and informed consent was waived (IRB No. H-2012-121-1183). We searched a radiology database between June 2019 and October 2020 that included data for MP-ASL performed with acetazolamide challenge in our institution for chronic cerebrovascular steno-occlusive dis-

ease. The patients were referred from the Department of Neurology to evaluate newly diagnosed chronic cerebrovascular steno-occlusive disease. Our institution has performed acetazolamide-challenged ASL perfusion-weighted MRI for clinical purposes. The patients were diagnosed with severe stenosis or total occlusion of the internal carotid artery (ICA) or proximal middle cerebral arterial (MCA, M1, or proximal M2 segment) on digital subtracted angiography (DSA) or MR angiography (MRA). The stenosis degree was determined using the North American Symptomatic Carotid Endarterectomy Trial criteria for proximal ICA lesions and the Warfarin–Aspirin Symptomatic Intracranial Disease study criteria for intracranial lesions (1, 12).

MRI ACQUISITION

All patients underwent brain MRI using a 3.0-T MR scanner (Discovery MR 750w, GE Healthcare, Milwaukee, WI, USA) with a 32-channel phased-array head coil. Basal MP-ASL perfusion-weighted MRI was obtained using three-dimensional (3D) spiral fast spin-echo sequences with a Hadamard-encoded pseudo-continuous ASL. The imaging parameters were as follows: repetition time (TR), 7311 ms; echo time (TE), 11.0 ms; flip angle (FA), 111°; readout, 4 arms × 640 samples; field of view (FOV), 240 × 240 mm; section thickness, 6 mm; number of excitations (NEX), 1; reconstructed resolution, 1.88×1.88 mm^2; and acquisition time, 4 min 33 s. We set Hadamard-encoded multiple PLDs using the following parameters: perfusion labeling time, 4 s; PLD, 1 s; number of delays, 7; and exponential delay spacing resulting in 7 PLDs of 1.00, 1.23, 1.50, 1.82, 2.21, 2.74, and 3.51 s with label durations of 0.23, 0.27, 0.32, 0.40, 0.52, 0.77, and 1.49 s, respectively. A proton density-weighted image with the same parameters was also obtained for CBF quantification.

Ten minutes after intravenous administration of acetazolamide (Zoladin injection, BC World Pharm, Seoul, Korea) at a dose of 14 mg/kg of body weight, acetazolamide challenge MP-ASL was obtained with the same acquisition parameters. T1-weighed 3D magnetization-prepared rapid acquisition gradient-echo sequences were obtained for structural imaging between the waiting times after intravenous administration of acetazolamide. The sequence parameters were as follows: TR = 7.5 ms; TE = 2.7 ms; FA = 12°; acquisition matrix = 256 × 256 × 256; FOV = 256 × 256 × 256 mm; reconstructed voxel size, $1 \times 1 \times 1$ mm^3; NEX, 1; and sagittal plane with multiplanar reconstruction.

The time-corrected CBF map was calculated by fitting the 7-delay ASL difference signals as a function of the PLD to the following equation:

$$\text{CBF (mL/100 g/min)} = 6000 \cdot \frac{e^{\delta/T_{1a}}}{2\varepsilon T_{1a} \left[e^{-\max(PLD-\delta,0)/T_{1t}} - e^{-\max(PLD+LD-\delta,0)/T_{1t}} \right]} \cdot \lambda \cdot \frac{M}{M_0}$$

where M is the signal difference of ASL control and labeled images; M_0 is the signal of proton density-weighted images; T_{1a} and T_{1t} are the longitudinal relaxation times of blood and tissue, respectively (1.65 and 1.2 seconds, respectively); ε is the combined efficiency of the labeling sequence and background suppression (0.85 × 0.75), and λ is the tissue-to-blood partition coefficient of water (0.9). The ATT map (δ) was measured as described by Dai et al. (13).

IMAGE ANALYSIS

The basal/acetazolamide MP-ASL images were processed using the FMRIB Software Library (FSL version 6.0.1; http://fsl.fmrib.ox.ac.uk/fsl) by a single investigator (I.H., with 9 years of experience in neuroradiology). The skull-stripped T1-weighted images were generated using the BET tool (14) and used as a structural reference. The skull-removed proton-density weighted images for CBF quantification were coregistered to T1-weighted images by six degrees of freedom rigid transformation using the FLIRT tool (15). Then, the transformation matrix was applied to time-corrected CBF and ATT maps. The time-corrected CBF and ATT maps were smoothed with a Gaussian kernel with a standard deviation of 4 mm. All coregistration results were verified visually by the investigator.

Sixteen spherical volumes of interest (VOIs; 2 cm in diameter) were drawn into bilateral cerebral cortical areas regarding the anterior circulation territory in the Montreal Neurological Institute 152 standard space (MNI 152) (Fig. 1). The T1-weighted images were affinely transformed into MNI 152 space, and VOIs were reverse transformed to each patient's T1-weighted images. Systematic measurement of basal and acetazolamide time-corrected CBF and ATT was then performed. The CVR and ATT change (ΔATT) were then calculated as follows:

$$CVR = (CBF_{acetazolamide} - CBF_{basal})/CBF_{basal}$$
$$\Delta ATT = ATT_{acetazolamide} - ATT_{basal}$$

The measured basal CBF, acetazolamide CBF, CVR, basal ATT, and ΔATT in each VOI from all patients were used for further statistical analysis.

STATISTICAL ANALYSIS

Descriptive statistics summarized demographic and clinical characteristics. For unilateral

Fig. 1. VOI templates for the Montreal Neurological Institute 152 standard space.
A, B. Sixteen VOIs are drawn around bilateral cerebral cortical areas within the anterior circulation territory.
VOI = volume of interest
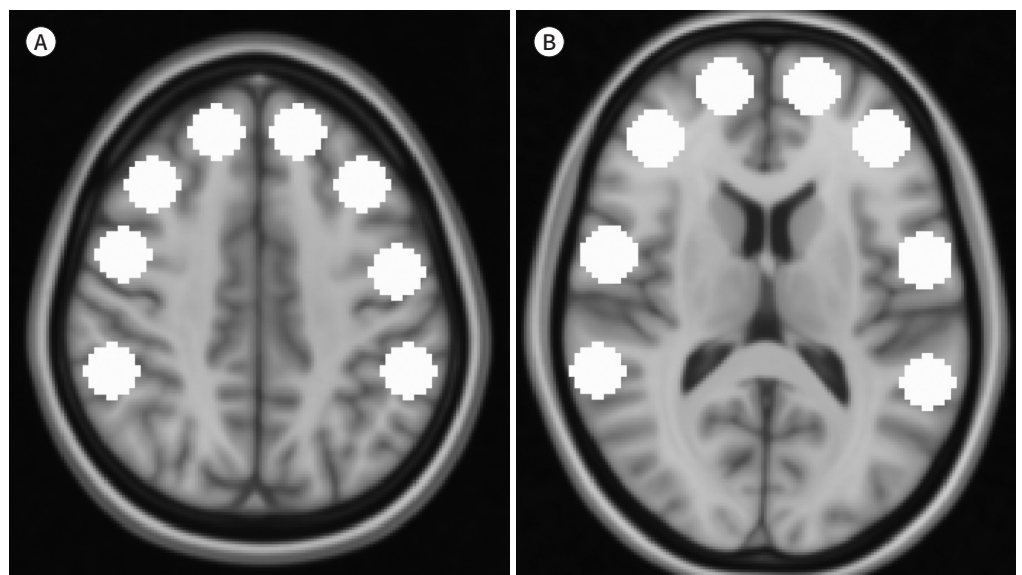
steno-occlusive disease, a pairwise comparison of perfusion metrics was performed between the steno-occlusion side and contralateral side by the signed-rank test for clustered data (16). Group comparison of perfusion metrics was then performed according to the degree of steno-occlusion (total occlusion vs. severe stenosis) on the steno-occlusion side. In bilateral cases, both hemispheres were regarded as a steno-occlusion side. Furthermore, we compared the perfusion metrics according to the presence of chronic territorial infarction or border-zone infarction lesions on T1-weighted images on the steno-occlusion side. The two-sample *t*-test for clustered data was performed with a subject as a cluster variable (17). Finally, correlation analysis between CVR and ΔATT was performed using Pearson's correlation coefficient (*r*). All statistical analyses were performed using the open-source statistical language (R for Windows, version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria). In all statistical tests, a *p* value of less than 0.05 was considered significant.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Finally, were 32 patients included in the study sample (25 male and 7 female). The mean and standard deviation of the age was 68.9 ± 10.6 years. Thirteen patients had right-sided stenosis, and 14 patients had left-sided stenosis. The stenosis sites and degree were as follows: proximal ICA severe stenosis (*n* = 15), proximal ICA occlusion (*n* = 6), proximal MCA severe stenosis (*n* = 4), and proximal MCA occlusion (*n* = 7). There were 5 patients with bilateral steno-occlusion as follows: 3 patients with proximal ICA occlusion and contralateral proximal ICA severe stenosis, one patient with bilateral proximal ICA severe stenosis, and one patient with bilateral proximal MCA occlusion. Twenty-one patients were diagnosed with DSA, and 11 patients were diagnosed with MRA. Fig. 2 illustrates a representative case.

All patients tolerated the acetazolamide-challenged MP-ASL studies well. There were no immediate adverse events or neurological deficits within the first day after acetazolamide challenge by medical record search.

PAIRWISE COMPARISON OF PERFUSION METRICS BETWEEN THE STENO-OCCLUSION SIDE AND CONTRALATERAL SIDE IN UNILATERAL STENO-OCCLUSIVE DISEASE

On the steno-occlusion side, the basal CBF and acetazolamide CBF were lower, and ATT was significantly prolonged (all *p* < 0.001) (Table 1). The CVR was significantly reduced on the steno-occlusion side (38.5% ± 35.2% vs. 50.7% ± 27.4%, respectively, *p* = 0.016). In addition, the ATT was significantly less shortened after acetazolamide challenge on the steno-occlusion side than on the contralateral side (-97 ± 140 ms vs. -169 ± 114 ms, respectively, *p* < 0.001).

COMPARISON OF PERFUSION METRICS ACCORDING TO THE DEGREE OF STENO-OCCLUSION

Interestingly, hemispheres with total occlusion showed significantly higher basal CBF than severe stenosis (56.4 ± 23.9 vs. 49.0 ± 17.0 mL/100 g/min, respectively, *p* = 0.032). The CVR was significantly reduced in total occlusion compared with severe stenosis (26.2% ± 28.8%

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vs. 41.4% ± 34.1%, respectively, p = 0.004). The basal ATT and ΔATT were not significantly different in total occlusion and severe stenosis (p = 0.989 and p = 0.717, respectively, Table 2).

COMPARISON OF PERFUSION METRICS ACCORDING TO THE PRESENCE OF CHRONIC INFARCTION LESIONS

Six patients had chronic territorial infarction or borderzone infarction lesions on the steno-occlusion side. All patients with bilateral steno-occlusion had chronic infarction lesions on at least one side. In patients with chronic infarction, the basal CBF and acetazolamide CBF of the steno-occlusion side were significantly reduced, and the basal ATT was more delayed (all p < 0.001, Table 3). The CVR was lower in patients with chronic infarction but was marginally significant (29.6. ± 39.1% vs. 38.9. ± 28.7%, respectively, p = 0.076). Furthermore,

Fig. 2. Representative case.
A-G. A 74-year-old male was diagnosed with right proximal ICA occlusion **(A)** and left proximal ICA severe stenosis **(B)** based on digital subtraction angiography findings (lateral projection). The basal time-corrected CBF map **(C)** demonstrates decreased perfusion in the right ICA territory. The acetazolamide-challenged CBF map **(D)** reveals substantial augmentation of CBF in the left cerebral hemisphere and the right posterior circulation territory. In contrast, no substantial CBF augmentation is noted in the right ICA territory, suggesting an impaired cerebrovascular reservoir. The axial T1-weighted images **(E)** reveals chronic infarction in the right inferior frontal lobe and right basal ganglia (repetition time, 7.5 ms; echo time, 2.7 ms). The basal ATT map **(F)** shows delayed ATT in the right ICA territory. On the acetazolamide-challenged ATT map **(G)**, the ATT is reduced in the left cerebral hemispheres (please note the color change), but the ATT change in the right ICA territory is minimal.
ATT = arterial transit time, CBF = cerebral blood flow, ICA = internal carotid arterial
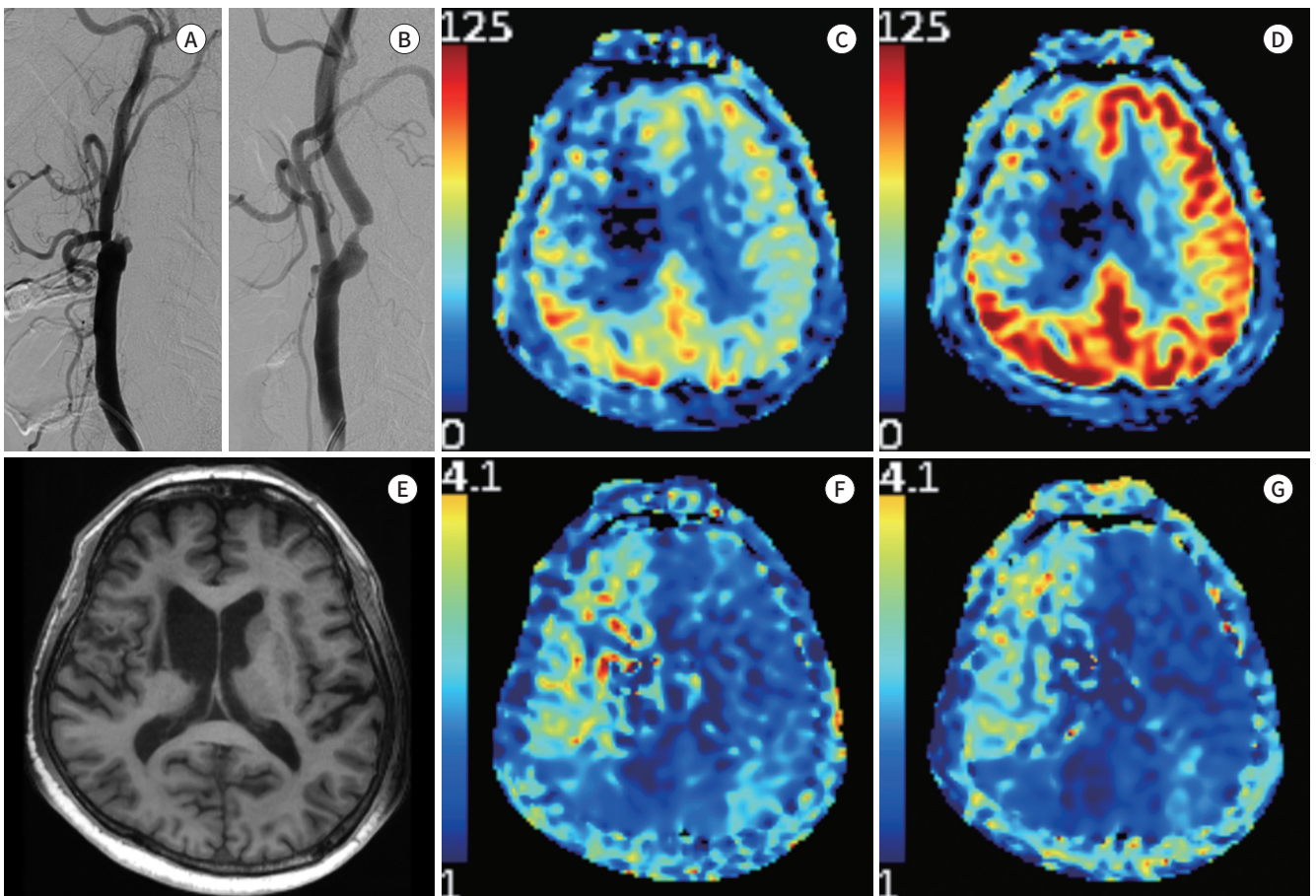
Table 1. Comparison of Ipsilateral and Contralateral Perfusion Metrics in Unilateral Steno-Occlusive Disease (n = 27)

	Steno-Occlusion Side	Contralateral Side	*p*-Value*
Basal CBF (mL/100 g/min)	53.1 ± 21.5	56.8 ± 18.9	< 0.001
Acetazolamide CBF (mL/100 g/min)	70.3 ± 24.7	82.9 ± 22.7	< 0.001
CVR (%)	38.5 ± 35.2	50.7 ± 27.4	0.016
Basal ATT (ms)	1624 ± 335	1435 ± 192	< 0.001
ΔATT (ms)	-97 ± 140	-169 ± 114	< 0.001

Data are presented as mean ± standard deviation.
*Pairwise comparison between the steno-occlusion side and the contralateral side.
ATT = arterial transit time, ΔATT = ATT change, CBF = cerebral blood flow, CVR = cerebrovascular reservoir

Table 2. Comparison of Perfusion Metrics in Severe Stenosis and Total Occlusion

	Severe Stenosis (n = 23)*	Total Occlusion (n = 14)*	*p*-Value
Basal CBF (mL/100 g/min)	49.0 ± 17.0	56.4 ± 23.9	0.032
Acetazolamide CBF (mL/100 g/min)	66.7 ± 21.5	69.7 ± 27.4	0.481
CVR (%)	41.4 ± 34.1	26.2 ± 28.8	0.004
Basal ATT (ms)	1762 ± 273	1761 ± 344	0.989
ΔATT (ms)	-98 ± 144	-89 ± 115	0.717

Data are presented as mean ± standard deviation.
*Number of steno-occlusion sides (including 5 bilateral steno-occlusions).
ATT = arterial transit time, ΔATT = ATT change, CBF = cerebral blood flow, CVR = cerebrovascular reservoir

Table 3. Comparison of Perfusion Metrics Associated with Chronic Infarction Lesions

	With Chronic Infarction (n = 13)*	Without Chronic Infarction (n = 24)*	*p*-Value
Basal CBF (mL/100 g/min)	41.3 ± 16.6	57.5 ± 19.7	< 0.001
Acetazolamide CBF (mL/100 g/min)	51.2 ± 20.3	76.8 ± 20.6	< 0.001
CVR (%)	29.6 ± 39.1	38.9 ± 28.7	0.076
Basal ATT (ms)	1933 ± 280	1668 ± 270	< 0.001
ΔATT (ms)	-54 ± 135	-117 ± 128	0.013

Data are presented as mean ± standard deviation.
*Number of steno-occlusion sides (including 5 bilateral steno-occlusions).
ATT = arterial transit time, ΔATT = ATT change, CBF = cerebral blood flow, CVR = cerebrovascular reservoir

the ATT was less shortened in patients with chronic infarction (-54 ± 135 vs. -117 ± 128 ms, respectively, p = 0.013).

CORRELATION OF CVR AND ATT CHANGE BY ACETAZOLAMIDE CHALLENGE

There was a negative linear correlation between CVR and ΔATT (r = -0.250, p < 0.001) in all VOIs pooled together. Scatterplots are presented in Fig. 3. However, ΔATT was less correlated with CVR on the steno-occlusive side (r = -0.130, p = 0.025). In the contralateral hemispheres, ΔATT was negatively correlated with CVR (r = -0.327, p < 0.001).
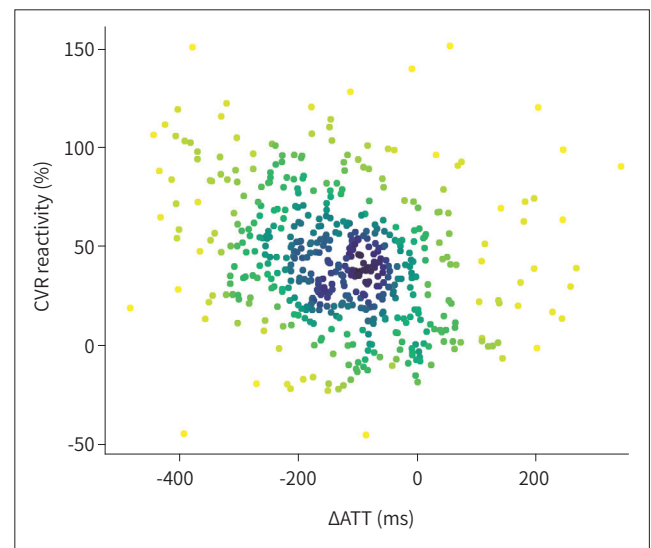
Fig. 3. A scatterplot of CVR and ΔATT. ΔATT is negatively correlated with the CVR.
ΔATT = arterial transit time change, CVR = cerebrovascular reservoir

DISCUSSION

Our study demonstrated MP-ASL-based acetazolamide-induced perfusion changes in chronic steno-occlusive disease. In unilateral steno-occlusion cases, the steno-occlusion side showed a significantly reduced CVR (38.5% vs. 50.7% $p = 0.016$) and less shortening of ATT after acetazolamide challenge (-97 ms vs. -169 ms, $p < 0.001$). The CVR was significantly reduced in the total occlusion group compared with the severe stenosis group (26.2% vs. 41.4%, $p = 0.004$). The CVR was lower in the hemispheres with chronic infarction, but was not significant (29.6% vs. 38.9%, $p = 0.076$). However, the magnitude of ΔATT was smaller in hemispheres with chronic infarction (-54 ms vs. -117 ms, $p = 0.013$).

In a previous study, the CVR was evaluated by acetazolamide-challenged MP-ASL in moyamoya disease (18), showing that the CVR gradually decreases with the stenosis degree. In this previous study, however, severe stenosis and occlusion were considered as a single category. Our study demonstrated that there was a certain difference in CVR between patients with severe stenosis and total occlusion in patients with carotid or intracranial steno-occlusion. Interestingly, the basal CBF was higher in the total occlusion group than in the severe stenosis group. A previous study also found a paradoxical increase in basal CBF by increasing stenosis severity. This may be partially explained by the fact that labeled protons in more severe stenosis spend more time in the arterial blood, where T1 relaxation time is longer than in brain tissue, and gives greater ASL perfusion signal after ATT correction (18).

There are several pieces of evidence that impaired CVR is associated with stroke in high-grade carotid stenosis or intracranial stenosis (6, 19). Furthermore, it is believed that preserved CVR may indicate a lower risk of stroke regardless of the degree of carotid artery stenosis (20). Basal CBF was significantly decreased in hemispheres with chronic infarction, which might be due to the reduced oxygen demand of infarcted tissue and might not necessarily indicate a higher risk of further stroke. Although our study did not evaluate new acute stroke, patients with chronic infarction showed marginally lower CVRs ($p = 0.076$).

The ATT can be obtained only by MP-ASL. It was negatively correlated with CVR; hence, it

has been proposed as a surrogate marker of CVR impairment without acetazolamide challenge (18, 21). However, little is known about the ATT changes caused by acetazolamide challenge. Previous CT and MR perfusion studies have reported a reduction in the mean transit time (MTT) after acetazolamide challenge (22, 23). Although ATT is known to be correlated with MTT (24), the ATT is the traveling time of labeled blood between the labeling plane and the imaging plane, while MTT is the average transit time of blood through a given brain region (25). In our study, ATT changes were significantly blunted in hemispheres with chronic infarction and negatively correlated with the CVR. The novel role of ATT changes in the assessment of CVR and stroke risk may be investigated in future research. Meanwhile, there was a concern in using ASL for acetazolamide challenge because it changes the ATT, which may affect absolute CBF quantification. However, MP-ASL can provide time-corrected CBF regardless of the ATT change. A recent study has shown that ATT and time-corrected CBF by MP-ASL are longitudinally stable, supporting their use in a vasoactive challenge study (26).

Although there is no standardization of published studies that have evaluated CVR, acetazolamide-challenged brain perfusion single-photon emission computed tomography (SPECT) is one of the most readily available nuclear medicine imaging techniques that provide cross-sectional images (27, 28). However, SPECT has disadvantages of radiation exposure and limited absolute quantification (29). In contrast, MP-ASL can provide absolute CBF measures without radiation exposure. Particularly, absolute CVR might be useful for identifying CVR impairment in significant bilateral steno-occlusive disease. Meanwhile, there are no widely accepted criteria for impaired CVR. The proposed criteria used to define an abnormal response to acetazolamide include less than a 10% increase in the absolute CBF or less than an absolute increase of 10 mL/100 g/min (28). A prior study demonstrated that acetazolamide-challenged standard ASL shows a 30–45% increase in CBF in healthy subjects (30). In our study, the mean CVR on the contralateral side was 50.7%, which was higher than that of the prior healthy subject study. It is possible that transit time correction may affect absolute CVR. Therefore, a comparative study with reference standards, such as SPECT or PET, is warranted to assess the diagnostic performance of acetazolamide-challenged MP-ASL and to obtain robust criteria for impaired CVR.

The present study had several limitations. First, the retrospective study design had a potential selection bias. Second, we did not consider the difference between proximal carotid stenosis and MCA stenosis. The anterior cerebral arterial territory may not be affected in cases of MCA stenosis. Finally, we used relatively small spherical VOIs in the anterior circulation territory for simplicity, which was motivated by the Alberta stroke program early CT score (9, 31). However, the VOI size was relatively small and not all-inclusive for the affected hemispheres. An exhaustive VOI template should be used for exact and extensive measurements.

In conclusion, the CVR evaluated with acetazolamide-challenged MP-ASL showed a significant difference according to the degree of steno-occlusion. Furthermore, acetazolamide-challenged MP-ASL could evaluate the ATT change that was significantly different according to the presence of chronic infarction, suggesting clinical relevance. Acetazolamide-challenged MP-ASL may provide an MRI-based CVR evaluation tool for chronic steno-occlusive disease.

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대한영상의학회지

만성 뇌혈관 협착폐색증에서 아세타졸아미드 부하 다상 동맥스핀표지 자기공명관류영상으로 평가한 뇌혈류 예비능과 동맥 통과 시간의 변화

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목적 만성 뇌동맥 협착-폐색증에서 아세타졸아미드 부하 다상 동맥 스핀 표지(multi-phase arterial spin labeling; 이하 MP-ASL) 자기공명관류영상을 이용하여 뇌혈류 예비능(cerebrovascular reservoir; 이하 CVR)과 동맥 통과 시간(arterial transit time; 이하 ATT)의 변화를 탐색하였다.

대상과 방법 2019년 6월부터 2020년 10월까지 새롭게 만성 협착-폐색증으로 진단되어 아세타졸아미드 부하 MP-ASL을 시행한 환자를 후향적으로 모집하였다. 부하 전후의 뇌혈류(cerebral blood flow), CVR, 부하전 ATT 및 부하 전후의 ATT 변화량을 중증 협착과 완전 폐색간, 만성 뇌경색 병변의 유무에 따라 비교하였다.

결과 5명의 양측성 협착-폐색을 포함하여 총 32명의 환자가 본 연구에 포함되었다. CVR은 완전 폐색에서 중증 협착보다 유의하게 낮았다(26.2% ± 28.8% vs. 41.4% ± 34.1%, p = 0.004). ATT의 변화는 두 군간 유의한 차이는 없었다(p = 0.717). 만성 뇌경색 병변의 유무에 따른 CVR의 통계적 차이는 미미하였다(29.6% ± 39.1% vs. 38.9% ± 28.7%, p = 0.076). 하지만, 만성 뇌경색 병변이 있는 환자에서 ATT의 단축 정도는 유의하게 작았다(-54 ± 135 vs. -117 ± 128 ms, p = 0.013).

결론 만성 협착-폐색증에서 아세타졸아미드 부하 MP-ASL 검사는 MRI 기반의 CVR 평가 도구로 사용될 수 있다.

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