Detection of Stenosis Progression in Intracranial Vertebral Artery Dissection Using Carotid Ultrasonography

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Background: The purpose of this study was to assess whether carotid ultrasonography indices detect arterial stenosis progression in patients with vertebral artery (VA) dissection. *Methods:* This was a retrospective, single-center, observational study that enrolled patients with intracranial VA dissection who were admitted from January 2011 to June 2017. Magnetic resonance angiography (MRA) was done on admission and followed up at a median 20 days after onset (interquartile range [IQR] 9-58 days), and ultrasonography was performed at a median of 22 (interquartile range 7-56) days. Peak systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity (MV), and pulsatility index (PI) were measured by ultrasonography, and the ratio of each follow-up value to the baseline (follow-up/baseline) value was calculated. Two stroke neurologists categorized into 3 groups by morphological changes of the dissected vessel: patients with stenosis progression (progression group: P-group); those with no remarkable change or dilatation improved (stable group: S-group); and those with stenosis regression or dilatation enlargement (enlargement group: E-group). Ultrasonography indices were compared among the groups. *Results:* Of the 42 patients who were enrolled to this study, 39 patients underwent ultrasonography and MRA on both admission and follow-up. The PI ratio was significantly higher in the P-group than in the S-group ($1.96 \pm .80$ versus $.98 \pm .44$, $P = .02$) and in the E-group (versus $.65 \pm .35$, $P < .01$). There were no significant differences in the PSV ratio, EDV ratio, and MV ratio. *Conclusions:* In patients with VA dissection, the PI ratio on ultrasonography is a promising index to detect stenosis progression.

Key Words: Vertebral artery dissection—carotid ultrasonography—magnetic resonance angiography—pulsatility index

Introduction

Arterial dissection was identified in 7% of ischemic stroke patients under 50 years of age in a Japanese multicenter study and is one of the most important stroke etiologies.[1] Patients with intracranial artery dissection often develop morphological changes of the dissected artery, mainly in the early phase after onset. The changes cause stenosis or occlusion of vessels and sometimes lead to ischemic stroke.[2] The changes are observed by magnetic resonance angiography (MRA) or digital subtraction angiography, but they are often detected several days after onset, because these examinations cannot be performed frequently and easily, and they take a relatively long time. Carotid ultrasonography (CU) can be easily performed in

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a short time, and it can easily detect blood flow velocity change caused by intracranial arterial stenosis. Although flow velocity assessment using CU may detect morphological changes of intracranial arteries in patients with intracranial artery dissection, the relationship between flow velocity measured by CU and morphological changes of the dissected artery is unknown. The purpose of this study was to examine whether flow velocity indices measured by CU are useful to detect morphological changes of dissected arteries on MRA in patients with vertebral artery (VA) dissection.

Methods

All authors had full access to the data, analytic methods, and study materials. The data that support the findings of this study are available from the corresponding author on reasonable request.

Participants

This was a retrospective, single-center, observational study. From a prospective stroke registry (NCVC Stroke registry),[3,4] patients diagnosed with intracranial VA dissection within 30 days after onset from January 2011 to June 2017, based on the consensus criteria reported by Debette et al,[5] were enrolled. Moreover, patients with bilateral VA dissection and who did not undergo either CU or MRA on admission were excluded.

Procedure

MRA

The dissected VA morphology on MRA on admission and at follow-up and sequential changes of the VA were assessed by 2 stroke neurologists as blinded assessors. First, the patients were classified into 2 groups by MRA on admission: the stenosis group, defined as patients with occlusion or greater than or equal to 50% stenosis compared to proximal diameter; and the nonstenosis group, defined as patients with less than 50% stenosis, without stenosis, or with dilatation. Second, patients in each stenosis or nonstenosis group were classified into 3 subgroups based on the research plan of International Intracranial Artery Dissection Study (Clinical Trials Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02756091): the progression group (P-group), defined as patients with newly appearance of stenosis (newly appearance of >50% stenosis compared to baseline) or progression (increase in size of stenosis >50% compared to baseline); the stable group (S-group), defined as those with no remarkable change or improvement of dilatation (reduction in size of dilatation by >20% compared to baseline); and the enlargement group (E-group), defined as those with improvement of stenosis (reduction in size of stenosis >50% compared to baseline) or dilatation enlargement (increase in size of dilatation by >20% compared to baseline; Fig 1).

CU

CU was performed at 2 points (on admission with baseline MRA information and at follow-up without follow-up MRA information). CU was conducted by each attending physician using the same ultrasonography machine (LOGIQ, GE Healthcare UK Ltd, Amersham Place, Little Chalfont, England), and the timing of the follow-up CU was within 7 days before/after follow-up MRA. Four CU

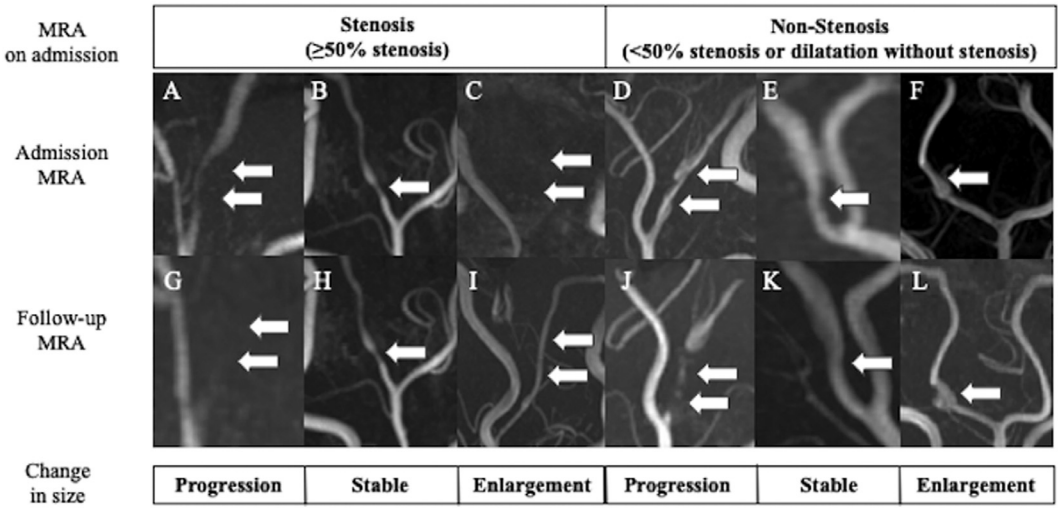

Figure 1. *Representative examples of stenosis or nonstenosis in dissected vertebral arteries on initial magnetic resonance angiography (MRA) and morphological changes on follow-up MRA. Arrows indicate lesions caused by artery dissection. First, each patient is classified into stenosis group (≥50% stenosis; A-C) or nonstenosis group (<50% stenosis or dilatation without stenosis; D-F) by MRA on admission. Second, we classified patients into 3 groups; progression group (A → G and D → J), stable group (B → H and E → K) or enlargement group (C → I and F → L) by assessing morphological change between MRA on admission and follow-up according to the definition described in the part of methods.*

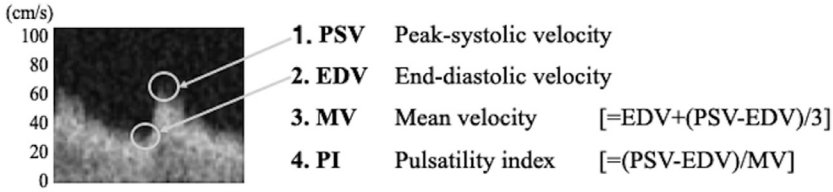

Figure 2. *Definitions of 4 indices of carotid ultrasonography examinations. We assess 4 indices of carotid ultrasonography: (1) peak systolic velocity (PSV), (2) end-diastolic velocity, (3) mean velocity (MV) calculated by EDV + (PSV-EDV)/3, (4) pulsatility index (PI) calculated by (PSV-EDV)/MV.*

indices were used to assess sequential changes: peak systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity (MV), and pulsatility index (PI; Fig 2). These flow velocities of the VA were obtained between the transverse process at the C3-4, C4-5, or C5-6 levels of the cervical spine. The sample volume (2-3 mm, depending on the diameter of the VA) was set within the VA and flow velocities were measured, with taking care to maintain an adequate angle of less than or equal to 60° between the beam and the flow direction of VA.[6] The change of each CU index was expressed by the ratio calculated from each value at follow-up divided by that at admission.

Statistical Analysis

The relationships between the changes in vessel morphology on MRA and each CU index from admission to follow-up were examined by *t* tests and Steel-Dwass tests, as appropriate. A receiver-operating characteristic curve analysis was used to determine cut-offs of significant CU indices for predicting stenosis progression or appearance. All analyses were performed using SAS software (Cary, NC), and the level of significance was set at $P < .05$ (2-tailed).

Results

Forty-two patients were enrolled (Supplementary Fig 1). Table 1 shows the patients' baseline characteristics. The mean age was 51 years, 13 patients were female, and 26 patients had ischemic stroke. Based on the MRA on admission, 22 patients were classified into the stenosis group, and 20 patients into the nonstenosis group. Patients in the stenosis group had significantly lower PSV (28 ± 16 versus 41 ± 10 cm/s, $P < .01$), EDV (4 ± 5 versus 13 ± 6 cm/s, $P < .01$), and MV (11 ± 7 versus 22 ± 8 cm/s, $P < .01$) and higher PI (3.74 ± 3.87 versus $1.28 \pm .40$, $P < .01$) than those in the nonstenosis group (Fig 3).

Of these patients, 3 were excluded from the analyses of morphological changes from admission to follow-up since they did not undergo follow-up CU. The period from admission to follow-up was 22 (interquartile range 7-56) days for CU and 20 (interquartile range 9-58) days for MRA. Of the 39 patients, 7 were classified into the P-group, 20 into the S-group, and 12 into the E-group (Fig 4). On analysis of the EDV ratio, 8 patients (S-group: 3 patients, E-group: 5 patients) were excluded because their EDVs on admission were 0 cm/s. There were no significant differences in the PSV ratio, EDV ratio, and MV ratio, but the PI ratio was significantly higher in the P-group than in the S-group ($1.96 \pm .80$ versus $.98 \pm .44$, $P = .02$) and in the E-group (versus $.65 \pm .35$, $P < .01$; Fig 5). On receiver-operating characteristic curve analysis, the PI ratio was the most useful index to detect stenosis progression or appearance (cut-off value >1.64, sensitivity 71%, specificity 97%; Table 2, Supplementary Fig 2).

Discussion

In this study, the relationships between changes of blood flow velocity of the affected VA on CU and changes in vessel morphology on MRA were examined in patients with VA dissection. Patients with stenosis on MRA on admission had lower PSV, EDV, and MV and higher PI than those without. Moreover, the ratio of PI measured by CU was the most useful index to detect morphological changes of the intracranial VA on MRA.

The outcome of intracerebral artery dissection was relatively favorable,[7,8] but patients with stenosis sometimes develop ischemic stroke, and patients with aneurysms can develop subarachnoid hemorrhage.[9,10] Early detection of vessel morphology changes seems to be important since the duration of antithrombotic therapy depends on the morphological changes.[11-13] Although changes in vessel morphology could be observed by MRA and the lesion

Table 1. *Baseline characteristics*

Age, years	51 ± 10
Women	13 (31)
Systolic blood pressure on admission, mm Hg	154 ± 27
Diastolic blood pressure on admission, mm Hg	103 ± 17
Diagnosis of ischemic stroke on admission	26 (62)
Follow-up period of CU from admission, days	22 [7-56]
Follow-up period of MRA from admission, days	20 [9-58]
MRA on admission	
Stenosis	22 (52)
Nonstenosis	20 (48)
Mild stenosis or mild dilatation	16
Dilatation	4

Abbreviations: CU, carotid ultrasonography; MRA, magnetic resonance angiography.

n (%) or mean ± standard deviation or medians [interquartile range].

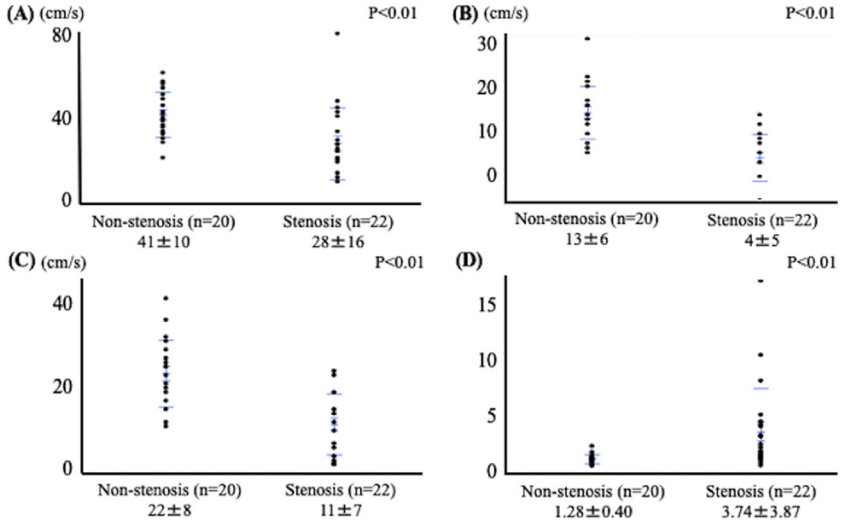

Figure 3. *Comparisons of 4 indices of carotid ultrasonography between the stenosis and nonstenosis groups. (A) Peak systolic velocity (PSV), (B) end-diastolic velocity (EDV), (C) mean velocity (MV), (D) pulsatility index (PI). In each figure, the vertical bars at center indicate standard error and horizontal bars at the outermost indicate standard deviation. Patients in stenosis group on admission have lower PSV, EDV, MV, and higher PI significantly.*

treated if necessary, it is difficult to perform MRI frequently in many institutes because of the high cost. Some previous studies showed the usefulness of ultrasonography to diagnose intracerebral artery dissection and to follow-up the changes in vessel morphology using B-mode or color Doppler images, but the relationships between changes in vessel morphology and flow velocity indices of CU are unknown (Supplementary Table 1).[14-19] The present study is also unique in that it examined patients with intracranial artery dissection diagnosed by the recent criteria reported by Debette et al.[5] In this study, 55% of patients had occlusion or stenosis, and 10% had dilatation on admission MRA. These rates were almost equivalent to those of previous studies.[20]

Patients with stenosis on admission MRA had lower PSV, EDV, and MV and higher PI than those without. As the peripheral vascular resistance increases with progression of stenosis in an intracranial artery, the diastolic blood flow decreases, the difference between the systolic blood flow and the diastolic blood flow increases, and the PI value also increases.[10,11] Although PSV has been known to increase at lesions with severe stenosis, this study did not include patients with extracranial artery dissection, and no patients had severe stenosis at the site of CU examination.[21] Moreover, PSV is considered to decrease as the whole blood flow of the VA decreases due to intracranial stenosis of the VA. Thus, patients with stenosis had lower PSV, EDV, and MV and higher PI than those without stenosis in this study of patients diagnosed with intracranial VA dissection.

In this study, the P-group had significantly higher PI ratio than the E-group and S-group. The PI ratio tended to be lower in the E-group than in the S-group. Although EDV also seems to be useful to predict improvement of stenosis, the EDV ratio often could not be calculated when the baseline EDV was 0 cm/s. In the present study,

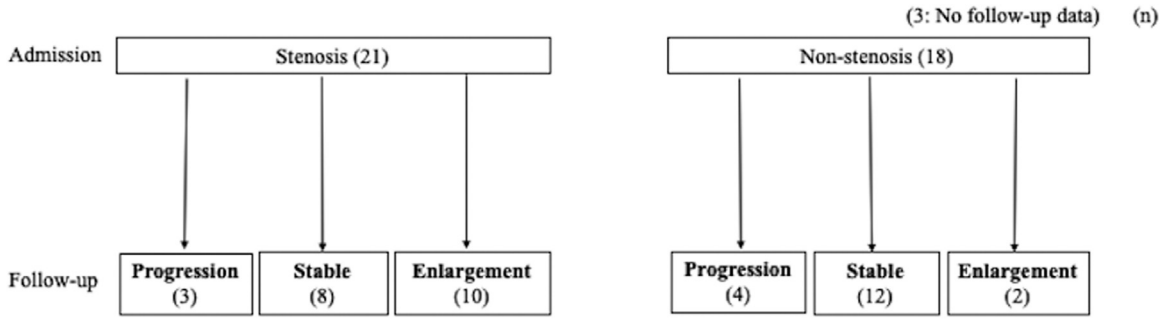

Figure 4. *Results of morphological changes in dissected vertebral arteries on follow-up magnetic resonance angiography in the stenosis or nonstenosis group. Of 21 patients classified into stenosis group on admission MRA by 2 stroke neurologists, 3 patients are classified into progression group, 8 into stable group, and 10 into enlargement group. In the same way, 4 patients in nonstenosis group are classified into progression group, 12 into stable group, and 2 into enlargement group.*

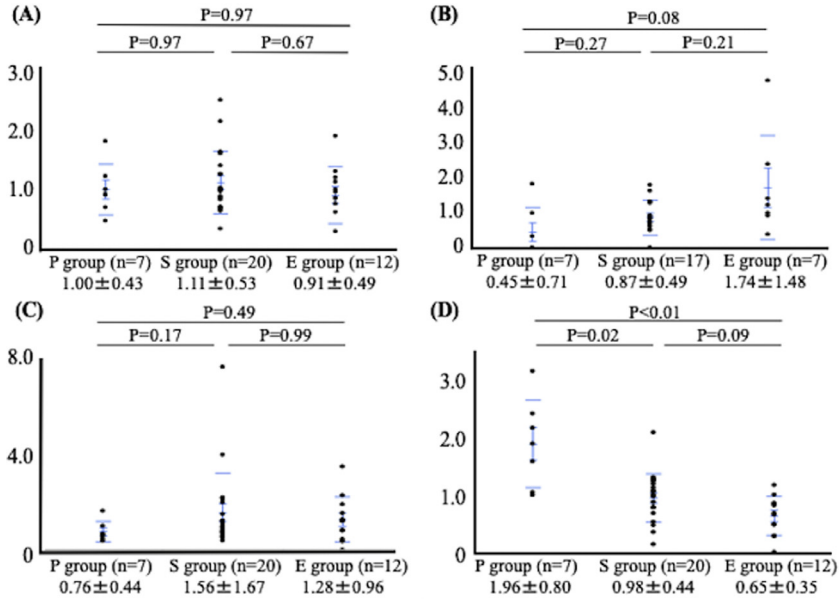

Figure 5. *CU indices of changing vessels from admission to follow-up magnetic resonance angiography in the stenosis group. (A) Ratio of peak systolic velocity (PSV ratio), (B) ratio of end-diastolic velocity (EDV ratio), (C) ratio of mean velocity (MV ratio), (D) ratio of pulsatility index (PI ratio). In each figure, the vertical bars at center indicate standard error and horizontal bars at the outermost indicate standard deviation. In analysis of the EDV-ratio, 8 patients (S group: 3 patients and E group: 5 patients) are excluded because their EDVs on admission are 0 cm/s. Of 4 indices, only PI ratio shows significant differences between P-group (progression group) and S-group (stable group) or E-group (enlargement group).*

Table 2. *Receiver-operating characteristic curve analysis to predict stenosis progression or appearance*

	P-group versus S-group/E-group				
	Cut-off	Sensitivity, %	Specificity, %	AUC	*P* value
PSV ratio	<.51	86	28	.51	.88
EDV ratio	<.33	71	92	.75	.03
MV ratio	<.67	71	78	.71	.07
PI ratio	>1.64	71	97	.89	<.01

Abbreviations: AUC, area under the curve; E-group, enlargement group; EDV ratio, end-diastolic velocity ratio; MV ratio, mean velocity ratio; P-group, progression group; PI ratio, pulsatility index ratio; PSV ratio, peak systolic velocity ratio; S-group, stable group.

there was no significant difference between follow-up EDV in the E-group and that in the S-group in 8 patients with EDV = 0 cm/s on admission CU (Supplementary Fig 3). Therefore, the PI ratio is a reliable indicator to detect improvement or progression of stenosis of the intracranial VA.

One of the limitations of the present study was the small sample size. Thus, the relationships between CU indices and improvement or enlargement of dilatation could not be discussed, because only a few patients with dilatation without stenosis were included. Second, in cases with stenosis that involved the posterior inferior cerebellar artery, it is possible that the reperfusion of blood flow to the posterior inferior cerebellar artery, as well as improvement of the structure, may affect the CU indices. Third, PI should be affected by proximal VA lesion (V1 segment) when a patient had an atherosclerosis potential. To investigate these details in the future, further studies with a large number of patients will be needed.

Conclusions

In this study, the relationships between CU indices and changes in vessel morphology on MRA were examined. PSV, EDV, MV, and PI on CU were useful to differentiate patients with stenosis of the dissected VA from those without. The PI ratio between baseline and follow-up measured by CU is a promising index to detect stenosis progression or its appearance in patients with intracranial VA dissection.

Author Contributions

S.W., M.K., Y.N., N.M., T.I., K.Y., T.M., and Y.Y. contributed to the concept and rationale for this study. S.W.,

M.K., and N.M. contributed to statistical analysis. K.M., M.I., and K.T. provided study supervision.

Conflicts of Interest

The authors have no conflicts to declare.

Ethical Approval

The study protocol was approved by the ethical review committee of the National Cerebral and Cardiovascular Center.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.04.033.

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