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A comparison of transcranial Doppler and magnetic resonance imaging for long term changes in middle cerebral artery stenosis

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ABSTRACT

Objectives: Intracranial arterial stenosis may progress or regress, of which the diagnosis is important to predict the risk of stroke or to evaluate the response of treatment. Transcranial Doppler (TCD) seems to be useful for this purpose, however, optimal diagnostic criteria have not been validated yet. Our study was designed to compare TCD changes with magnetic resonance angiography (MRA) to validate optimal TCD criteria for progression or regression of middle cerebral artery (MCA).

Patients and methods: We prospectively enrolled patients who visited our neurology department due to MCA stenosis on TCD examination. Brain MRA was used to identify patients with stenosis of the same site of MCA. Progression or regression was defined by change of MRA grading (normal, mild, moderate, severe or occlusion). Various criteria of mean flow velocity (MFV) difference and percent change were assessed. To register more patients for reliable analysis, additional patients with the same inclusion criteria were recruited retrospectively. All patients enrolled in the study were symptomatic or asymptomatic atherosclerotic MCA stenosis.

Results: Eighteen patients were enrolled and 21 MCAs with completed follow-up TCD and MRA were analyzed (mean age 68.4 years, mean follow-up 17.8 months). In addition, 40 MCAs from 30 retrospective patients were also analyzed (mean age 65.7 years, mean follow-up 22.3 months). Among assessed criteria, the most optimal cutoff value for the progression of stenosis was 20 cm/s, at which the sensitivity and specificity were 100% and 91% in prospective group, and were 80% and 93% in retrospective group. In the % difference analysis, prospective group showed sensitivity 100% and specificity 82% in the 20% cutoff. The retrospective group showed sensitivity 80% and specificity 93% in the 15% cutoff. However, results of the regression group were not consistent.

Conclusions: Diagnosis of progression of MCA stenosis with serial TCD examination is feasible and MFV change of 20 cm/s and % change of 15–20% are suggested as optimal cut-off value but not in the regression. These criteria would be useful for the clinical research and real-world practice.

1. Introduction

Intracranial arterial stenosis (ICAS) is a major cause of ischemic stroke, especially in Asian population [1,2]. Atherosclerosis, a dynamic process, is a common pathologic substrate, which has been known to progress or regression [3–5]. Progression of ICAS is associated with increased risk of stroke or other related vascular events [3,4]. On the other hand, regression of atherosclerotic plaque is also probable in ICAS with medical treatment as in coronary or carotid artery stenosis [6–8]. Therefore, accurate diagnosis of progression or regression is important to predict the risk of stroke or to modify patient's treatment.

Conventional angiography is a gold standard to evaluate the ICAS, however, its invasiveness is not suitable for serial evaluation. Although magnetic resonance angiography (MRA) or computerized tomography angiography may be an alternative [9–11], higher cost and hazard of contrast agents are limitations for repeated measures.

On the other hand, transcranial Doppler sonography (TCD), a non-invasive and 99widely used tool for the diagnosis of ICAS [9], can be appropriate for the serial evaluation. Several TCD studies have been published previously, however the diagnostic criteria for progression or regression had not been validated yet [3–5].

Our study was prospectively designed to compare stenotic changes

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on TCD with MRA to validate the optimal TCD criteria for progression or regression of middle cerebral artery (MCA).

2. Materials and methods

2.1. Criteria for study participants

We prospectively enrolled patients with MCA stenosis who met TCD criteria (mean flow velocity (MFV) ≥ 80 cm/s, asymmetry index increased by more than 30% compared to the contralateral MCA, when the distal MCA velocity increases (M1: M2 ratio 1.1 or higher), and local increase in velocity is accompanied by secondary findings of stenosis such as bruit, spectral widening) [12] and MRA criteria (≥ 50% narrowing) [13] simultaneously. All patients enrolled in the study were symptomatic or asymptomatic atherosclerotic MCA stenosis.

Exclusion criteria were as following: [1] occlusion of MCA on MRA [2] suboptimal temporal windows [3] more than 50% of stenosis or occlusion of the ipsilateral internal carotid artery [4] life expectancy of less than two years. We obtained informed consent from all patients before conducting the study. This study was conducted under approval at Seoul Metropolitan Government–Seoul National University Boramae Medical Center Institutional Review Board (IRB) (No. 06-2011-220). We enrolled patients prospectively for two years. However, the number of registered patients was not enough (about 33%), so the recruitment of patients was considered retrospectively. Therefore, patients with similar inclusion/exclusion criteria who performed follow-up TCD examination and MRA were retrospectively recruited with further approval of IRB (Fig. 1).

2.2. Follow-up TCD and brain MRA

Follow-up TCD and brain MRA were performed 18 months later. Brain MRA was performed with 3.0-Tesla three-dimensional time-of-flight method. The time-of-flight images were processed by maximum intensity-projection algorithm and used for analysis. The degree of stenosis was classified as mild (< 50%), moderate (≥ 50%), severe (focal signal loss with the presence of distal flow), or occlusion. Progression was defined as worsening of the degree on the follow-up MRA, while regression was defined as improvement of the degree of stenosis. Two neurologists (Y.D.L and K.H.M) interpreted MRA images not only without knowing the other examiner's judgement but, without patient's clinical background. When the two neurologists differ in opinion, they discussed and built a consensus. TCD was performed according to the standard protocol (Spencer PMD150, USA) [14] by two same qualified sonographers with many years of experience.

Patient was examined after being sufficiently rested with a supine position in a dark and quiet room to keep the patient physically and mentally stable. We also checked for anemia or uncontrolled blood pressure. MRA and TCD results were not shared between the neurologists and sonographers. The procedure is as follows. Set the probe to a depth of 50 mm, and place it in the patient's zygomatic arch. Move the probe to find the MCA flow towards the probe. Middle M1 is measured at depths of 45–55 mm, and M1 origin is measured at depths of 60–65 mm. Record the information (MFV, PSV, etc.) that can be identified on the detected waveform. We did not use the two-dimensional ultrasound imaging of TCD for analysis. So insolation angle correction was not possible. TCD values of other major cerebral arteries including MCA were considered together. In detail, we determined that there was significant stenosis only when a significant change of flow velocity was observed in the MCA without any significant difference in flow velocities of the other vessels compared to the previous examinations. We also measured several times to eliminate technical errors as much as possible. Experts with many years of experience have conducted TCD.

2.3. Statistical analysis

Sensitivity, specificity, positive predictive value, and negative predictive value were calculated according to the various cutoff values of MFV (10 cm/s, 15 cm/s, 20 cm/s, 25 cm/s, 30 cm/s, 10%, 15%, 20%, 25% and 30%). Receiver operating characteristic (ROC) analysis was additionally performed. All statistical analyses including cutoffs were individually investigated in each cohort.

3. Results

A total of 27 patients were enrolled and 21 MCAs from 18 patients who completed follow-up TCD examination and MRA were finally analyzed (mean age 68.4 years, female 38%, mean follow-up period 17.8 months). In addition, 40 MCAs from 30 patients with same inclusion criteria were also included (mean age 65.7 years, female 10%, mean follow-up period 22.3 months) (Table 1, Fig. 1). In the distribution of MCA stenosis on the initial brain MRA, there were 12 MCAs with moderate stenosis and 9 MCAs with severe stenosis in the prospective group. The retrospective group consisted of 28 MCAs with moderate stenosis and 12 MCAs with severe stenosis. According to the MRA criteria, progression and regression rate were 9.5% and 38.1% in prospective group, while were 12.5% and 15% in retrospective group. Of the total 61 MCAs, 45 MCAs were associated with symptomatic ischemic stroke and the remaining 16 MCAs were asymptomatic.

Among assessed criteria, the most optimal cutoff value for the progression of stenosis was 20 cm/s, at which the sensitivity and specificity were 100% and 91% in prospective group, and were 80% and 93% in retrospective group. In the % difference analysis, prospective group showed sensitivity 100% and specificity 82% in the 20% cutoff. The retrospective group showed sensitivity 80% and specificity 93% in the 15% cutoff. In the cm/s difference analysis for regression, prospective group showed sensitivity 88% and specificity 73% in the

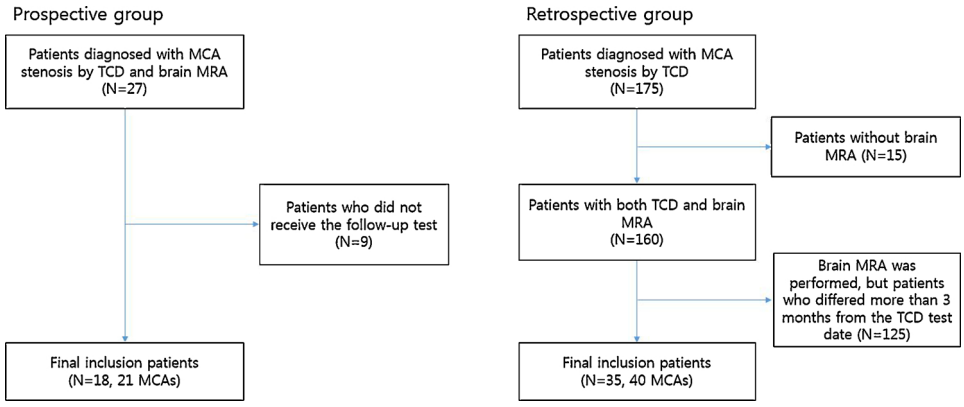

Fig. 1. Flow chart of patient selection in retrospective group. TCD: transcranial Doppler, MRA: magnetic resonance image, MCA: middle cerebral artery.

Table 1
Demographic data and vascular risk factors.

Variables	Prospective group (n = 21)*	Retrospective group (n = 40)	Total (n = 61)
Age, years	68.4 ± 6.7	65.7 ± 12.9	66.6 ± 11.2
Female (%)	8 (38)	4 (10)	12 (20)
Hypertension (%)	17 (81)	29 (73)	46 (75)
Diabetes (%)	11 (52)	15 (38)	26 (43)
Hyperlipidemia (%)	7 (33)	26 (65)	33 (54)
Smoking (%)	3 (14)	10 (25)	13 (21)
Habitual drinking (%)	7 (33)	23 (58)	30 (49)
MFV in baseline (cm/s)	126.0 ± 32.5	120.2 ± 28.1	122.2 ± 29.8

Values are presented mean ± standard deviation, unless indicated otherwise.
*n is the number of MCAs used in the analysis.
MFV: mean flow velocity.

10 cm/s cutoff. The retrospective group showed sensitivity 67% and specificity 93% in the 20 cm/s cutoff. In the % difference analysis for regression, prospective group showed sensitivity 75% and specificity 82% in the 10% cutoff. The retrospective group showed sensitivity 67% and specificity 93% in the 15% cutoff (Table 2).

In ROC analysis for the prospective group, both area under curve (AUC) of MFV difference (cm/s) and percent change (%) was 0.909 ($P = 0.076$) for the progression (Fig. 2), while cm/s and % difference was 0.977 ($P = 0.001$) and 0.943 ($P = 0.001$) for the regression respectively (Fig. 3). In ROC analysis for the retrospective group, AUC of cm/s and % difference was 0.831 ($P = 0.002$) and 0.855 ($P = 0.012$) for the progression (Fig. 4), while cm/s and % difference was 0.661 ($P = 0.22$) and 0.649 ($P = 0255$) for the regression respectively (Fig. 5).

4. Discussion

Our results suggest that TCD is a proper modality for serial examination in patients with ICAS and MFV change of 20 cm/s may be the optimal diagnostic criteria for progression of MCA stenosis. In the % difference, change of 15–20% was expected as a cutoff for diagnosing the progression of stenosis.

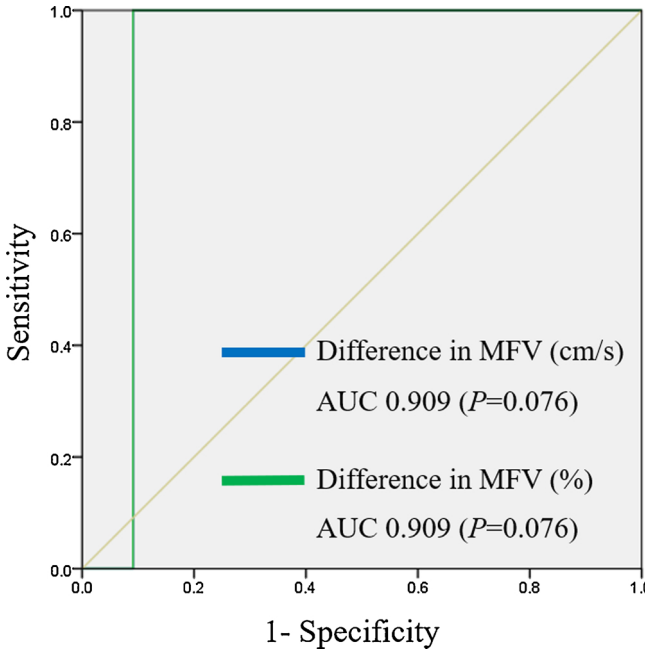

Fig. 2. In prospective group, the ROC curve for correlation between the mean blood flow velocity change of the cranial ultrasound and the degree of cerebral artery stenosis in the brain MRA (progression and static group). Blue: mean flow velocity (cm/s); Green: mean flow velocity (%). ROC: Receiver operating characteristic, MRA: magnetic resonance image (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

ICAS is fairly dynamic state and the frequency of progression or regression has been variably reported. The variability may be due to the difference of study population (symptomatic or asymptomatic), timing of examination (acute stroke period or not), duration of observation period, or treatment modalities. Above all, diagnostic methods and criteria for progression or regression seem to be very important. One MRA study including 102 patients with 5.7 years of follow-up revealed 3-fold higher rate of progression for symptomatic stenosis compared

Table 2
Sensitivity and specificity according to the various cutoff values.

Prospective		Difference of MFV (cm/s)					Percent change of MFV (%)				
		10	15	20	25	30	10	15	20	25	30
Progression	Sensitivity (%)	100	100	100	50	0	100	100	100	50	50
vs.	Specificity (%)	73	82	91	91	91	82	82	82	91	91
Static	PPV (%)	40	50	67	50	0	50	50	50	50	50
	NPV (%)	100	100	100	91	83	100	100	100	91	91
Regression	Sensitivity (%)	88	75	75	63	50	75	63	50	38	13
vs.	Specificity (%)	73	82	91	91	91	82	82	82	91	91
Static	PPV (%)	70	75	86	83	80	75	71	67	75	50
	NPV (%)	89	82	83	77	71	82	75	69	67	59
Retrospective		**Difference of MFV (cm/s)**					**Percent change of MFV (%)**				
		10	15	20	25	30	10	15	20	25	30
Progression	Sensitivity (%)	80	80	80	60	60	80	80	60	60	60
vs.	Specificity (%)	79	86	93	97	100	83	93	97	97	100
Static	PPV (%)	40	50	67	75	100	44	67	75	75	100
	NPV (%)	96	96	96	93	94	96	96	93	93	94
Regression	Sensitivity (%)	67	67	67	67	50	67	67	50	17	0
vs.	Specificity (%)	79	86	93	97	100	83	93	97	97	100
Static	PPV (%)	40	50	67	80	100	44	67	75	50	–
	NPV (%)	92	93	93	93	91	92	93	90	85	83

MFV: mean flow velocity; PPV: positive predictive value; NPV: negative predictive value.

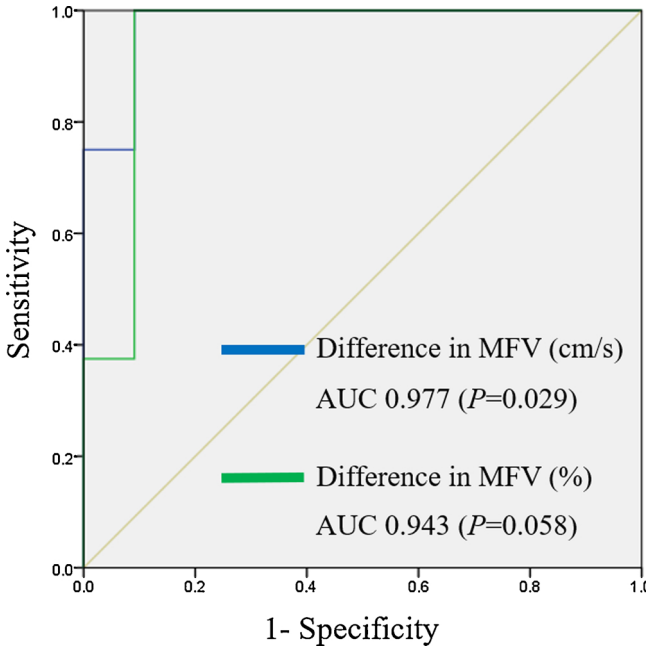

Fig. 3. In prospective group, the ROC curve for correlation between the mean blood flow velocity change of the cranial ultrasound and the degree of cerebral artery stenosis in the brain MRA (regression and static group). Blue: mean flow velocity (cm/s); Green: mean flow velocity (%). ROC: Receiver operating characteristic, MRA: magnetic resonance image (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

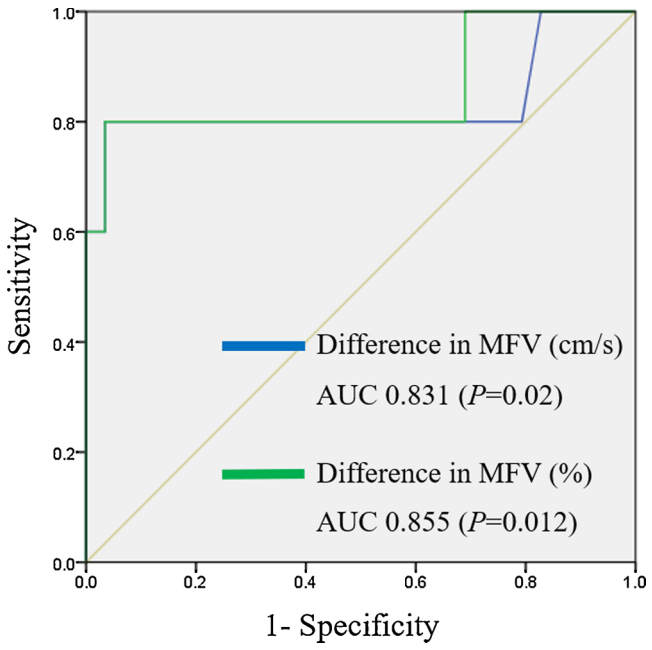

Fig. 4. In retrospective group The ROC curve for correlation between the mean blood flow velocity change of the cranial ultrasound and the degree of cerebral artery stenosis in the brain MRA (progression and static group). Blue: mean flow velocity (cm/s); Green: mean flow velocity (%). ROC: Receiver operating characteristic, MRA: magnetic resonance image (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

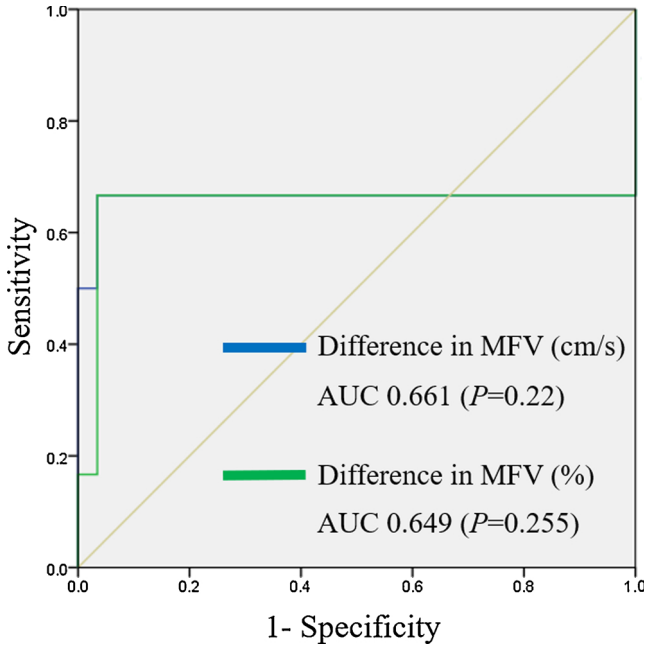

Fig. 5. In retrospective group The ROC curve for correlation between the mean blood flow velocity change of the cranial ultrasound and the degree of cerebral artery stenosis in the brain MRA (regression and static group). Blue: mean flow velocity (cm/s); Green: mean flow velocity (%). ROC: Receiver operating characteristic, MRA: magnetic resonance image (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

with asymptomatic stenosis (22 vs. 8%, p < 0.01) [10]. Other TCD studies have reported the rate of progression ranged from 9.1–32.5% [3–5]. Although MFV change of 30 cm/s or 20 cm/s [5], or change of peak systolic velocity [4] was used as diagnostic criteria, these criteria had not been validated (Table 3).

Serial examinations of patients with ICAS may be important to observe the natural course and treatment response of stenotic vessels. Recent advances of medical treatment provide new insight for the management of ICAS. Intensive medical treatment including dual antiplatelet therapy, high dose statin, blood pressure lowering and life style modification decreased the risk of stroke recurrence in patients with ICAS [15]. In other study, cilostazol may prevent the progression of ICAS compared with aspirin [10]. In case of progression, treatment modification such as increment of statin dose, changing antiplatelet regimens, or more aggressive control of risk factors, may be considered. TCD is easy-to-perform in routine clinical practice and seems to be an optimal tool for serial examination of ICAS, if there are adequate diagnostic criteria.

In the TCD, MFV is affected by several factors. Major factors include vessel diameter, cerebral blood flow, age, sex, blood viscosity, carbon dioxide partial pressure, blood pressure, sleep, and exercise. As mentioned in the methods section, we kept the patient and laboratory condition constant to exclude as much as possible the confounding factors that affect TCD examination. Also, results of TCD differ according to the angle of blood flow and sound wave. Large angles increase the likelihood that the blood flow velocity will be measured lower than the actual value. Therefore, the tester should take special consideration of these matters.

In our study, there were two false-positive and one false-negative cases. False-positive cases were associated with timing of TCD

Table 3
Comparison of TCD studies regarding progression or regression of MCA stenosis.

	Arenillas et al.[3] (n = 40)	Wong et al.[†4] (n = 143)	Jeon et al.[†5] (n = 103)	This Study[§] (n = 61)
Age	62.9 ± 9.5	64.3 ± 12.4	-[‡]	66.6 ± 11.1
Sex, female (%)	10 (25.0)	48 (33.6)	35 (34.0)	12 (19.7)
Inclusion criteria	MFV ≥80 cm/s	PSV ≥140 cm/s or AI ≤ -21%	MFV ≥90 cm/s	MFV ≥ 80 cm/s and MRA (≥ 50%)
Median follow-up, month	25.5-27.8	6	6	22.3
Criteria for progression and regression	MFV 30 cm/s	PSV grade[‖]	MFV 20 cm/s or 20%	MFV 20 cm/s
Progression (%)	32.5	9.1	12.6	11.4
Regression (%)	7.5	29.4	87.4 (stable state + regression)	23.0

† Including occlusion of the MCA.
‡No data was provided for the age of total patients.
‖Progression if the grade is increased; regression if the grade is same or decreased; grade I (140–209 cm/s), grade II (210–280 cm/s), and grade III (> 280 cm/s).
§ This is a study conducted by the authors.
MCA: middle cerebral artery; MFV: mean flow velocity; PSV: peak systolic velocity; AI: asymmetry index; MRA: magnetic resonance angiography.

examination performed in acute stroke period. MFV may decrease by thrombotic occlusion or increase by recanalization or compensatory hyperperfusion in acute stroke. Therefore, the judgement of progression or regression by change of MFV needs caution in patients whose TCD (15)was performed in acute stroke period. In one false-negative case, decrement of MFV was only 14 cm/s, which did not meet the regression criteria (20 cm/s).

TCD monitoring is also important for evaluating vessel spasm in patients with aneurysmal subarachnoid hemorrhage (SAH). In aneurysmal SAH patients, it is unclear whether a patient with MCA MFV of 120–200 cm/s could be diagnosed with vasoconstriction [16]. Other study reported that MCA MFV 120 cm/s was reliable cutoff, but there is still controversy [17]. Both chronic stenosis and vasospasm are comparable in terms of vascular stenosis. Chronic stenosis and vasospasm are common in that the rate of blood vessels increases when the disease worsens. Meanwhile, vasospasm shows varying degrees of stenosis and relaxation in different areas of the vessels in a short period of time. Therefore, even if the degree of MCA stenosis is constant, the degree of stenosis of other blood vessels can change, which might affect the flow velocity of MCA. A patient diagnosed with aneurysmal SAH is also more likely to be under unstable condition, making it difficult to control the confounding factors. Chronic stenosis progresses over a long period of time. In addition, the patient status can be managed relatively stably during the examination.

As the vessel stenosis progresses, the pulsatility index (PI) of the post-stenotic area decreases and the downstream wave changes. If PI and downstream spectrum can be applied to the cutoffs derived from this study, the progression of stenosis will be more accurately predicted. These parameters have not yet been studied to predict the progression of intracranial artery stenosis. Therefore, this would be a good research topic.

This study has several limitations. First, we measured blood flow without a 2-dimentional image on the TCD test. Even for experienced sonographers, it is impossible to reduce the insonation angle error to less than 15% without a 2-dimentional image. In a follow-up study, a 2-dimentional image should be added to the TCD test. Second, semi-quantitative MRA grading method was used as defining the degree of stenosis, which may not sensitively detect mild change of progression or regression. Although direct measure of diameter changes in conventional angiography is the gold standard, its invasiveness seems not to be acceptable for this purpose of clinical studies. Alternatively, semi-quantitative MRA method was also used in other trials [10,11,13], so we except this method may be acceptable. Third, the sample size was quite small. Therefore, it is necessary to study more patients to verify the reliability of the results. Due to the difficulty of patient enrollment and completeness of follow-up, methods of analysis were modified lately with approval of IRB. Retrospective patients with same inclusion criteria who performed follow-up TCD and MRA were also recruited for the comparison. these results need further validation by prospective, large-scaled studies.

Diagnosis of progression of MCA stenosis with serial TCD examination is feasible and MFV changes of 20 cm/s and % change of 15–20% are suggested as the most optimal criteria. These validated criteria would be useful for the clinic research and real-world practice.

5. Conclusions

Diagnosis of progression of MCA stenosis with serial TCD examination is feasible and MFV changes of 20 cm/s and % change of 15–20% are suggested as the most optimal criteria, but not in the regression. These assessed criteria would be useful for the clinical research and real-world practice.

Declarations of interest

None.

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