

Impact of Asymmetric Middle Cerebral Artery Velocity on Functional Recovery in Patients with Transient Ischemic Attack or Acute Ischemic Stroke

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일과성허혈발작 및 급성뇌경색환자에서 경두개도플러로 측정된 중간대뇌동맥 비대칭 지수가 환자 예후에 미치는 영향

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This study examined whether the difference in the middle cerebral artery (MCA) velocities can predict the prognosis of stroke and whether the prognostic impact differs among stroke subtypes. Transient ischemic attack (TIA) or acute ischemic stroke patients, who underwent a routine evaluation and transcranial Doppler (TCD), were included in this study. The MCA asymmetry index was calculated using the relative percentage difference in the mean flow velocity (MFV) between the left and right MCA: $(|RMCA\ MFV - LMCA\ MFV| / \text{mean MCA MFV}) \times 100$. The stroke subtypes were determined using the TOAST classification. Poor functional outcomes were defined as a mRS score ≥ 3 at 3 months after the onset of stroke. A total of 988 patients were included, of whom 157 (15.9%) had a poor functional outcome. Multivariable analysis showed that only the MCA asymmetry index was independently associated with a poor functional outcome. ROC curve analysis showed that adding the MCA asymmetry index to the prediction model improved the discrimination of a poor functional outcome from acute ischemic stroke (from 88.6% [95% CI, 85.2 ~ 91.9] to 89.2% [95% CI, 85.9 ~ 92.5]). The MCA asymmetry index has an independent prognostic value for predicting a poor short-term functional outcome after an acute cerebral infarction. Therefore, TCD may be useful for predicting a poor functional outcome in patients with acute ischemic stroke.

Key words: Transcranial doppler ultrasonography, Middle cerebral artery, Asymmetry

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INTRODUCTION

Transcranial Doppler (TCD) ultrasonography is used to noninvasively find any symptoms of intracranial

atherosclerosis by measuring the mean flow velocity (MFV) and pulsatility index (PI) of basal cerebral arteries. A large increase in MFV indicates vessel narrowing due to cerebrovascular diseases, which is dependent on the

extent of arterial stenosis and strongly related to vascular risk factors [1]. In addition, the PI, which is used to estimate hemodynamics in portions distal to insonated vessels, is associated with peripheral resistance at the level of basal cerebral arteries, and consequently with disorders related to the small vessels [2]. Most studies in stroke research have investigated these 2 parameters. Some studies have shown that an increased flow velocity is a reliable parameter for assessing focal intracranial stenosis and has a prognostic value for stroke recurrence [3,4]. Other researchers have reported that an elevated PI is associated with cerebrospinal fluid pressure, cognitive performance, and infarct volume in patients with lacunar infarcts [5-7]. However, there is relatively little information on the laterality of each parameter, which includes the association between the lateral difference and some disorders such as cluster headache and acute intracerebral hemorrhage [8, 9]. Especially, a few studies have addressed the relation of the middle cerebral artery (MCA) asymmetry index to the prognosis of patients with transient ischemic attack (TIA) or acute ischemic stroke.

The laterality of the MFV means the relative difference between the MFVs of the left and right MCAs, which is called the MCA asymmetry index as an illuminating term. The MCA asymmetry index may be increased in the presence of intracranial arterial disease [10]. In the present study, we aimed to evaluate whether the MCA asymmetry index, measured in patients with acute ischemic stroke, has a prognostic value for predicting short-term functional outcome and whether this prognostic value differs among stroke subtypes.

MATERIALS AND METHODS

1. Patients

This study was a hospital-based, retrospective observational study. There were 7,462 candidates who were admitted to the neurology department because of acute brain infarction or TIA within 7 days of symptom onset, between January 2001 and December 2014, and were prospectively registered in the Yonsei Stroke Registry. Of

them, we excluded 3,023 patients according to the exclusion criteria. Of the remaining 4,439 candidates, 988 patients completed the TCD measurements of the MFVs of both MCAs during hospitalization.

2. Evaluation

The patients required at least 1 vascular imaging study, including conventional angiography, magnetic resonance angiography (MRA), or computed tomographic angiography (CTA). Standard systemic investigations were performed in every patient, which included 12-lead electrocardiography (ECG), chest radiography, and blood tests. Carotid duplex sonography, transthoracic echocardiography, transesophageal echocardiography, and 24-h Holter ECG monitoring were performed in selected patients. TCD was a part of the standard evaluation to obtain the MCA asymmetry index, except in patients with poor temporal window in either temple. The demographics, vascular risk factors, and neurologic examination including the National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin Scale (mRS) score at 3 months after stroke onset were collected at baseline. We excluded patients with a history of old stroke, malignancy, and stroke of other causes, and/or those without data on the NIHSS score at admission, mRS score at 3 months after stroke onset, and complete laboratory study or cerebral angiography. The Institutional Review Board (IRB) of Severance Hospital, Yonsei University Health System approved this study and waived the need for informed consent because of the retrospective and observational nature of the analysis (IRB 4-2016-1151).

3. Measurement of TCD parameters

The patients underwent TCD examination (TC8080, Nicolet, Stockport, UK) within 7 days of admission. All TCD recordings were carried out by 2 medical technicians. In all patients, peak systolic flow velocity (PSV) and end-diastolic flow velocity (EDV) were measured with a handheld 2-MHz probe in both MCAs. The MCAs were insonated through the trans-temporal window at various depths from 44 to 68 mm. The MFV value was auto-

matically calculated by the Doppler machine by using the mean of 5 cycles, according to the formula $MFV=EDV+(PSV-EDV)/3$. The PI value was simultaneously calculated as $(PSV-EDV)/MFV$ [4]. The recorded MFV and PI values were measured for at least 2 depths to include hemodynamic information on the proximal MCA (M1, 58-68 mm) and the distal MCA (M2, 44-56 mm). The 2 highest MFVs and PIs, measured in both proximal and distal portions, were finally averaged to derive the ultimate MFV and PI for statistical analysis, respectively. We also created an asymmetry index (MCA asymmetry index) by using the bilateral ultimate MFVs to investigate whether the difference of both ultimate MFVs has prognostic value for predicting functional outcome after acute cerebral infarction, and whether the prognostic value differs among stroke subtypes. The MCA asymmetry index was calculated as the following formula [11];

$$\text{The MCA asymmetry index} = 100 \times \frac{|RMCA \text{ MFV} - LMCA \text{ MFV}|}{(RMCA \text{ MFV} + LMCA \text{ MFV})/2}$$

4. Data collection for analysis

We collected the patients' baseline characteristics including sex, age, severity of neurological deficit (NIHSS score) at admission, details of risk factors, and premorbid use of medications (Table 1). The NIHSS score is a tool used to objectively quantify the impairment caused by a stroke. The high score is indicative of more severe impairment [12]. Hypertension was diagnosed when a patient was using antihypertensive medications or had systolic arterial pressures ≥ 140 mm Hg or diastolic arterial pressures ≥ 90 mm Hg on repeated measurements during admission [13]. Diabetes mellitus was diagnosed when a patient had taken an oral hypoglycemic agent or insulin or had fasting plasma glucose level ≥ 7.0 mmol/L [14]. Hypercholesterolemia was diagnosed when a patient had taken lipid-lowering agents after a diagnosis of hypercholesterolemia or had low-density lipoprotein cholesterol level ≥ 4.1 mmol/L, or total cholesterol level ≥ 6.2 mmol/L

[15]. Current smoking was defined as having smoked a cigarette within 1 year before admission. Peripheral artery disease was determined when the patient had an ankle-brachial index of < 0.9 .

Table 1. Clinical characteristics of included patients

	Study patients (N = 988)
Age, y	63.71 ± 12.18
Sex (men)	684 (69.2)
NIHSS score at admission	4.40 ± 5.21
Use of thrombolysis treatment	83 (8.4)
Stroke subtype	
LAA	173 (17.5)
CE	273 (27.6)
LAC	86 (8.7)
SUD	379 (38.4)
TIA	77 (7.8)
Risk factors	
Hypertension	380 (38.5)
Diabetes mellitus	168 (17.0)
Hypercholesterolemia	131 (13.3)
Current smoking	171 (17.3)
Coronary artery disease	247 (25.0)
Peripheral artery disease	23 (2.3)
Premorbid medication	
Antiplatelet	293 (29.7)
Anticoagulant	57 (5.8)
Statin	162 (16.4)
Antihypertensive	399 (40.4)
Laboratory findings	
Hemoglobin, g/dL	14.32 ± 1.78
Cholesterol, mmol/L	182.05 ± 41.89
Triglyceride, mmol/L	125.02 ± 80.98
Low-density lipoprotein, mmol/L	114.75 ± 37.36
Glucose, mmol/L	140.39 ± 57.02
hs-CRP, nmol/L	10.01 ± 77.67
Albumin, g/dL	4.17 ± 0.45
Blood urea nitrogen, mmol/L	16.32 ± 7.48
Hemodynamic studies	
baPWV, m/s	18.88 ± 5.03
PI of RMCA	0.84 ± 0.32
PI of LMCA	0.86 ± 1.51
MFV of RMCA, cm/s	57.37 ± 28.90
MFV of LMCA, cm/s	55.47 ± 29.08
MCA asymmetry index	42.36 ± 59.13

Data are expressed as mean ± standard deviation or number (%). The MCA asymmetry index indicates the percentage of difference between the mean velocities of the LMCA and RMCA. Abbreviations: NIHSS, National Institutes of Health Stroke Scale; LAA, large-artery atherosclerosis; CE, cardioembolism; LAC, small-vessel occlusion; SUD, stroke of undetermined etiology owing to multiple causes or negative evaluation; TIA, transient ischemic attack; baPWV, brachial-ankle pulse wave velocity; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; PI, pulsatility index; MFV, mean flow velocity.

5. Classification of stroke subtype

We used the TOAST (Trial of Org 10172 in the Acute Stroke Treatment) classification to subdivide the patients into 4 groups: those with small vessel occlusion (LAC), large-artery atherosclerosis (LAA), cardioembolism (CE), and stroke of undetermined cause (SUD) [12]. Cerebral angiographic findings were obtained from digital subtraction angiography, MRA, or CTA, which were performed at admission, to classify the stroke subtype. All cerebral angiographic findings and the stroke subtypes were evaluated and determined during the weekly stroke conference, after a consensus was reached by stroke specialists. The patients were then prospectively registered in the Yonsei Stroke Registry.

6. Determination of functional outcome

Stroke-related functional outcome was assessed using the mRS score through a direct interview performed by a physician or through a telephone interview conducted by a well-trained research nurse after 3 months from stroke onset. The mRS consists of 6 different grades of disability, from a score of 0 for “no symptoms at all”; to 5 for “severe

disability or bedridden, incontinent, and requiring constant nursing care and attention”; and to 6 for death. We defined good and poor functional outcomes as mRS scores of <3 and ≥ 3 , respectively [12].

7. Statistical analysis

Statistical significance of intergroup differences was assessed using the χ^2 test for categorical variables and the Mann-Whitney U-test for non-normal continuous variables. After yielding the cutoff value of the MCA asymmetry index, the χ^2 test was used to analyze the association between stroke subtype and MCA asymmetry index cutoff value. Before investigating the predictive effect of the MCA asymmetry index for poor functional outcome, the patients were subdivided into tertile groups (T1-T3) according to the level of MCA asymmetry index. Then, we performed multivariable logistic regression with adjustments for sex, age, and variables that exhibited a P -value of <0.05 in the univariable analyses. For evaluating the discriminatory ability of the MCA asymmetry index in predicting functional outcomes, receiver operating characteristic curve analysis was used. The area under the curve (AUC) was calculated, and the optimal cutoff value

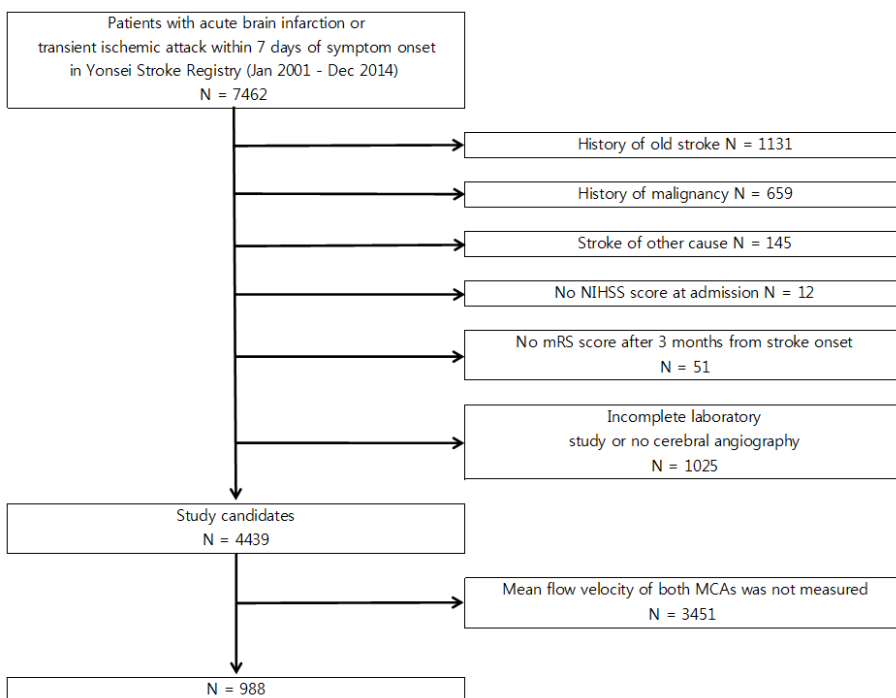


Figure 1. Flowchart of the inclusion and exclusion criteria. NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; MCA, middle cerebral artery.

of MCA asymmetry index was determined at the level with the highest Youden index (sensitivity + specificity-1). To measure the improvement in predictive ability by adding the MCA asymmetry index, we computed the change of AUC between the multivariable models with and without the MCA asymmetry index cutoff value. All statistical analyses were performed using the Windows SPSS package version 20.0 (SPSS Inc., Chicago, IL, USA). A 2-sided *P*-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 7,462 patients with acute ischemic stroke were registered in the Yonsei Stroke Registry. After eliminating 3,023 patients according to the

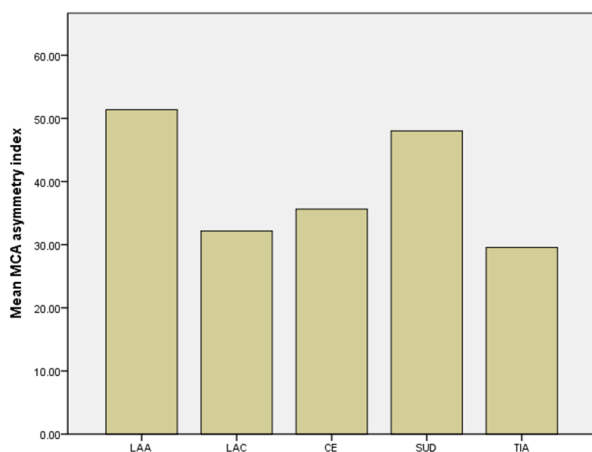


Figure 2. Mean MCA asymmetry index according to stroke subtype in the total group. LAA, large-artery atherosclerosis; LAC, small-vessel occlusion; CE, cardioembolism; SUD, stroke of undetermined etiology owing to multiple causes or negative evaluation; TIA, transient ischemic attack.

exclusion criteria, 4,439 candidates remained for this study. Of these, 988 subjects who had completed the measurements of MFVs of both MCAs were finally included (Figure 1).

The characteristics of the participants are summarized in Table 1. In a total of 988 patients, the mean age was 63.71 ± 12.18 years and the proportion of men was 69.2%. The mean MCA asymmetry index value was $42.36 \pm 59.13\%$, and the median (interquartile range) was 17.61 (8.02-41.31). Of the stroke subtypes, LAA had the highest MCA asymmetry index, followed by SUD in the total group (Figure 2, Table 2). According to the mRS score at 3 months after stroke onset, the patients were subdivided into 2 groups: good functional outcome (mRS score <3) and poor functional outcome (mRS score ≥ 3) [12]. The poor functional outcome group consisted of 157 (15.9%) patients. Poor functional outcome was positively associated with older age, higher NIHSS score at admission, higher level of high-sensitivity C-reactive protein, higher brachial-ankle pulse wave velocity (baPWV), higher PI of the right MCA (RMCA) and left MCA (LMCA), and higher MCA asymmetry index. Use of thrombolysis treatment, LAA, LAC, TIA, hemoglobin, hs-CRP, albumin, and both MFVs were negatively associated with poor functional outcome (Table 3). In univariable analysis to evaluate the association between stroke subtype and MCA asymmetry index cutoff value, the group with higher MCA asymmetry index included more patients with LAA but fewer patients with CE (Table 4). In the multivariable analysis including diverse forms of the MCA asymmetry index (tertiles, cutoff value, and continuous variable), only the optimal cutoff point of the MCA asymmetry index remained as an

Table 2. Association between stroke subtype and MCA asymmetry cutoff value

	LAA	LAC	CE	SUD	TIA
PI of RMCA	0.80 (0.65~0.96)	0.87 (0.73~1.00)	0.86 (0.69~1.00)	0.84 (0.71~1.03)	0.79 (0.72~0.95)
PI of LMCA	0.78 (0.63~0.93)	0.81 (0.69~0.96)	0.85 (0.72~1.00)	0.83 (0.70~0.98)	0.80 (0.70~0.96)
MFV of RMCA, cm/s	57.5 (45.0~73.8)	55.3 (43.6~68.1)	51.0 (40.3~63.0)	55.0 (41.5~70.0)	57.5 (45.3~71.8)
MFV of LMCA, cm/s	57.0 (43.3~75.8)	54.0 (43.8~62.9)	52.5 (40.0~62.5)	51.0 (39.0~68.0)	58.0 (48.8~70.5)
MCA asymmetry index	28.14 (11.02~57.78)	17.02 (7.69~29.09)	13.64 (6.34~30.98)	20.28 (9.13~52.85)	14.14 (7.05~32.52)

Data are expressed as median [interquartile range].

Abbreviations: LAA, large-artery atherosclerosis; LAC, small-vessel occlusion; CE, cardioembolism; SUD, stroke of undetermined etiology owing to multiple causes or negative evaluation; TIA, transient ischemic attack; baPWV, brachial-ankle pulse wave velocity; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; PI, pulsatility index; MFV, mean flow velocity.

Table 3. Clinical characteristics between good and poor functional outcomes

	Good Outcome (mRS 0-2; N = 831)	Poor Outcome (mRS 3-6; N = 157)	P-value
Male sex	582 (70.0)	102 (65.0)	0.207
Age, y	63.07 (54.36~71.01)	72.74 (63.16~78.45)	<0.001 [†]
NIHSS score at admission	2.0 (1.0~4.0)	8.0 (4.5~14.5)	<0.001 [†]
Use of thrombolysis treatment	60 (7.2)	23 (14.6)	0.002*
Risk factors			
Hypertension	340 (65.4)	40 (71.4)	0.364
Diabetes mellitus	148 (28.5)	20 (35.7)	0.257
Hypercholesterolemia	114 (21.9)	17 (30.4)	0.153
Current smoking	157 (30.2)	14 (25.0)	0.419
Coronary artery disease	27 (5.2)	3 (5.4)	1
Peripheral artery disease	21 (4.0)	2 (3.6)	1
Stroke subtype			
LAA	133 (76.9)	40 (23.1)	0.021*
CE	223 (81.7)	50 (18.3)	0.593
LAC	78 (90.7)	8 (9.3)	0.035*
SUD	321 (84.7)	58 (15.3)	0.721
TIA	76 (98.7)	1 (1.3)	<0.001 [†]
Laboratory findings			
Hemoglobin, g/dL	14.5 (13.4~15.5)	14.0 (12.6~15.2)	0.001*
hs-CRP, nmol/L	1.6 (0.8~4.2)	3.6 (1.6~12.5)	<0.001 [†]
Cholesterol, mmol/L	180.0 (154.0~209.0)	175.0 (144.5~206.0)	0.055
Albumin, g/dL	4.2 (4.0~4.5)	4.0 (3.8~4.3)	<0.001 [†]
Glucose, mmol/L	120.0 (104.0~155.0)	124.0 (107.0~157.0)	0.234
Blood urea nitrogen, mmol/L	14.8 (11.9~18.6)	14.8 (12.0~20.2)	0.293
Creatinine, umol/L	0.87 (0.74~1.02)	0.85 (0.70~1.05)	0.447
Hemodynamic studies			
baPWV, m/s	17.68 (14.94~20.75)	20.89 (17.56~25.43)	<0.001 [†]
PI of RMCA	0.82 (0.69~0.98)	0.92 (0.75~1.05)	<0.001 [†]
PI of LMCA	0.81 (0.69~0.96)	0.87 (0.69~1.05)	0.041*
MFV of RMCA, cm/s	55.0 (43.0~69.0)	50.0 (36.8~67.0)	0.008*
MFV of LMCA, cm/s	54.5 (43.0~68.0)	46.5 (32.3~64.3)	<0.001 [†]
MCA asymmetry index	15.91 (7.73~36.24)	28.75 (13.01~78.67)	<0.001 [†]

Data are expressed as median [interquartile range] or number (%).

The MCA asymmetry index indicates the percentage of difference between the mean velocities of the LMCA and RMCA.

* $P < 0.05$.

[†] $P < 0.001$.

Abbreviations: mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; LAA, large-artery atherosclerosis; CE, cardioembolism; LAC, small-vessel occlusion; SUD, stroke of undetermined etiology owing to multiple causes or negative evaluation; TIA, transient ischemic attack; baPWV, brachial-ankle pulse wave velocity; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; PI, pulsatility index; MFV, mean flow velocity.

independent predictor of poor functional outcome. No significant interaction between stroke subtype and poor functional outcome was noted. NIHSS score at admission, use of thrombolysis treatment, and baPWV were still significant after adjusting for confounding variables (Table 5). In the receiver operating characteristic curve analysis (Figure 3), when the continuous value of the MCA asymmetry index was considered a predictor of poor functional outcome, the AUC was 61.5% (95% confidence interval [CI], 56.7-66.4). The optimal cutoff point of the

MCA asymmetry index was >16.53 m/s (at this point, the sensitivity was 69.4% and the specificity was 50.8%). When we compared the AUC of multivariable models with and without the MCA asymmetry index, the AUC was increased from 88.6% (95% CI, 85.2-91.9) to 89.2% (95% CI, 85.9-92.5).

DISCUSSION

In this study, we found that a higher MCA asymmetry

Table 4. Association between stroke subtype and MCA asymmetry cutoff value

Stroke subtypes	At optimal cut-point		P-value
	MCA asymmetry index ≤ 16.53	MCA asymmetry index > 16.53	
LAA	58 (33.5)	115 (66.5)	$< 0.001^{\dagger}$
CE	162 (59.3)	111 (40.7)	$< 0.001^{\dagger}$
LAC	40 (46.5)	46 (53.5)	0.653
SUD	166 (43.8)	213 (56.2)	0.139

Data are expressed as a number (%).

The MCA asymmetry index indicates the percentage of difference between the mean velocities of the left and right MCAs.

$^{\dagger} P < 0.001$.

Abbreviations: LAA, large-artery atherosclerosis; CE, cardioembolism; LAC, small-vessel occlusion; SUD, stroke of undetermined etiology owing to multiple causes or negative evaluation.

index was related to LAA and significantly associated with poor functional outcome. TCD parameters have been used to diagnose and predict intracranial vascular disease. Annemarie et al reported that cerebral flow velocity was influenced by conventional cardiovascular risk factors including age, sex, diabetes, and total serum cholesterol [16]. Moreover, Wakerley et al demonstrated that PI was influenced by intracranial pressure [5]. Other studies reported that an increased PI was associated with cognitive impairment and a larger infarct volume in patients with lacunar stroke [6, 7]. Concerning the relationship between TCD parameters and prognosis, MFV and PI were independent prognostic factors for recurrent vascular events in patients with transient ischemic attack or minor ischemic stroke [4] and also useful to predict short-term functional outcome in stroke

Table 5. Predictive value of the MCA asymmetry index for poor functional outcomes

	Univariable		Multivariable	
	OR (95% CI)	P-value	HR (95% CI)	P-value
Male sex	0.793 (0.554~1.137)	0.208	0.763 (0.355~1.640)	0.488
Age, y	1.067 (1.049~1.085)	0.001*	1.012 (0.975~1.051)	0.530
NIHSS score at admission	1.231 (1.190~1.273)	$< 0.001^{\dagger}$	1.271 (1.179~1.369)	$< 0.001^{\dagger}$
Use of thrombolysis treatment	2.206 (1.319~3.689)	0.003*	0.285 (0.088~0.916)	0.035*
Hemoglobin, g/dL	0.855 (0.780~0.938)	0.001*	1.021 (0.800~1.301)	0.869
hs-CRP, nmol/L	1.001 (0.999~1.002)	0.466	0.999 (0.990~1.008)	0.797
Albumin, g/dL	0.341 (0.238~0.487)	$< 0.001^{\dagger}$	0.873 (0.393~1.938)	0.738
baPWV, m/s	1.001 (1.001~1.002)	$< 0.001^{\dagger}$	1.110 (1.035~1.190)	0.004*
PI of RMCA	1.842 (1.085~3.126)	0.024*	1.612 (0.450~5.782)	0.464
PI of LMCA	1.003 (0.899~1.118)	0.964	2.195 (1.007~4.783)	0.048*
Stroke subtype				
LAA	1.665 (1.061~2.612)	0.027*	1.368 (0.598~3.130)	0.459
CE	1.241 (0.819~1.879)	0.308	0.420 (0.175~1.010)	0.053
LAC	0.568 (0.260~1.238)	0.155	1.161 (0.372~3.623)	0.797
SUD	1		1	
MCA asymmetry index tertiles				
T1: < 10.79	1		1	
T2: 10.79~29.86	1.485 (0.924~2.385)	0.102	1.493 (0.642~3.471)	0.352
T3: > 29.86	2.721 (1.750~4.229)	$< 0.001^{\dagger}$	2.143 (0.898~5.113)	0.086
At optimal cut-point				
MCA asymmetry index > 16.53	2.343 (1.625~3.378)	$< 0.001^{\dagger}$	2.420 (1.176~4.978)	0.016*
As a continuous variable				
MCA asymmetry index, per SD (59.13)	1.005 (1.002~1.007)	$< 0.001^{\dagger}$	1.003 (0.997~1.009)	0.375

Data were derived from logistic regression analysis.

The MCA asymmetry index indicates the percentage of difference between the mean velocities of the LMCA and RMCA.

* $P < 0.05$.

$^{\dagger} P < 0.001$.

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; baPWV, brachial-ankle pulse wave velocity; RMCA, right middle cerebral artery; LMCA, left middle cerebral artery; PI, pulsatility index; LAA, large-artery atherosclerosis; CE, cardioembolism; LAC, small-vessel occlusion; SUD, stroke of undetermined etiology owing to multiple causes or negative evaluation; CI, confidence interval; OR, odds ratio; T, tertile.

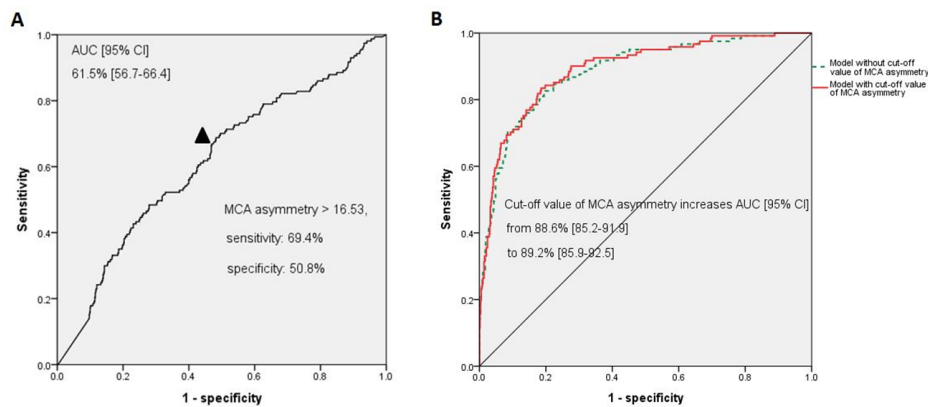


Figure 3. Results of receiver operating characteristic analysis using the percentage of difference between the mean velocities of both MCAs (MCA asymmetry index; continuous variable). (A) Receiver-operating characteristic curve using the MCA asymmetry index alone for identifying poor functional outcome after stroke. Black arrow indicates the optimal cutoff point of the MCA asymmetry index, which maximizes the Youden index. (B) Change in the AUC after the addition of the cutoff value of the MCA asymmetry index to the multivariable model for predicting poor functional outcome. Adjustments were made for following variables: sex, age, National Institute of Health Stroke Scale score at admission, use of thrombolysis treatment, stroke subtype, hemoglobin level, high-sensitivity C-reactive protein level, triglyceride level, albumin level, pre-morbid medication (antihypertensive) use, pulsatility index of the right MCA, pulsatility index of the left MCA, and brachial-ankle pulse wave velocity. AUC, area under the curve; CI, confidence interval; MCA, middle cerebral artery.

patients with recanalization after intravenous thrombolysis [17]. However, these studies did not deal with the asymmetric MCA MFV. Some studies reported that MCA flow asymmetry was a marker of underlying carotid disease and stroke [10], and suggested that it could be used as an alternative to perfusion-diffusion mismatch in predicting the presence of salvageable brain tissue in patients with acute ischemic stroke [18]. In addition, central nervous system infections might be associated with the asymmetric PI in the preliminary study [19]. In comparison with this study, they did not consider short-term functional outcome and other stroke subtypes, and also did not carry out the research on stroke patients, respectively. Thus, it is insufficient to fully understand the relation of asymmetric MCA MFV to prognosis of stroke.

We sought to determine whether a higher MCA asymmetry index influences poor functional outcome in TIA and acute ischemic stroke, and whether there is any significant difference among stroke subtypes according to the MCA asymmetry index. We demonstrated that a higher MCA asymmetry index was associated with LAA, as expected. TCD ultrasonography mainly reflects the hemodynamic information of the proximal MCA, owing to restricted insonation, and thus abnormally increased or decreased velocity reflects a pathophysiologic condition

in large arteries such as the proximal MCA [3]. Although To help simplify the stratification of high-risk patients, we yielded a cutoff value from the MCA asymmetry index as a continuous variable by using receiver operating characteristic curve analysis. Of the hemodynamic parameters, only the cutoff value had an independent association with poor functional outcome, and adding the MCA asymmetry index to the prediction model significantly improved the discrimination ability for poor functional outcome. This means that the MCA asymmetry index measured during the acute phase of stroke can independently predict the 3-month functional prognosis; thus, this novel index should be considered a crucial marker for identifying patients with severe stroke-related disabilities. In addition to the MCA asymmetry index, higher NIHSS score at admission and baPWV were also independently associated with poor functional outcome. These findings are in line with preceding researches, which reported that these factors were independent variables predicting the 3-month functional prognosis in patients with acute ischemic stroke [12, 20]. Baracchini et al reported that MCA no-flow measured in the acute phase of ischemic stroke was an independent predictor of poor long-term outcome categorized according to the Barthel index score; however, the MCA asymmetry index was not independently

associated [21]. Although their study might be similar in design to our study, the Barthel index does not completely correspond with the mRS used in our study. In addition, we presented the MCA asymmetry index of <16.53 as an independent predictor of poor outcome, and then demonstrated that adding the independent predictor into the prediction model improved the discrimination of poor long-term outcome in patients with acute ischemic stroke.

This study has several limitations. First, the statistical power decreased rather more than expected owing to the loss of a few subjects who did not meet our rigorous inclusion criteria. Second, there are concerns about a coincident increase or decrease in the MVF of both sides in certain pathological conditions, which has no effect on the asymmetric index. Third, TCD parameters were obtained by two medical technicians they have experience for 11 years and 7 years, respectively. Although previous study reported that TCD had a high level of interobserver agreement in skilled personnel [22], technical difference may exist. Thus, the same skilled and well trained technicians are needed to improve the reliability in further studies. Finally, the MCA asymmetry index presented in this study is not an intrinsic value. Nevertheless, it is important to find and create a variety of indicators for predicting prognosis in stroke patients. Therefore, we recommend an MCA asymmetry index value of >16.53 as a factor for stratifying patients with acute ischemic stroke, which may be helpful in predicting the 3-month functional prognosis.

The MCA asymmetry index has an independent prognostic value for predicting poor short-term functional outcome after acute cerebral infarction. Therefore, TCD may be a useful method for predicting poor functional outcome in patients with TIA and acute ischemic stroke.

요약

본 연구는 일과성허혈발작 및 급성뇌경색환자에서 양쪽 중간대뇌동맥의 혈류속도 차이가 예후를 예측할 수 있는 지표가 될 수 있고, 이러한 예후예측력이 뇌졸중 아형 간에 차이가 있는지를 관찰하는 것이다. 모든 대상자는 일과성허혈발작 및 급성

뇌경색환자들이며, 기본적인 평가와 경두개도플러검사(TCD)가 실시되었다. 중간대뇌동맥 비대칭 지수(MCA asymmetry index)는 다음의 공식에 의해 구해졌다; $MCA\ asymmetry\ index = (RMCA\ MFV - LMCA\ MFV) / \text{mean}\ MCA\ MFV \times 100$. 뇌경색 분류는 TOAST classification에 따라 진행되었다. 나쁜 예후(poor functional outcome)는 mRS score ≥ 3 at 3 months after stroke onset로 정의하였다. 총 988명의 급성뇌경색환자가 분석에 포함되었고, 그 중 157명(15.9%)이 나쁜 예후를 가지고 있었다. 뇌경색 하위유형 및 여러 혼란변수를 보정 후 실시한 다변량분석에서 중간대뇌동맥 비대칭 지수만 유일하게 독립적으로 나쁜 예후와 연관성을 보였다. ROC curve 분석에서 중간대뇌동맥 비대칭 지수를 예측모형에 투입하였을 때 투입 전에 비해 나쁜 예후를 예측하는 능력이 상승하는 것을 관찰하였다(from 88.6% [95% CI, 85.2-91.9] to 89.2% [95% CI, 85.9-92.5]). 급성뇌경색환자에서 중대뇌동맥 비대칭 지수는 나쁜 예후를 독립적으로 예측하였다. 따라서 경두개도플러검사는 급성뇌경색환자에서 나쁜 예후를 예측하는데 유용하게 사용될 수 있을 것이다.

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REFERENCES

1. Jin BH. Correlation of gender/age and measurement indices of transcranial Doppler ultrasonography. *Korean J Clin Lab Sci.* 2010;42:155-160.
2. Kidwell CS, el-Saden S, Livshits Z, Martin NA, Glenn TC, Saver JL. Transcranial Doppler pulsatility indices as a measure of diffuse small-vessel disease. *J Neuroimaging.* 2001;11:229-235.
3. Rorick MB, Nichols FT, Adams RJ. Transcranial Doppler correlation with angiography in detection of intracranial stenosis. *Stroke.* 1994;25:1931-1934.
4. Wijnhoud AD, Koudstaal PJ, Dippel DW. The prognostic value of pulsatility index, flow velocity, and their ratio, measured with TCD ultrasound, in patients with a recent TIA or ischemic stroke. *Acta Neurol Scand.* 2011;124:238-244.
5. Wakerley BR, Kusuma Y, Yeo LL, Liang S, Kumar K, Sharma AK et al. Usefulness of transcranial Doppler-derived cerebral hemodynamic parameters in the noninvasive assessment of intracranial pressure. *J Neuroimaging.* 2015;25:111-116.
6. Altmann M, Thommessen B, Rønning OM, Benth JS, Reichenbach AS, Fure B. Middle cerebral artery pulsatility index is associated with cognitive impairment in lacunar stroke. *J Neuroimaging.* 2016;26:431-435.

7. Kim Y, Lee H, An SA, Yim B, Kim J, Kim OJ, et al. The effect of pulsatility index on infarct volume in acute lacunar stroke. *Yonsei Med J.* 2016;57:950-955.
8. Micieli G, Bosone D, Cavallini A, Rossi F, Pompeo F, Tassorelli C, et al. Bilateral asymmetry of cerebral blood velocity in cluster headache. *Cephalalgia.* 1994;14:346-351.
9. Mayer SA, Thomas CE, Diamond BE. Asymmetry of intracranial hemodynamics as an indicator of mass effect in acute intracerebral hemorrhage. A transcranial Doppler study. *Stroke.* 1996;27:1788-1792.
10. Brint SU, Al-Khalidi HR, Vatel B, Hier DB. MCA flow asymmetry is a marker for cerebrovascular disease. *Neurol Res.* 1996;18:163-167.
11. Zanette EM, Fieschi C, Bozzao L, Roberti C, Toni D, Argentino C et al. Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. *Stroke.* 1989;20:899-903.
12. Nam HS, Kim HC, Kim YD, Lee HS, Kim J, Lee DH, et al. Long-term mortality in patients with stroke of undetermined etiology. *Stroke.* 2012;43:2948-2956.
13. Jones DW, Hall JE. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and evidence from new hypertension trials. *Hypertension.* 2004;43:1-3.
14. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2003;26(Suppl 1):5-20.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
16. Wijnhoud AD, Koudstaal PJ, Dippel DW. Relationships of transcranial blood flow Doppler parameters with major vascular risk factors: TCD study in patients with a recent TIA or nondisabling ischemic stroke. *J Clin Ultrasound.* 2006;34:70-76.
17. Wunderlich MT, Goertler M, Postert T, Schmitt E, Seidel G, Gahn G et al. Recanalization after intravenous thrombolysis: does a recanalization time window exist? *Neurology.* 2007;68:1364-1368.
18. Restrepo L, Razumovsky AY, Ziai W, Barker PB, Beauchamp NJ, Wityk RJ. Transcranial Doppler markers of diffusion-perfusion mismatch. *J Neuroimaging.* 2003;13:34-42.
19. Kargiotis O, Safouris A, Magoufis G, Stamboulis E, Tsivgoulis G. Transcranial color-coded duplex in acute encephalitis: current status and future prospects. *J Neuroimaging.* 2016;26:377-82.
20. Kim J, Song TJ, Kim EH, Lee KJ, Lee HS, Nam CM, et al. Brachial-ankle pulse wave velocity for predicting functional outcome in acute stroke. *Stroke.* 2014;45:2305-2310.
21. Baracchini C, Manara R, Ermani M, Meneghetti G. The quest for early predictors of stroke evolution: can TCD be a guiding light? *Stroke.* 2000;31:2942-2947.
22. McMahon CJ, McDermott P, Horsfall D, Selvarajah JR, King AT, Vail A. The reproducibility of transcranial Doppler middle cerebral artery velocity measurements: implications for clinical practice. *Br J Neurosurg.* 2007;21:21-27.