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ORIGINAL ARTICLE

Regional Arterial Stiffness is Inversely Correlated with Flow Velocity in the MCA on Transcranial Doppler Sonography

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ABSTRACT

Background: Although flow velocities of basal cerebral arteries have been reported to be associated with age, the exact cause of the age dependency of flow velocities has not been elucidated. **Methods:** We recruited patients presenting with an ischemic stroke or transient ischemic attack. Averaged mean flow velocity of both MCAs (amFV) was calculated using transcranial Doppler examination. The association between quartiles of amFV and pulse wave velocity (PWV) was tested with ordinal regression analyses. **Results:** Forty-eight patients (32 males, 56.73±12.29 years), 10 with TIA and 38 with ischemic strokes, were included. PWVs for the heart-carotid, carotid-brachial, right heart brachial, left brachial-ankle, and heart-femoral had inverse association with ordinal amFV. Finally heart-carotid pulse wave velocity was significantly associated with quartiles of amFV after adjustment of covariates. **Conclusions:** Arterial stiffness was inversely associated with the cerebral blood flow velocity of the MCA. The association between arterial stiffness and cerebral blood flow velocity showed regional difference. ***Journal of Neurosonology 1(1):39-45, 2009***

Key Words: Blood flow velocity, Transcranial Doppler Ultrasound, Arterial stiffness, Pulse wave velocity, Cerebral infarction

INTRODUCTION

Since the introduction of transcranial Doppler ultrasonography (TCD) by Asalid in 1982,[1] TCD has been known to aid in the diagnosis of cerebrovascular diseases noninvasively at the bedside. Recent studies have reported that the clinical usefulness of TCD includes not only the detection of arterial stenoses, but also the detection of microemboli and the assessment of functional status of brain.[2,3]

Among the parameters of a TCD examination, flow velocities of basal cerebral arteries are the most important because the diagnosis of arterial stenosis is based on elevated blood flow velocity at the point of maximum arterial narrowing.[4] The age dependency of cerebral blood flow velocity has been well established.[5-7] Cerebral blood flow tends to decrease with advancing age.[8] Similar findings have been reproduced in several transcranial sonographic studies.[5-7, 9-11] Flow velocities of basal cerebral arteries decrease abruptly during adolescence, are stable or mildly decrease during middle age and, again, markedly decreased after the age of 40 years.[9] This age dependency is preserved among stroke patients.[7] The decrease in flow velocities with age has been speculated to relate with dilatation of major arteries and reduction of flow within parenchymal vessels, alteration of elasticity, vasomotor reactivity, changes in autoregulation, and dilative vasculopathy.[5,6] However, the precise cause of age dependency of flow velocities of cerebral arteries is unclear.

Arterial stiffness is caused by aging of the arterial system, which is accompanied by structural changes including degeneration of elastin, increases in collagen and thickening of the arterial wall[12] and is known as one of the important determinants of

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increasing systolic pressure and pulse pressure.[13] The changes with aging also include the process of arteriosclerosis, which results in gradual dilatation and hardening of the large arteries.[14] Therefore, age is an important determinant of arterial stiffness.[13] Arterial stiffness was also suggested as a possible mechanism for the age dependence of cerebral blood flow velocity measured using TCD.[9]

Pulse wave velocity (PWV), a measurement of the speed of the pressure waves along arterial segments, is the most frequently used index of arterial stiffness.[15] Recently, using regional PWV, the clinical impact of arterial stiffness in different regions has been elucidated.[16]

We hypothesized that the decreased flow velocity with increasing age could be associated with arterial stiffness. Therefore, the aims of this study were to determine whether arterial stiffness was associated with cerebral flow velocity and whether the different regional PWVs had different effects on cerebral flow velocities.

METHODS

1. Subjects

We retrospectively selected patients presenting with an ischemic stroke or transient ischemic attack (TIA) between April 2007 and December 2007 from the prospectively collected data from the Korea University Stroke Registry, anSan arm (KUSR-S). Eligibility for inclusion required minor infarction [TIA, lacunar infarction or infarction on non-middle cerebral artery (non-MCA) territory], an adequate imaging study including brain magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA), no significant stenosis of MCA or internal cerebral artery (ICA) defined by MRA, mild neurological sequelae (modified Rankin score $\leq$3) and no chronic devastating illness such as cancer. Among 250 patients admitted during the study period, 68 who met the eligibility criteria were recruited and underwent standardized transcranial Doppler examination (TCD) and pulse wave velocity (PWV). After TCD, 20 patients with poor temporal windows or abnormalities of the MCA or ICA were excluded. Thus, 48 patients were included in this study. The study protocol was approved by the institutional review board.

2. Clinical assessment

Detailed demographic and clinical variables were collected. Hypertension was defined as either the combination of a self- reported high blood pressure diagnosis and the use of antihypertensive medications or blood pressure recordings that consistently exceeded 140/90 mm Hg beyond the second week after stroke. Diabetes was defined as either a fasting glucose $\geq$126 mg/dL or self-reported use of insulin or oral hypoglycemic agents. Levels of total cholesterol, triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL) were analyzed from fasting blood. We also assessed patient levels of high-sensitivity C-reactive protein (hsCRP), hematocrit, fasting glucose and homocysteine. Body mass index (BMI) was calculated as weight (Kg) / height $(m)^2$. Smoking status was assigned as either current/past smoker or non-smoker. Stroke subtype was classified based on previously published guidelines.[17] TIAs were recorded separately.

3. Arterial stiffness

Arterial stiffness was assessed by PWV on right and left sides using an automated system (VP2000, Colin Medical Technology, Japan) and applying previously published methods.[18] In brief, the measurement of PWV was usually performed a week after the onset of stroke. Before PWV measurement, blood pressure was checked in a sitting position after 10 minutes of rest. Electrocardiogram, bilateral brachial and ankle blood pressures, and carotid and femoral arterial pulse waves were simultaneously measured. Heart sounds S1 and S2 were detected by a microphone set on the left edge of the sternum at the third intercostal space. Ten second intervals of bilateral brachial and posterior tibial arterial pressure waveforms were recorded using extremity cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor wrapped around both arms and ankles.

The waveform analyzer measures time intervals between S2 and the notch of carotid pulse wave (T*hc*), between S2 and the notch of brachial pulse wave (T*hb*), between pulse waves of the carotid and femoral arteries (T*cf*), between pulse waves of the carotid and brachial arteries (T*cb*), between brachial and tibial arteries (T*ba*), and between pulse waves of the femoral and tibial (ankle) arteries (T*fa*). The sum of T*hc* and T*cf* gives the time for pulse waves to travel form the heart (aortic orifice) to the femoral artery (T*hf*). Also, the waveform analyzer estimates the path

lengths automatically. PWV was calculated for each arterial segment from the distance between the two arterial recording sites divided by transit time.

Ankle-brachial index (ABI) was measured to exclude occlusive disease to the lower extremities. Pressures were measured in the right arm and both ankles (tibial artery) automatically. Systolic blood pressure (SBP) in the ankle was divided by the SBP in the arm to create an ABI separately on each side. The ABIs of all subjects were ≥0.90.

4. Standardized TCD examination

TCD examination was performed by one experienced ultrasonographer using the same TCD equipment (Pioneer TC 8080, Nicolet Biomedical, Inc., Madison, WI, USA) at the bedside. Detailed descriptions of TCD techniques have been previously published.[19] The proximal sections of the arteries that make up the Circle of Willis were examined via the transtemporal and transorbital window. The posterior circulation, including both vertebral and basilar arteries was examined through the suboccipital window by lying the patients on their side. The internal carotid artery and external carotid artery were examined through the submandibular window. We used the mFV of the MCA as a representative of mFV of cerebral arteries because MCA is most readily detected among the basal cerebral arteries and have a straight course and run parallel with ultrasound beam. The patients with mFV of the MCA above 100 m/sec were considered as having significant stenosis and were excluded from this study.[4]

5. Statistical analyses

Statistical analysis was performed using SPSS (version 10.0), and results with p values <0.05 were regarded as significant. Because of the high correlation coefficient of mFV of MCAs on the left and right sides (Pearson's correlation coefficient 0.685, p<0.001), we calculated the averaged mean FV (amFV).

The associations between amFV and clinical variables were tested using Pearson correlation and Chi-square tests or Fisher's exact tests according to their distribution. The test for trend was performed by ordinal regression analyses with ordinal quartiles of amFV as dependent variables and regional PWVs as independent variables after adjustment for age and homocysteine using a logit link function. Cut-off points for quartiles of amFV were 43.75, 52.00, and 67.375 m/sec. Furthermore, we performed ordinal regression analyses to investigate associations between quartiles of amFV and regional PWVs. We used three types of model: model 1 (unadjusted), model 2 (adjusted for previous history of stroke and homocysteine), and model 3 (adjusted for previous history of stroke, homocystein, and age). Because homocysteine levels and a previous history of stroke were significantly associated with quartiles of amFV, we chose them as covariates for adjustment. Also, although age had no significant association with quartiles of amFV, age was added to the list of covariates for model 3.

RESULTS

1. Subjects

The final number of patients recruited was 48 (32 males, 56.73±12.29 years old), including 10 patients with TIA and 38 with ischemic strokes (Table 1). Nineteen patients with classification of large artery atherosclerosis, cardioembolism or undetermined

Table 1. Baseline characteristics of the patients

	(n=48)
Age, years	56.73±12.29
Gender (male)	32 (66.7)
Hypertension	17 (35.4)
Diabetes mellitus	7 (14.6)
Smoking	17 (35.4)
Previous stroke	7 (14.6)
Classification of stroke	
Transient ischemic attack	10 (20.8)
Large artery atherosclerosis	4 (8.3)
Cardioembolism	1 (2.1)
Small vessel occlusion	19 (39.6)
Undetermined etiology	14 (29.2)
Total cholesterol, mg/dl	185.83±33.68
Low density lipoprotein, mg/dl	116.29±28.91
High density lipoprotein, mg/dl	47.60±13.13
Triglycerides, mg/dl	122.60±64.65
High sensitivity C-reactive protein, mg/dl	0.29±0.587
Homocysteine, μmol/l	11.60±8.57
Hemoglobin A_{1c}, %	5.92±1.01
Glucose (fasting), mg/dl	134.06±44.65
Body mass index, kg/m^2	23.65±2.52
Systolic blood pressure, mmHg	148.06±23.94
Diastolic blood pressure, mmHg	87.43±16.36
Pulse rate, bpm	67.07±10.72
Abnormal ankle-brachial index	0 (0)
Averaged mean flow velocity of MCAs, cm/sec	56.5 (17.47)

Values are n (%) or mean±SD.

etiology had lesions on posterior circulation territories. One patient with a cardioembolic origin had a patent foramen ovale. Other baseline characteristics of the subjects were presented in Table 1.

2. Correlation between regional PWVs and amFV

In terms of PWVs, amFV was inversely correlated with hcPWV (correlation coefficient -0.459, p=0.002), cbPWV (-0.458, p=0.002), RhbPWV (-0.374, p=0.009), hfPWV (-0.438, p=0.003), RbaPWV (-0.296, p=0.041), and LbaPWV (-0.327, p=0.023). The averaged pulsatility index from right and left MCA had positive correlations with age (0.380, p=0.008) and hcPWV (0.337, p=0.008). No significant association was found between the averaged pulsatility index and other PWVs.

3. Association of quartiles of mean flow velocity with clinical factors

The quartiles of mean flow velocity had significant inverse correlations with homocysteine (Pearson's correlation coefficient -0.341, p=0.018) and positive previous history of stroke (Fisher's exact test, p=0.009) (Table 2). Other clinical variables including systolic and diastolic blood pressure had no significant association with quartiles of amFV.

4. Ordinal regression analyses

Regional PWVs showed trends of decrement by increasing quartiles of amFV (Fig. 1). The trends were significant for hcPWV (estimate -0.451, p=0.007), cbPWV (estimate -1.126, p=0.014), RhbPWV (estimate -0.737, p=0.017), LbaPWV (estimate -0.186, p=0.040), and hfPWV (estimate -0.363, p=0.022) after ordinal regression analyses (Table 3). After adjustment for homocysteine and a previous history of stroke (model 2), hcPWV (estimates -0.432, p=0.010) showed significant associations with quartiles of amFV and RhbPWV (estimates -0.601, p=0.057) and hfPWV (estimates -0.300, p=0.060) and it showed trends of inverse associations with quartiles of amFV. After adjustment for homocysteine, previous history of stroke and age (model),

Table 2. Clinical data according to quartiles of averaged mean flow velocity of MCAs

	Q1	Q2	Q3	Q4	Total
Age	62.92±12.50	57.38±10.32	53.64±16.34	52.67±7.79	56.73±12.29
Gender, male (%)	9 (75.0)	9 (69.2)	8 (72.7)	6 (60.0)	32 (66.7)
Hypertension, (%)	6 (50.0)	6 (46.2)	1 (9.1)	4 (33.3)	17 (35.4)
Diabetes, (%)	4 (33.3)	1 (7.7)	0 (0)	2 (16.7)	7 (14.6)
Smoking, (%)	4 (33.3)	6 (46.2)	3 (27.3)	4 (33.3)	17 (35.4)
Prior stroke, (%)*	0 (0)	5 (38.5)	2 (18.2)	0 (0)	7 (14.5)
Mechanisms of stroke					
TIA	2 (16.7)	2 (15.4)	4 (36.4)	2 (16.7)	10 (20.8)
LAA	0 (0)	2 (15.4)	1 (9.1)	1 (8.3)	4 (8.3)
CE	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (2.1)
SVO	6 (50.0)	6 (46.2)	1 (9.1)	6 (50.0)	19 (39.6)
UDE	3 (25.0)	3 (23.1)	5 (45.5)	3 (25.0)	14 (29.2)
Systolic BP, mmHg	161.42±25.31	138.25±24.24	142.64±25.43	149.50±15.77	148.06±23.94
Diastolic BP, mmHg	91.50±18.99	80.75±18.04	86.64±16.79	90.75±9.88	87.43±16.36
Pulse rate, rate/minutes	66.17±7.79	63.92±11.90	69.82±9.09	68.83±13.33	67.06±10.72
Hematocrit, %	42.41±4.90	41.30±3.40	39.61±3.61	40.15±4.07	40.90±4.05
hsCRP, mg/dl	0.29±0.38	0.22±0.26	0.58±1.15	0.12±0.10	0.29±0.59
BMI, kg/m^2	23.87±3.14	24.07±2.55	22.35±1.52	24.18±2.44	23.65±2.52
Total cholesterol, mg/dl	189.08±26.37	191.08±44.30	168.20±24.96	191.58±32.16	185.83±33.68
LDL-cholesterol, mg/dl	120.00±24.42	124.08±36.54	98.09±27.04	120.83±20.34	116.29±28.91
HDL-cholesterol, mg/dl	46.14±15.45	47.23±13.34	49.09±10.03	48.08±14.04	47.60±13.13
Triglycerides, mg/dl	139.58±55.92	126.15±69.20	91.73±49.17	130.08±77.22	122.60±64.65
Fasting glucose, mg/dl	133.00±34.82	143.77±68.75	132.10±29.38	126.25±32.87	134.06±44.65
Homocysteine, μmol/l*	17.49±15.45	8.98±2.01	10.50±2.28	9.54±3.73	11.60±8.57

Values are n (%) or mean±SD. *p<0.05.
Cut-off points for quartiles of averaged mean flow velocity of MCAs were 43.75, 52.00, and 67.375 cm/sec. TIA; transient ischemic attacks, LAA; large artery atherosclerosis, SVO; small vessel occlusion, UDE; undetermined etiology, BP; blood pressure, hsCRP; high sensitivity C-reactive protein, BMI; body mass index.

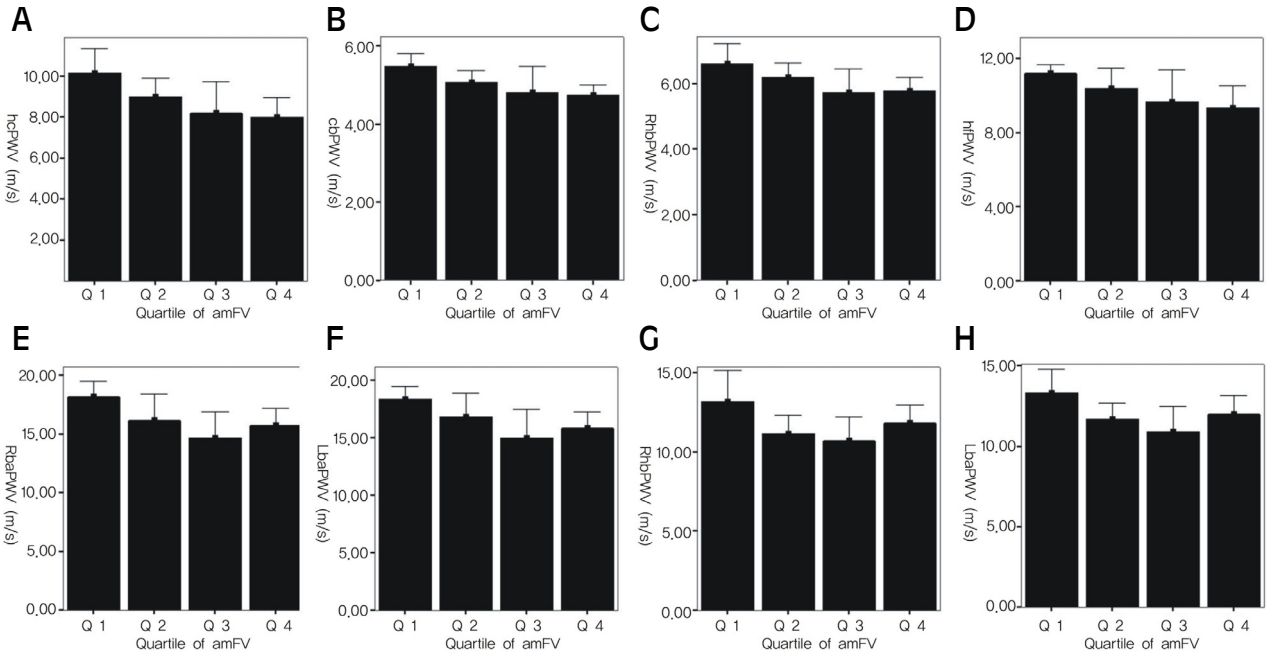

Fig. 1. Pulse wave velocities according to the quartile of averaged mean flow velocities of right and left MCA.

Cut-off points for quartiles (Q1–Q4) of averaged mean flow velocity of MCAs were 43.75 m/sec, 52.00 m/sec, and 67.375 m/sec. hcPWV; heart-carotid pulse wave velocity, cbPWV; carotid-femoral PWV, RhbPWV; heart-brachial PWV, hfPWV; heart-femoral PWV, RfaPWV; right femoral-ankle PWV, and LfaPWV; left femoral-ankle PWV.

hcPWV (estimates -0.432, p=0.020) had a significant association with quartiles of amFV.

DISCUSSION

In this study, we found that arterial stiffness measured by PWVs had a significant inverse relationship with blood flow velocity of MCA in stroke patients. The relationship persisted after adjusting for clinical factors including age. Furthermore, the association between PWV and blood flow was influenced by the location of arterial stiffness.

Age dependency of cerebral blood flow velocity of basal cerebral arteries is incompletely understood. Kety reported that the gradual decrement of cerebral blood flow and oxygen consumption resulted in a reduction of cerebral blood flow velocity.[8] Hennerici et al. suggested that elasticity alterations, increase in vasomotor tone, changes in cerebral autoregulation, dilative arteriopathy, and development of nonocclusive atherosclerosis were associated with the age dependency of cerebral blood flow velocity changes.[5] Kreja et al. explained that the decrease in flow velocity and the increase in resistivity indexes is due to stiffened, dilated and tortuous arteries.[6] Based on that

Table 3. Ordinal regression analysis of averaged mean flow velocity of MCAs in relation to regional PWVs

	Estimates (95% CI)		
	Model 1	Model 2	Model 3
hcPWV	-0.451 (-0.781; -0.121)*	-0.432 (-0.761; -0.102)*	-0.432 (-0.797; -0.067)†
cbPWV	-1.126 (-2.028; -0.224)†	-0.165 (-0.583; 0.253)	-0.776 (-1.770; 0.219)
RhbPWV	-0.737 (-1.344; -0.131)†	-0.601 (-1.221; 0.018)	-0.441 (-1.094; 0.212)
RbaPWV	-0.170 (-0.341; 0.002)	-0.137 (-0.318; 0.044)	-0.099 (-0.286; 0.088)
LbaPWV	-0.186 (-0.363; -0.008)†	-0.147 (-0.331; 0.037)	-0.032 (-0.084; 0.020)
hfPWV	-0.363 (-0.673; -0.053)†	-0.300 (-0.613; 0.013)	-0.260 (-0.598; 0.078)
RfaPWV	-0.190 (-0.437; 0.057)	-0.125 (-0.409; 0.160)	-0.100 (-0.374; 0.174)
LfaPWV	-0.241 (-0.512; 0.030)	-0.158 (-0.838; 2.158)	-0.109 (-0.4112; 0.195)

*p<0.01, †p<0.05. Values were estimates and its 95% confidence interval (95% CI) from ordinal regression analyses (logit link function). Quartiles of averaged mean flow velocity of MCAs were used as dependant variables. Model1 is unadjusted, model 2 is adjusted for previous history of stroke and homocysteine and model 3 is adjusted for previous history of stroke, homocysteine and age.

report, they suggested that the more elastic vessels damp the pulse and pressure wave more effectively than do stiff older vessels. Thus, aging increases the pulse wave velocity.[6] We examined the correlation between cerebral blood flow velocity and arterial stiffness measured by PWV. Our results were somewhat different from the aforementioned results in that arterial stiffness, but not age, was associated with decrements in mean flow velocity. The significant association between hcPWV and quartiles of amFV persisted after adjusting for age. The results imply that arterial stiffness is an important determinant of cerebral blood flow velocity. The results support the suggestion by Kreja et al. that arterial stiffness could cause decreases in cerebral blood flow velocity.

Increased aortic stiffness has been associated with atherosclerosis in the aorta and other sites such as the coronary artery.[20, 21] In recent years, regional PWV has been increasingly measured as an alternative to PWV.[16, 22] Kimoto et al. reported that increase of hfPWV or hcPWV were associated with diabetes whereas the impact of diabetes on faPWV and hbPWV were negligible.[16] Tillin et al. reported that cfPWV is a better indicator of atherosclerosis than cbPWV or faPWV. Our data showed regional differences in association with flow velocity MCA. Among the regional PWVs, only hcPWV showed a significant association with flow velocity of MCA while RhbPWV and hfPWV showed only suggestions of associations. Other regional PWVs were less associated with flow velocity of MCA. These results imply that arterial stiffness measured in the proximal aorta or the carotid artery was more directly associated with flow velocity of MCA. Anatomical proximity is one possible explanation for the differential associations. The unique hemodynamic property of cerebral blood flow can also affect the differential association.[23] The brain is exposed to highly pulsatile pressure due to upstream vasodilation. Pulsations of pressure and flow thereby extend directly into the brain. Therefore, the blood flow velocity of MCA could be more readily affected by proximal aortic or carotid flow than by the peripheral arteries. Aging is another possible mediator of the connection between regional PWVs and cerebral blood flow velocity. As described, cerebral blood flow velocity decreases with advancing age.[5-7] Arterial stiffness is also differentially affected by aging.[20] Advancing age increases aortic PWV to a larger degree than PWV of upper and lower extremities.[20]

The retrospective and cross-sectional nature of this study makes it necessary for further investigations to confirm the findings. The small number of subjects limits the generalization of the results. Because we used only the mean velocity MCA to represent cerebral blood flow, blood flow velocities of other basal cerebral arteries were not considered. Because the measurement of the TCD and PWV was performed after the index strokes, the parameters could be influenced by the strokes. However, we tried to exclude potential confounding factors such as stenosis of anterior circulation on MRA, infarction in MCA territory, and abnormal wave form on TCD examination. Furthermore, we considered other clinical and laboratory factors that could cause a change of cerebral flow velocity such as blood pressure, heart rate, hematocrit, cholesterol status and vascular risk factors. To minimize the impact of stroke on measured parameters, the measurement of PWV and TCD were performed after 7 days from index stroke.

In conclusion, arterial stiffness was inversely correlation with cerebral flow velocity of MCA, even after adjustment for age. The association between arterial stiffness and cerebral blood flow velocity showed regional differences. Further investigation is needed to better understand the pathophysiological basis and the rheological properties of intracranial arterial stiffness.

REFERENCES

1. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769-774.
2. Zuromskis T, Wetterholm R, Lindqvist JF, Svedlund S, Sixt C, Jatuzis D, et al.. Prevalence of micro-emboli in symptomatic high grade carotid artery disease: A transcranial Doppler study. Eur J Vasc Endovasc Surg 2008;35:534-540.
3. Knecht S, Deppe M, Ebner A, Henningsen H, Huber T, Jokeit H, et al. Noninvasive determination of language lateralization by functional transcranial Doppler sonography: A comparison with the Wada test. Stroke 1998;29:82-86.
4. Navarro JC, Lao AY, Sharma VK, Tsivgoulis G, Alexandrov AV. The accuracy of transcranial Doppler in the diagnosis of middle cerebral artery stenosis. Cerebrovasc Dis 2007;23:325-330.
5. Hennerici M, Rautenberg W, Sitzer G, Schwartz A. Transcranial Doppler ultrasound for the assessment of intracranial arterial flow velocity--part 1. Examination technique and normal values. Surg Neurol 1987;27:439-448.
6. Krejza J, Mariak Z, Walecki J, Szydlik P, Lewko J, Ustymowicz A. Transcranial color Doppler sonography of basal cerebral arteries in 182 healthy subjects: Age and sex variability and normal reference values for blood flow parameters. AJR 1999;172:213-218.
7. Grolimund P, Seiler RW. Age dependence of the flow velocity in the basal cerebral arteries--a transcranial Doppler ultrasound study. Ultrasound Med Biol 1988;14:191-198.

8. Kety SS. Human cerebral blood flow and oxygen consumption as related to aging. Res Publ Assoc Res Nerv Ment Dis 1956;35: 31-45.
9. Ringelstein EB, Kahlscheuer B, Niggemeyer E, Otis SM. Transcranial Doppler sonography: Anatomical landmarks and normal velocity values. Ultrasound Med Biol 1990;16:745-761.
10. Vriens EM, Kraaier V, Musbach M, Wieneke GH, van Huffelen AC. Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: Reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. Ultrasound Med Biol 1989;15:1-8.
11. Tsuchiya T, Yasaka M, Yamaguchi T, Kimura K, Omae T. Imaging of the basal cerebral arteries and measurement of blood velocity in adults by using transcranial real-time color flow Doppler sonography. AJNR 1991;12:497-502.
12. Lakatta EG. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part III: Cellular and molecular clues to heart and arterial aging. Circulation 2003;107: 490-497.
13. Laurent S, Boutouyrie P. Recent advances in arterial stiffness and wave reflection in human hypertension. Hypertension 2007;49: 1202-1206.
14. McEniery CM, Wilkinson IB, Avolio AP. Age, hypertension and arterial function. Clin Exp Pharmacol Physiol 2007;34:665-671.
15. Hirata K, Kawakami M, O'Rourke MF. Pulse wave analysis and pulse wave velocity: A review of blood pressure interpretation 100 years after Korotkov. Circ J 2006;70:1231-1239.
16. Kimoto E, Shoji T, Shinohara K, Inaba M, Okuno Y, Miki T,et al. Preferential stiffening of central over peripheral arteries in type 2 diabetes. Diabetes 2003;52:448-452.
17. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke treatment. Stroke 1993;24: 35-41.
18. Munakata M, Ito N, Nunokawa T, Yoshinaga K. Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. Am J Hypertens 2003;16:653-657.
19. Alexandrov A. Cerebrovascular ultrasound in stroke prevention and treatment. 1st ed. New York: Blackwell Publishing, 2004.
20. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation 1989;80:78-86.
21. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, et al. Association between arterial stiffness and atherosclerosis: The Rotterdam study. Stroke 2001;32:454-460.
22. Tillin T, Chambers J, Malik I, Coady E, Byrd S, Mayet J,et al. Measurement of pulse wave velocity: Site matters. J Hypertens 2007;25:383-389.
23. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic of therapy. Hypertension 2005;46:200-204.