**Increased Basilar Artery Pulsatility Index Is Associated with Neurological Deterioration after Stroke**

**Basilar Artery Pulsatility Index and Stroke Progression**

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**Abstract**

**Background and Purpose:** Higher pulsatility of middle cerebral artery (MCA) is known to be associated with stroke progression. We investigated whether basilar artery pulsatility index (BA PI) can predict neurological deterioration after acute cerebral infarction.

**Methods:** A total of 708 consecutive patients with acute ischemic stroke patients who had been through transcranial Doppler (TCD) were included. The neurological deterioration was defined as two or more increase of National Institutes of Health Stroke Scale after admission. The patients were categorized into quartiles according to the BA PI. Multivariate logistic regression analysis was performed to examine whether the BA PI is independently associated with neurological deterioration.

**Results:** The mean age, hemoglobin A1c, homocysteine, cerebral atherosclerosis burden, and the proportion of the patients with female sex, hypertension, diabetes mellitus, old lacunes and neurological deterioration also increased with the BA PI. Multivariate logistic regression analysis including age, sex, vascular risk factors, homocysteine and cerebral atherosclerosis burden showed that the highest BA PI quartile group was independently associated with neurological deterioration (odds ratio, 2.06; confidence interval, 1.04 - 4.09; *p*, 0.039). The BA PI was well correlated with the right MCA PI (r, 0.757; p<0.001 by Pearson correlation analysis), although MCA could not be measured by transcranial Doppler in 234 patients (33.1%) due to poor temporal window.

**Conclusions:** The BA PI could predict neurological deterioration among acute stroke patients, which is not influenced by temporal window.

**Keywords*:*** Pulsatility index, Basilar artery, Neurological deterioration, Transcranial Doppler Sonography, TCD, PI

**Introduction**

Acute ischemic stroke patients sometimes suffer from neurological deterioration (ND), which occurs in 10% - 58% after acute stroke and results in poor prognosis and mortality.1-5 Several clinical factors are known to be associated with ND, such as old age, diabetes mellitus (DM), hypertension (HTN), smoking habit, coronary heart disease, low density on initial computed tomography (CT), change of middle cerebral artery (MCA) flow velocity, increased stroke severity, impaired cerebral hemodynamic reserve, blood glucose level, proinflammatory cytokine level, blood pressure (BP).5-10 In mechanistic perspective, failed intracranial collateral blood flow or elevated intracranial pressure may lead to decreased cerebral perfusion, thereby causing ND.2 It has been reported that elevated MCA pulsatility index (MCA PI) has association with deterioration of lacunar cerebral infarction.11

Since the stiffness of large arteries is linked with silent cerebral infarction, cerebral microbleeds, white matter hyperintensities and lacunar cerebral infarction, it is important to measure cerebral arterial stiffness to predict ND after stroke.12-18 The pulsatility index (PI) of intracranial cerebral arteries, measured by transcranial Doppler ultrasonography (TCD), was reported to reflect the resistance of the downstream arteries and the compliance of large cerebral arteries.11, 19-21 Recent study demonstrated that elevated MH, hemispheric small vessel disease, and that of the vertebral artery (VA) correlates with increment of pontine hyperintensities.11 However, the MCA PI is often unobtainable in considerable number of elderly patients due to poor acoustical temporal bone window. Basilar artery pulsatility index(BA PI) measured by transforaminal window can be an excellent alternative in this situation. Therefore we investigated whether BA PI can predict ND after acute stroke.

**Methods**

**Patients and evaluation**

From January 2014 to December 2015, the consecutive patients with acute cerebral infarction or transient ischemic attack who had been through TCD study were retrospectively reviewed. This study was reviewed and approved by the institutional review board of Chung-Ang University hospital (C2013110), and was conducted in accordance with the 1964 Helsinski declaration and its later amendments or comparable ethical standards. Their medical history, clinical manifestations, and vascular risk factors were reviewed from a stroke registry at the Chung-Ang University Hospital. The ND was defined as two or more increase on National Institutes of Health Stroke Scale (NIHSS) as previous studies.22, 23

Each patient was examined with brain magnetic resonance imaging (MRI) and CT angiography, and acute cerebral infarction was determined by hyperintensity on diffusion-weighted image matched with hypointensity on apparent diffusion coefficients map of brain MRI. We also gathered information about microvascular and macrovascular arteriopathy.

Old lacune was determined by round or ovoid shaped hypointense lesion which is encompassed by hyperintense rim with sized less than 1.5cm in one of the perforating artery territories. Cerebral microbleed was defined as round or ovoid shaped hypointense lesion on susceptibility-weighted image excluding traumatic hemorrhage or calcification lesion.

Cerebral atherosclerosis score was calculated by sum of intracranial arteries stenosis score from CT angiography. The stenosis of intracranial arteries was identified at bilateral anterior/middle/posterior cerebral arteries, basilar artery, intracranial portion of internal carotid arteries and vertebral arteries and scored as follows: 0, no stenosis; 1, stenosis less than 50%; 2, stenosis more than 50% but not occlusion; 3, occlusion, as described previously.

**Transcranial Doppler sonography examination**

TCD was performed within 7 days of admission and was carried out with a 2MHz probe using Companion III (Nicolet EME, UK) by a medical technician. In all patients, the sonographic parameters, including peak systolic flow velocities (PSV), peak diastolic velocities (PDV) and mean flow velocities were measured with probe in the bilateral middle cerebral arteries, BA and so on. All sonographic measurements of the BA were performed through transforaminal window with insonation depth of 80 to 100 mm in lying position. The PI was measured according to the Gosling formula [{peak systolic velocity (PSV) – peak diastolic velocity (PDV)}/{(PSV+2PDV)/3}] as previous studies.20, 24 All results were interpreted by certified neurologist.

**Statistical analysis**

All statistical analyses were performed with SPSS (version 21.0; IBM Corporation, Armonk, NY, USA) and R (version 3.5.1, July 2, 2018). First, the patients were divided into 4 groups according to the quartile of the BA PI. The differences between groups were assessed using the Fisher’s exact or Pearson’s χ2 tests for categorical variables, Mann-Whitney *U*-tests or Kruskal-Wallis tests for comparing the NIHSS and cerebral atherosclerosis score (CAS) and Student’s *t*-tests or one-way analysis of variance tests for continuous variables. Data are expressed as means ± standard deviation for continuous variables and number (%) for categorical variables. The correlation of the BA PI and the MCA PI was analyzed by Pearson correlation analysis for ascertaining whether the BA PI was changed correspondingly by various conditions which affected the MCA PI or not. Second, the patients were grouped into two groups: patients with ND and those without ND. Bivariate analyses were performed to derive factors associated with ND. The differences between groups were assessed using the Pearson’s χ2 tests for categorical variables, Mann-Whitney *U*-tests for comparing the NIHSS and CAS and Student’s *t*-tests for continuous variables. Multivariable logistic regression analyses using a forward stepwise method were performed to find independent factor related to ND with adjustments for confounding factors derived from bivariate analysis. The results were presented as adjusted odds ratios (OR) with 95% confidence intervals (95% CI). The value of *p* less than 0.05 was regarded as statistically significant.

**Results**

A total of 779 consecutive patients with acute ischemic stroke or transient ischemic attack (TIA) were registered to the Chung-Ang university hospital stroke registry during the study period. Among them, 708 patients (mean age, 68.2 ± 13.0 years; 347 female patients) who had been through TCD were finally included. The mean BA PI was 0.96 ± 0.23 and the patients were categorized as four subgroups according to their BA PI values with the following cut-off points: 0.80, 0.94 and 1.10 (Table 1). As the BA PI increase, mean age, NIHSS at admission, serum homocysteine level, HbA1c level and the proportion of female, hypertension, diabetes mellitus and the presence of old lacune increased. (Table 1). The proportion of patients who experienced ND also higher in higher BA PI group. The BA PI was well correlated with right MCA PI (r=0.757, p<0.001, Fig. 1), but not with left MCA PI (r=0.019, p=0.68).

ND occurred in 92 patients (13.0%). The comparison between the patients with ND and those without it revealed that ND was associated with older age, higher systolic blood pressure (SBP), higher NIHSS at admission, current smoking state, the presence of atrial fibrillation, and higher CAS (Table 2). The BA PI was higher in patients with ND (1.02 ± 0.26) than neurologically stable patients (0.95 ± 0.22). Bivariable analyses showed that old age, female, high SBP, CAS, current smoking state, atrial fibrillation, higher NIHSS at admission and the higher BA PI were associated with ND (Table 2). Multivariable logistic regression model including age, female sex, hypertension, diabetes mellitus, the presence of old lacune from brain MRI, and CAS revealed that the highest BA PI quartile was independently associated with ND (OR, 2.06; 95% CI, 1.04 - 4.09; *p*=0.039, Table 3).

**Discussion**

In this study including 708 acute stroke patients who had been through TCD examination, ND occurred in 13.0% patients which is similar to previous results (10% - 58%).1, 4, 5, and the proportion of deteriorated patients was highest among the highest BA PI quartile group. Multivariable logistic regression analysis adjusting clinical and imaging variables disclosed that BA PI is an independent factor associated with ND. Although right MCA PI was well correlated with BA PI, the detection of MCA PI was not possible among 252 (33.05%) patients due to poor temporal windows.

Pulsatile flow, accompanied with large arteries and transduced to distal cerebral arteries, can result in cerebrovascular endothelial failure, blood brain barrier disruption, cerebral autoregulation abnormality, perfusion decrease during diastolic phase and increase of the endothelial shear stress.11, 13, 17, 18, 28 Several studies have demonstrated that elevated PI is linked with inverse nonlinear relationship of cerebral perfusion pressure and linear relationship of intracranial pressure, increased cerebral vascular resistance and cerebral small vessel disease burden.22, 30, 31 Our study also showed that the tendency of cerebral microbleeds, suggesting small vessel disease burden which was due to disrupted blood brain barrier and increased cerebral arterial stiffness, increased in accordance with increase of the BA PI.

It have been reported that an elevation of the MCA PI has association with deterioration of lacunar cerebral infarction.11 Usually, the appropriate results from MCA cannot be obtained due to poor acoustical temporal windows in approximately 5% - 20% of patients as previous studies.25 In contrary to the MCA PI, BA PI can be measured irrespective of temporal bone windows. Previous study reported that the BA PI increased earlier than the MCA PI in patients with microangiopathy accompanied with DM because vessels in the posterior cerebral circulation have fewer adrenergic neurons which regulates vascular tone in response to stimulations than those in anterior.21

Several limitations exist in this study. First, the cross-sectional design of our analyses limits our ability to determine a causal relationship between BA PI and ND. Second, BA PI was only measured at admission, which yielded no data regarding the temporal change during acute cerebral infarction. Third, attempting to predict ND with only TCD may be incorrect since the hemodynamic change after a stroke is a dynamic process. Fourth, this study was performed in one hospital with Korean population, which might not be generalized to other ethnic populations. The strength of the study is that we constructed a multivariable logistic model including clinical, laboratory and imaging variables and confirmed independent association between the BA PI and ND.

This study illustrated clinical and laboratory characteristics of stroke patients according to BA PI quartile. The highest BA PI was independently associated with ND after acute stroke, suggesting increased cerebral arterial stiffness is linked to further neuronal injury after cerebral infarction. Further studies are warranted to develop therapeutic strategy to prevent secondary neuronal injury by modulating cerebral arterial stiffness.

**Conflict of interest**

The authors have no conflict of interest to disclose.

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**Table 1. Clinical characteristics of the study population according to basilar artery pulsatility index**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Group 1  N=178 | Group 2  N=192 | Group 3  N=219 | Group 4  N=119 | P value |
| Age (years) | 59.7 ± 14.0 | 66.5 ± 12.0 | 72.0 ± 10.4 | 76.3 ± 8.7 | <.001‡ |
| Sex, female, n (%) | 73 (41.0) | 90 (46.9) | 119 (54.3) | 65 (54.6) | .03**\*** |
| Vascular risk factors |  |  |  |  |  |
| Hypertension, n (%) | 96 (53.9) | 121 (63.0) | 147 (67.1) | 96 (80.7) | <.001‡ |
| Diabetes mellitus, n (%) | 39 (21.9) | 64 (33.3) | 87 (39.7) | 49 (41.2) | <.001‡ |
| Smoking, n (%) | 53 (29.8) | 50 (26.0) | 62 (28.3) | 28 (23.5) | .64 |
| Atrial fibrillation, n (%) | 29 (16.3) | 40 (20.8) | 42 (19.2) | 31 (26.1) | .22 |
| Previous stroke, n (%) | 16 (9.0%) | 22 (11.5%) | 25 (11.4%) | 18 (15.1%) | .45 |
| SBP (mm Hg) | 145 ± 25.8 | 145 ± 26.6 | 150 ± 28.1 | 149 ± 26.9 | .07 |
| Laboratory variables |  |  |  |  |  |
| Hematocrit (%) | 41.0 ± 6.33 | 40.8 ± 5.64 | 39.6 ± 5.52 | 40.0 ± 5.48 | .07 |
| Leukocytes (109/L) | 7.80 ± 2.83 | 8.62 ± 6.46 | 8.41 ± 3.24 | 8.04 ± 3.67 | .27 |
| Fasting blood glucose (mmol/L) | 3.40 ± 1.51 | 3.70 ± 1.45 | 3.70 ± 1.57 | 3.86 ± 1.67 | .059 |
| HbA1c (%) | 5.99 ± 1.35 | 6.07 ± 1.32 | 6.37 ± 1.43 | 6.31 ± 1.34 | .024**\*** |
| Total cholesterol (mmol/L) | 4.82 ± 1.26 | 4.66 ± 1.31 | 4.74 ± 1.25 | 4.66 ± 1.30 | .68 |
| LDL cholesterol (mmol/L) | 2.80 ± 0.89 | 2.77 ± 0.95 | 2.80 ± 0.89 | 2.75 ± 0.90 | .94 |
| hsCRP (mmol/L) | 0.16 ± 0.56 | 0.19 ± 0.56 | 0.21 ± 0.63 | 0.37 ± 1.05 | .07 |
| Homocysteine (μmol/L) | 14.9 ± 7.53 | 14.6 ± 6.28 | 15.2 ± 6.20 | 16.8 ± 6.89 | .045**\*** |
| Basilar artery PI | 0.70 ± 0.08 | 0.87 ± 0.04 | 1.04 ± 0.05 | 1.32 ± 0.18 | <.001‡ |
| Cerebral microbleeds, n (%) | 70 (39.3) | 86 (44.8) | 101 (46.1) | 55 (46.2) | .52 |
| Old lacune, n (%) | 104 (58.4) | 121 (63.0) | 162 (74.0) | 90 (75.6) | .001† |
| CAS, median(IQR) | 2 (0 - 5) | 3 (0 - 6) | 4 (1 - 7) | 4 (2 - 6) | .007† |
| Neurological progression, n (%) | 19 (10) | 20 (10) | 28 (10) | 25 (20) | .03**\*** |

All numerical values are expressed as means ± SD.

MI, Myocardial infarction; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HbA1c, Hemoglobin A1c; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; hsCRP, high sensitivity C-Reactive Protein; PSV, Peak Systolic Velocity; DV, Diastolic Velocity; PI, Pulsatility index; Rt MCA, Right Middle Cerebral Artery; Lt MCA, Left Middle Cerebral Artery.; CAS, Cerebral Atherosclerosis Score.

Differences between groups using the analysis of chi-square test and the one way analysis of variance test, Kruskal-Wallis tests for comparing the cerebral atherosclerosis score (CAS).

**\***P<0.05, † P<.01, ‡P<.001

**Table 2. The comparison of the patients with and without neurological deterioration\***

|  |  |  |  |
| --- | --- | --- | --- |
|  | Neurological deterioration (-)  (n= 616) | Neurological deterioration (+)  (n= 92) | P value |
| Age (years) | 67.7 ± 13.2 | 71.2 ± 11.2 | .016 ‡ |
| Sex, female, n (%) | 293 (47.6) | 54 (58.7) | .06† |
| Hypertension, n (%) | 396 (64.3) | 64 (69.6) | .383 |
| Diabetes mellitus, n (%) | 206 (33.4) | 33 (35.9) | .733 |
| Smoking, n (%) | 177 (28.7) | 16 (17.4) | .031 ‡ |
| Atrial fibrillation, n (%) | 113 (18.3) | 29 (31.5) | .005 ‡ |
| Previous stroke, n (%) | 68 (11.0) | 13 (14.1) | .488 |
| SBP (mm Hg) | 146.3 ± 27.1 | 153.2 ± 25.7 | .023 ‡ |
| Hematocrit (%) | 40.4 (5.9) | 40.4 (5.0) | 0.954 |
| Leukocytes (109/L) | 8.21 ± 4.43 | 8.51 ± 3.75 | .485 |
| Fasting blood glucose (mmol/L) | 3.65 ± 1.59 | 3.70 ± 1.19 | .704 |
| HbA1c (%) | 6.20 ± 1.42 | 6.07 ± 1.04 | .278 |
| Total cholesterol (mmol/L) | 4.74 ± 1.30 | 4.67 ± 1.07 | .565 |
| LDL cholesterol (mmol/L) | 2.78 ± 0.92 | 2.77 ± 0.84 | .898 |
| hsCRP (mmol/L) | 0.22 ± 0.66 | 0.25 ± 0.84 | .725 |
| Homocysteine (μmol/L) | 15.40 ± 6.92 | 14.16 ± 5.09 | .043 ‡ |
| Basilar artery PI | 0.95 ± 0.22 | 1.02 ± 0.26 | .01 ‡ |
| Rt MCA PI (n=474) | 0.92 ± 0.21  (n=422) | 0.97 ± 0.27  (n=52) | 0.208 |
| Cerebral microbleeds, n (%) | 267 (43.3) | 45 (48.9) | .37 |
| Old lacune, n (%) | 416 (67.5) | 61 (66.3) | .91 |
| CAS, median(IQR) | 3 (0 - 6) | 5 (2 - 8) | <.001 § |
| NIHSS score at admission, median (IQR) | 2 (0 - 5) | 6 (3 - 9) | <.001§ |

All numerical values are expressed as means ± SD.

MI, Myocardial infarction; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HbA1c, Hemoglobin A1c; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; hsCRP, high sensitivity C-Reactive Protein; PSV, Peak Systolic Velocity; DV, Diastolic Velocity; PI, Pulsatility index; Rt MCA, Right Middle Cerebral Artery; Lt MCA, Left Middle Cerebral Artery; CAS, Cerebral Atherosclerosis Score; NIHSS, National Institutes of Health Stroke Scale

Differences between groups using the analysis of chi-square test and the one way analysis of variance test, Mann-Whitney *U*-tests for comparing the NIHSS and the cerebral atherosclerosis score (CAS).

\*Univariably significant with P value ≤0.10 and considered in the multivariable model.

†P<0.1, ‡P<.05, §P<.001

**Table 3. Logistic regression analysis for determinants of early neurological deterioration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Bivariable analyses** | | **Multivariable analyses** | |
| **OR (95% CI)** | ***P*** | **Adjusted OR (95% CI)** | ***P*** |
| **BA PI** | 3.59 (1.46 - 8.79) | .005† | 2.29 (0.85 - 6.15) | .101 |
| **BA PI, quartiles** | | | | |
| **Q1 (0.42 – 0.80)** | 1 |  | 1 |  |
| **Q2 (0.80 – 0.94)** | 0.97 (0.50 - 1.89) | .936 | 0.97 (0.49 - 1.92) | .929 |
| **Q3 (0.94 – 1.10)** | 1.23 (0.66 - 2.28) | .518 | 1.02 (0.53 - 1.94) | .963 |
| **Q4 (1.10 – 2.50)** | 2.23 (1.16 - 4.26) | .016**\*** | 2.06 (1.04 - 4.09) | .039**\*** |

OR, Odds Ratio; CI, Confidence Interval; *P*, *P* value; BA PI, Basilar Artery Pulsatility index measured by Transcranial Doppler sonography

Group was divided into quartiles based on BA PI

Adjusted by Age, Sex, National Institutes of Health Stroke Scale at admission, Systolic blood pressure, Serum homocysteine level, Cerebral atherosclerosis score

**\***P<0.05, †P<.01

**Figure legend**

Figure 1. Correlation analysis between basilar artery and right middle cerebral artery pulsatility indices

The pulsatility index of basilar artery was well correlated with those value of right middle cerebral artery (n=456, r=0.757, p<0.001).