Increased pulsatility index of the basilar artery is a risk factor for neurological deterioration after stroke: a case control study

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

Methods: A total of 708 consecutive patients with acute ischemic stroke who had undergone transcranial Doppler (TCD) ultrasonography were included. ND was defined as an increase in the National Institutes of Health Stroke Scale scores by two or more points after admission. The patients were categorized into quartiles according to BA PI. Multivariable logistic regression analysis was performed to examine whether BA PI is independently associated with ND.

Results: BA PI was well correlated with the right ($n=474, r^2=0.573, P<0.001$) by Pearson correlation analysis although MCA PI could not be measured from right MCA ($n=234, 33.05\%$) and left MCA ($n=252, 35.59\%$) by TCD owing to insufficient temporal bone window. Multivariable logistic regression analysis including age, sex, cerebral atherosclerosis burden, National Institutes of Health Stroke Scale at admission, and the proportion of patients with current smoking status, hypertension, diabetes mellitus, atrial fibrillation revealed that the higher BA PI (odds ratio, 3.28; confidence interval, 1.07–10.17; $P=0.038$) was independently associated with ND.

Conclusions: BA PI, which would be identified regardless of temporal window, could predict ND among acute stroke patients.

Keywords: Basilar artery, Stroke, Transcranial Doppler sonography, Neurological deterioration

Background
Neurological deterioration (ND) occurs in 10 to 58% adult stroke patients and results in poor prognosis and mortality [1–5]. Several factors are known to be associated with ND, such as old age, diabetes mellitus (DM), hypertension (HTN), smoking habit, coronary heart disease, the size of low-density lesions as observed on initial computed tomography (CT), change in the flow velocity of middle cerebral artery (MCA), impaired cerebral hemodynamic reserve, blood glucose level, proinflammatory cytokine level, and blood pressure (BP) [5–10]. From a mechanistic perspective, failed intracranial collateral blood flow or elevated intracranial pressure may lead to decreased cerebral perfusion, thereby causing ND [2]. Because the stiffness of large arteries is linked with various cerebral small vessel disease phenotypes including cerebral microbleeds, white matter hyperintensities, and lacunar cerebral infarction, it may be plausible that increased cerebral arterial stiffness is associated...
with ND after stroke [11–17]. The pulsatility index (PI) of intracranial cerebral arteries, as measured by tran-
scranial Doppler (TCD) ultrasonography, is known to re-
fect the resistance of downstream arteries and com-
pliance of large cerebral arteries [17–20]. Recent study re-
ported that elevated MCA PI is independently associ-
ated with ND among lacunar stroke patients [17]. How-
ever, in 18% of patients with acute ischemic stroke or
 transient ischemic attack (TIA), MCA PI is unobtain-
due to poor acoustical temporal bone window; It
is known that a poor acoustical temporal bone window
is more common in not only elderly patients, but also
female patients and those with thick skull [21].

The basilar artery (BA) PI can be measured through
the transforaminal approach, which the transducer
is placed just below the occipital protuberance and
directed towards the nasal bridge. However, the clin-
cal significance of BA PI among stroke patients has not
been appreciated yet. We investigated whether BA PI
can predict ND after acute stroke.

Methods
Patients and evaluation
From January 2014 to December 2015, consecutive
patients with acute cerebral infarction and TIA who
had undergone TCD ultrasonography were retrospec-
tively reviewed. Their medical history, clinical manifes-
tations, and vascular risk factors were reviewed from a
stroke registry at the Chung-Ang University Hospital.
ND was defined as increase of two or more National
Institutes of Health Stroke Scale (NIHSS) score [22].
The NIHSS score was evaluated by a neurologist who
was unaware of TCD results regularly.

Each stroke patient was examined with brain mag-
netic resonance imaging (MRI) and CT angiography
(CTA). Cerebral small vessel disease burden was gath-
ered from MRI and cerebral atherosclerosis from brain
CTA. Old lacunes were determined by round or ovoid
hypointense lesions which were encompassed by an
hyperintense rim measuring < 1.5 cm in size at one of
the perforating artery territories. Cerebral microbleed
was defined as round or ovoid hypointense lesions
appearing on susceptibility-weighted images, excluding
traumatic hemorrhage or calcification lesions. Cerebral
atherosclerosis score (CAS) was calculated by the sum
of the degrees of stenosis of the intracranial arteries
on brain CTA. Stenosis of intracranial arteries was iden-
tified at bilateral anterior/middle/posterior cerebral
arteries, BA, intracranial portion of internal carotid
arteries, and vertebral arteries and scored as follows: 0,
no stenosis; 1, < 50% stenosis; 2, > 50% stenosis but no
occlusion; and 3, occlusion.

Transcranial Doppler ultrasonographic examination
Within 7 days of admission, TCD ultrasonography was
performed by an experienced medical technician with
a 2-MHz probe and Companion III (Nicolet EME, Bris-
tol, UK). The sonographic parameters including peak
systolic flow velocities (PSVs), peak diastolic veloc-
ities (PDVs), and mean flow velocities, were measured
from the bilateral MCAs, BA, and other sites. All
sonographic measurements of BA were performed via
a transforaminal window with an insonation depth
of 80–100 mm in the lying position. PI was calcu-
lated according to the Gosling formula \( \frac{(PSV – PDV)}{\frac{(PSV + 2PDV)}{3}} \) as described in previous stud-
ies [19, 23]. All the results from TCD ultrasonography
were interpreted by certified neurologists.

Statistical analysis
All statistical analyses were performed using IBM
SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) and R
ver. 3.5.1 (The R Foundation for Statistical Comput-
ing, Vienna, Austria; https://www.r-project.org/; July 2,
2018). First, the patients were divided into four groups
according to BA PI quartiles. The differences among
the groups for categorical variables were assessed using
the Fisher’s exact or Pearson chi-tests, the NIHSS and
CAS was compared using the Mann-Whitney U-tests
or Kruskal-Wallis tests, and the differences among the
groups for continuous variables were assessed using
Student t-tests or one-way analysis of variance tests.
Data are expressed as means ± standard deviation for
continuous variables and number (%) for categorical
variables. The correlation between BA PI and MCA PI
was analyzed by Pearson correlation analysis.

Second, the patients were grouped into patients with
and without ND to derive factors associated with ND.
The differences between the groups were assessed using
the Pearson chi-tests for categorical variables and the
Student t-tests for continuous variables. NIHSS and CAS
were compared using Mann-Whitney U-tests. Multivari-
able logistic regression analyses using a forward stepwise
method were performed to find independent factors
related to ND with adjustments for factors derived from
bivariate analysis. The results were presented as adjusted
odds ratios (ORs) with 95% confidence intervals (CIs). A
P-value of < 0.05 was regarded as statistically significant.
Multivariable logistic regression analysis included the fac-
tors with P-value less than 0.10 from bivariate analysis.

Results
A total of 779 consecutive patients with acute ischemic
stroke and TIA were registered in 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 undergone TCD ultrasonography were finally included. The mean BA PI was 0.96 ± 0.23, and the patients were categorized into four subgroups according to their BA PI values with the following cutoff points: 0.80, 0.94, and 1.10 (Table 1). As BA PI increases, mean age, right MCA PI, and the proportion of ND, females, HTN, DM, old lacunes, and white matter hyperintensity lesions also increased (Table 1). BA PI was well correlated with right MCA PI (n = 474, r² = 0.573, P < 0.001) but not well with left MCA PI (n = 456, r² = 0.0003, P = 0.684).

ND occurred in 92 patients (13.0%). Comparison between patients with and without ND revealed that ND was associated with older age, female, higher systolic BP (SBP), BA PI, CAS and NIHSS at admission, lower serum homocysteine level, not-current smoking state, presence of white matter hyperintensity lesions, and atrial fibrillation (Table 2). BA PI was higher in patients with ND (1.02 ± 0.26) than in neurologically stable patients (0.95 ± 0.22). Multivariable logistic regression model including age, female sex, history of HTN, DM, atrial fibrillation, current smoking status, SBP, serum homocysteine, old lacunes on brain MRI and CAS derived from brain CTA revealed that the higher BA PI (OR, 3.28; 95% CI, 1.07–10.17; P = 0.038) (Table 3) and highest BA PI quartile was independently associated with ND (OR, 2.39; 95% CI, 1.10–5.25; P = 0.028) (Table 3).

Discussion

In this study including 708 acute stroke patients who had undergone brain MRI, CTA, and TCD ultrasonographic examination, ND occurred in 92 patients (13%) and the proportion of patients with ND was the highest

Table 1 Clinical characteristics of the study population according to BA PI

| Characteristics                  | Group 1 (n = 178) a) | Group 2 (n = 192) b) | Group 3 (n = 219) c) | Group 4 (n = 119) d) | P-value |
|----------------------------------|----------------------|----------------------|----------------------|----------------------|---------|
| Age (yr)                         | 59.7 ± 14.0          | 66.5 ± 12.0          | 72.0 ± 10.4          | 76.3 ± 8.7           | <0.001*** |
| Female sex                       | 73 (41.0)            | 90 (46.9)            | 119 (54.3)           | 65 (54.6)            | 0.031*   |
| Neurological deterioration       | 19 (10.7)            | 20 (10.4)            | 28 (12.8)            | 25 (21.0)            | 0.033**  |
| Hypertension                     | 96 (53.9)            | 121 (63.0)           | 147 (67.1)           | 96 (80.7)            | <0.001*** |
| Diabetes mellitus                | 39 (21.9)            | 64 (33.3)            | 87 (39.7)            | 49 (41.2)            | 0.001**  |
| Current smoking                  | 53 (29.8)            | 50 (26.0)            | 62 (28.3)            | 28 (23.5)            | 0.644    |
| Atrial fibrillation              | 29 (16.3)            | 40 (20.8)            | 42 (19.2)            | 31 (26.1)            | 0.220    |
| Previous stroke                  | 40 (22.5)            | 37 (19.3)            | 44 (20.1)            | 31 (26.1)            | 0.497    |
| SBP (mmHg)                       | 144.8 ± 25.8         | 144.5 ± 26.6         | 150.4 ± 28.1         | 149.1 ± 26.9         | 0.074    |
| Hematocrit                       | 41.0 ± 63            | 40.8 ± 5.6           | 39.6 ± 5.5           | 400 ± 5.5            | 0.068    |
| Leukocytes (10³/L)               | 7.80 ± 2.83          | 8.62 ± 6.46          | 8.41 ± 3.24          | 8.04 ± 3.67          | 0.157    |
| Fasting blood glucose (mmol/L)   | 3.40 ± 1.51          | 3.70 ± 1.45          | 3.71 ± 1.57          | 3.87 ± 1.67          | 0.065    |
| HbA1c (%)                        | 5.99 ± 1.35          | 6.07 ± 1.32          | 6.37 ± 1.43          | 6.31 ± 1.34          | 0.027*   |
| Total cholesterol (mmol/L)       | 4.81 ± 1.26          | 4.67 ± 1.31          | 4.74 ± 1.25          | 4.67 ± 1.30          | 0.680    |
| LDL cholesterol (mmol/L)         | 2.81 ± 0.89          | 2.77 ± 0.95          | 2.79 ± 0.89          | 2.75 ± 0.90          | 0.943    |
| hsCRP (mmol/L)                   | 0.17 ± 0.57          | 0.19 ± 0.57          | 0.22 ± 0.64          | 0.37 ± 1.06          | 0.278    |
| Homocysteine (µmol/L)            | 14.94 ± 7.53         | 14.61 ± 6.28         | 15.19 ± 6.20         | 16.77 ± 6.89         | 0.051    |
| Right MCA PI (n = 474)           | 0.75 ± 0.13 (n = 138)| 0.87 ± 0.13 (n = 136)| 1.02 ± 0.16 (n = 137)| 1.23 ± 0.20 (n = 63)| <0.001***|
| Left MCA PI (n = 456)            | 1.26 ± 0.32 (n = 138)| 0.86 ± 0.11 (n = 127)| 1.03 ± 0.16 (n = 133)| 1.21 ± 0.21 (n = 58)| <0.001***|
| Cerebral microbleeds             | 70 (39.3)            | 86 (44.8)            | 101 (46.1)           | 55 (46.2)            | 0.520    |
| Old lacunes                      | 104 (58.4)           | 121 (63.0)           | 162 (74.0)           | 90 (75.6)            | 0.001**  |
| CAS                              | 2 (0–5)              | 3 (0–6)              | 4 (1–7)              | 4 (2–6)              | 0.181    |
| WMH lesion                       | 97 (54.5)            | 148 (77.1)           | 190 (86.8)           | 105 (88.2)           | <0.001***|
| NIHSS score at admission         | 2 (0–5)              | 2 (0–5)              | 2 (1–6)              | 3 (1–7)              | 0.079    |

Values are presented as means ± standard deviation, number (%), or median (interquartile range). Differences between groups were analyzed using the analysis of chi-square test and the one-way analysis of variance test. Kruskal-Wallis tests were used to compare the CAS between groups.

BA Basilar artery, PI Pulsatility index, SBP Systolic blood pressure, HbA1c Hemoglobin A1c, LDL Low-density lipoprotein, hsCRP High sensitivity C-reactive protein, MCA Right middle cerebral artery, CAS Cerebral atherosclerosis score, WMH White matter hyperintensity, NIHSS National Institutes of Health Stroke Scale

a) BA PI, 0.42–0.80; BA PI, 0.80–0.94; BA PI, 0.94–1.10; BA PI, 1.10–2.50

* P < 0.05, ** P < 0.01, *** P < 0.001
Table 2  Comparison among patients with and without neurological deterioration a)

| Variable                        | Neurological deterioration (−) (n = 616) | Neurological deterioration (+) (n = 92) | P-value |
|---------------------------------|----------------------------------------|----------------------------------------|---------|
| Age (yr)                        | 67.7 ± 13.2                            | 71.2 ± 11.2                            | 0.016*  |
| Female sex                      | 293 (47.6)                             | 54 (58.7)                              | 0.060** |
| Hypertension                    | 396 (64.3)                             | 64 (69.6)                              | 0.383   |
| Diabetes mellitus               | 206 (33.4)                             | 33 (35.9)                              | 0.733   |
| Current smoking                 | 177 (28.7)                             | 16 (17.4)                              | 0.031*  |
| Atrial fibrillation             | 113 (18.3)                             | 29 (31.5)                              | 0.005*  |
| Previous stroke                 | 129 (20.9)                             | 23 (25.0)                              | 0.454   |
| SBP (mmHg)                      | 146.3 ± 27.1                           | 153.2 ± 25.7                           | 0.023*  |
| Hematocrit                      | 40.4 ± 5.9                             | 40.4 ± 5.0                             | 0.954   |
| Leukocytes (10⁹/L)              | 8.21 ± 4.4                              | 8.51 ± 3.75                            | 0.485   |
| Fasting blood glucose (mmol/L)  | 3.65 ± 1.59                            | 3.70 ± 1.19                            | 0.704   |
| HbA1c (%)                       | 6.20 ± 1.42                            | 6.07 ± 1.04                            | 0.278   |
| Total cholesterol (mmol/L)      | 4.74 ± 1.30                            | 4.67 ± 1.07                            | 0.565   |
| LDL cholesterol (mmol/L)        | 2.78 ± 0.92                            | 2.77 ± 0.84                            | 0.898   |
| hsCRP (mmol/L)                  | 0.22 ± 0.67                            | 0.25 ± 0.85                            | 0.725   |
| Homocysteine (μmol/L)           | 15.40 ± 6.92                           | 14.16 ± 5.09                           | 0.043*  |
| Basilar artery PI               | 0.95 ± 0.22                            | 1.02 ± 0.26                            | 0.014*  |
| Right MCA PI (n = 474)          | 0.92 ± 0.21 (n = 422)                   | 0.97 ± 0.27 (n = 52)                   | 0.285   |
| Left MCA PI (n = 456)           | 1.09 ± 3.70 (n = 406)                   | 0.96 ± 0.24 (n = 50)                   | 0.170   |
| Cerebral microbleeds            | 267 (43.3)                             | 45 (48.9)                              | 0.373   |
| Old lacunes                     | 416 (67.5)                             | 61 (66.3)                              | 0.908   |
| WMH lesion                      | 461 (74.8)                             | 79 (85.9)                              | 0.029*  |
| NIHSS score at admission        | 2 (0–5)                                | 6 (3–9)                                | <0.001**|

Values are presented as means ± standard deviation, number (%), or median (interquartile range). Differences between groups were analyzed using the analysis of chi-square test and one-way analysis of variance test. Mann-Whitney U-tests were used for comparing NIHSS and CAS between groups.

SBP: Systolic blood pressure, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein, hsCRP: High sensitivity C-reactive protein, PI: Pulsatility index, MCA: Right middle cerebral artery, CAS: Cerebral atherosclerosis score, WMH: White matter hyperintensity, NIHSS: National Institutes of Health Stroke Scale

a) Univariably significant with a P-value of ≤0.10 and considered in a multivariable model

*P < 0.05, **P < 0.1, ***P < 0.01

Table 3  Logistic regression analysis for the determinants of early neurological deterioration

| Variable | Bivariable analyses | Multivariable analyses |
|----------|---------------------|------------------------|
|          | OR (95% CI)         | P-value | Adjusted OR (95% CI)a) | P-value |
| BA PI    | 3.59 (1.45–8.81)    | 0.005*  | 3.28 (1.07–10.17)      | 0.038** |
| BA PI, quartileb) |                      |          | 1                     |        |
| Q1 (0.42–0.80) | 1                   | 1        | 1.05 (0.52–2.15)       | 0.890  |
| Q2 (0.80–0.94) | 0.97 (0.50–1.89)    | 0.935    | 0.93 (0.45–1.90)       | 0.841  |
| Q3 (0.94–1.10) | 1.23 (0.66–2.28)    | 0.518    | 1.05 (0.52–2.15)       | 0.890  |
| Q4 (1.10–2.50) | 2.22 (1.16–4.26)    | 0.016**  | 2.39 (1.10–5.25)       | 0.028** |

BA PI measured by transcranial Doppler ultrasonography

OR: Odds ratio, CI: Confidence interval, BA PI: Basilar artery pulsatility index

a) Adjusted by age, sex, history of atrial fibrillation, current smoking status, National Institutes of Health Stroke Scale at admission, systolic blood pressure, serum homocysteine level, cerebral atherosclerosis score, and white matter hyperintensity lesion. b) Group was divided into quartiles based on BA PI

*P < 0.01, **P < 0.05
in the highest BA PI quartile group. Multivariable logistic regression analysis including clinical and imaging variables showed that BA PI is an independent factor associated with ND. Although right MCA PI was well correlated with BA PI, their detection was not possible owing to poor temporal windows among more than one third of the included patients. Exaggerated pulsatile cerebral blood flow can result in cerebrovascular endothelial failure, blood-brain barrier disruption, perfusion decrease during diastolic phase, and increase in endothelial shear stress [11, 13, 16, 17, 24]. Several studies have demonstrated that elevated PI is linked with an inverse nonlinear relationship of cerebral perfusion pressure and linear relationship of intracranial pressure as well as with an increased cerebral vascular resistance and cerebral small vessel disease burden [22, 25, 26]. Additionally, it has been demonstrated that the MCA PI and BA PI increase in patients with HTN [27, 28]. Our study also showed an increasing tendency of old lacunes and white matter hyperintensities according to the BA PI quartile, suggesting that small vessel disease burden is related to cerebral arterial stiffness.

Early ND with ischemia progression can occur due to decreased cerebral blood flow from parent artery or lack of collateral circulation. Previous study showed that higher pulsatility of MCA was associated with progression in lacunar infarction [29]. Since PI measured by transcranial Doppler sonography might reflect downstream arterial resistance and vascular perfusion status, elevated PI could be a possible indicator of stroke progression [29].

Elevated MCA PI is reported to be associated with deterioration of lacunar cerebral infarction [17]. Consistent with a previous report, MCA blood flow could not be detected in this study owing to poor acoustical temporal windows in more than 30% of patients [30]. Contrary to MCA PI, BA PI can be measured irrespective of temporal bone windows. Previous study showed that BA PI is well correlated with MCA PI among the lacunar stroke patients with DM [31]. Another previous study reported that BA PI increased earlier than MCA PI in patients with microangiopathy complicated with DM because vessels in the posterior cerebral circulation have fewer adrenergic neurons which regulate vascular tone in response to stimulations other than those in the anterior cerebral circulation [20].

The study has several limitations. 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, this study was performed in a single hospital in Seoul, Korea; therefore, more studies are required to generalize our findings. The strength of this study is that we constructed a multivariable logistic model including clinical, laboratory, and imaging variables of brain MRI and CTA and confirmed the independent association between BA PI and ND.

Conclusions
This study showed that high BA PI could be associated with ND in acute stroke patients. BA PI could help to predict ND among stroke patients, and proactive management strategy for at-risk stroke patients are required to prevent stroke progression.

Abbreviations
BA: Basilar artery; BP: Blood pressure; CAS: Cerebral atherosclerosis score; CI: Confidence interval; CT: Computed tomography; CTA: Computed tomography angiography; DM: Diabetes mellitus; HTN: Hypertension; MCA: Middle cerebral artery; MRI: Magnetic resonance imaging; ND: Neurological deterioration; NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio; PDV: Peak diastolic velocity; PI: Pulsatility index; PSV: Peak systolic flow velocity; SBP: Systolic blood pressure; TCD: Transcranial Doppler; TIA: Transient ischemic attack.

Supplementary Information
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Additional file 1.

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Authors’ contributions
IHY analyzed the data, wrote and revised the manuscript. JMK and KYP conceptualized and designed the study, and revised the manuscript. SHH and JR analyzed the data. All the authors have made substantial contributions so as to qualify for the authorship, and have read and approved the submission of the manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Institutional Review Board of Chung-Ang University Hospital (C2013110) and was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.
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