Neurology Asia 2023; 28(1) : 65 – 71

Relationship between pulsatility index and stroke severity in patients with unilateral pontine infarction due to small vessel occlusion

Yoon Jung Kang *MD*, Eugene Jung *MD*, Jinwoo No *MD*, Sang Min Sung *MD PhD*, Han-Jin Cho *MD PhD*

Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, Busan, South Korea

Abstract

Background: Pulsatility index (PI) is a useful hemodynamic index that is generally thought to reflect arterial stiffness and distal microvascular resistance. We hypothesized that the PI in the basilar artery is associated with stroke severity in patients with acute unilateral pontine infarction. *Methods:* We retrospectively enrolled 129 patients with acute unilateral pontine infarction due to small vessel occlusion who presented within 48 hours of symptom onset between January 2015 and December 2020. Transcranial Doppler studies were performed within 5 days of symptom onset in all patients. We analyzed the relationship between the PI measured in the basilar artery and initial stroke severity using correlation and multivariable regression analyses. *Results:* The median age of the patients was 68.0 years (IQR, 59.5–74.0) and 87 (67.4%) were male. The PI was positively correlated with the National Institutes of Health Stroke Scale (NIHSS) score ($r = 0.222$, $p = 0.011$) and ischemic lesion volume ($r = 0.187$, $p = 0.039$). Multivariable analysis confirmed that a higher PI was an independent and significant predictor of a higher admission NIHSS score (B, 2.530; 95% confidence interval, 0.195 to 4.866; $p = 0.034$). In the mediation analysis, ischemic lesion volume had a complete mediating effect on the relationship between the PI and NIHSS score at admission ($Z = 2.012$, $p = 0.043$). *Conclusions:* Increased PI in the basilar artery was associated with severe stroke in patients with acute unilateral pontine infarction.

Keywords: Ischemic stroke, transcranial Doppler, pulsatile flow, outcome

INTRODUCTION

Transcranial Doppler (TCD) is an ultrasound technique for measuring the velocity and direction of blood flow within intracranial and extracranial arteries. This simple and noninvasive technique has been widely used to obtain useful clinical information about cerebrovascular abnormalities such as cerebral artery stenosis or occlusion, vasospasm, microemboli, and cerebral vasoreactivity.[1]

The pulsatility index (PI), a TCD parameter, is a reliable indicator that reflects distal cerebrovascular resistance and has been reported to be inversely correlated with cerebral perfusion pressure.[2-5] In previous clinical studies, an increased PI in the middle cerebral artery (MCA) ipsilateral to the lesion was significantly associated with a larger ischemic lesion volume and higher frequency of early neurological deterioration in patients with acute lacunar infarction involving the MCA territory.[6,7] However, there have been few considerations regarding the relationship between PI in the basilar artery and stroke severity in patients with posterior circulation stroke.

This study aimed to investigate the impact of the PI measured in the basilar artery on initial stroke severity in patients with acute unilateral pontine infarction due to small vessel occlusion.

METHODS

Study population

We reviewed 2,712 patients with acute ischemic stroke who were admitted to the Neurology

Address correspondence to: Han-Jin Cho, MD, PhD, Department of Neurology, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan, South Korea, 49241. Tel.: +82-51-240-7317, E-mail: chohj75@pusan.ac.kr

Date of Submission: 28 September 2022; Date of Acceptance: 3 December 2022

https://doi.org/10.54029/2023ehc

Department within 48 hours of symptom onset between January 2015 and December 2020. Of these, 236 patients with unilateral isolated pontine infarction, as demonstrated by diffusion-weighted imaging (DWI), were initially included. We excluded patients who had any degree of basilar artery stenosis or occlusion (n = 19), stenosis >50% in the vertebral arteries (n = 22), high-risk potential sources of cardioembolism based on the Trial of Organization 10172 in Acute Stroke Treatment (TOAST) classification (n = 22)[8], and ischemic lesions greater than 20 mm in diameter (n = 63) to investigate the cases considered to be caused by the occlusion of a single perforating artery. We also excluded patients with a modified Rankin Scale score (mRS) ≥2 prior to the index stroke (n = 16), those who underwent acute reperfusion therapy (n = 7), and those who did not undergo a TCD study (n = 18). Ultimately, 129 patients were included. This study was approved by the hospital's institutional review board, which waived the requirement for informed consent.

Clinical parameters

We obtained data on baseline characteristics, systolic and diastolic blood pressure on admission, medication history, and vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking. Smoking status was categorized as current smoker or nonsmoker. Data on a history of ischemic stroke and ischemic heart disease were also collected.

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission. We collected the results of laboratory tests performed on admission, including hemoglobin, hematocrit, platelet count, glucose, prothrombin time, and C-reactive protein. The results for low-density lipoprotein cholesterol were obtained from blood tests conducted in the morning after admission, following an overnight fast.

TCD parameters

All patients underwent TCD studies within 5 days of symptom onset using an ultrasound device with a 2-MHz probe (PMD 150; Spencer Technologies, Seattle, WA, USA). The TCD examinations were performed by two trained technicians who were unaware of any clinical information about the studied patients. Peak systolic flow velocity (PSV) and end-diastolic flow velocity (EDV) were measured along the basilar artery through the suboccipital window at a depth of 80–100 mm. The mean flow velocity (MFV) was automatically derived as (PSV + 2EDV) / 3. The PI was calculated as (PSV – EDV) / MFV. We adopted TCD parameters measured at a depth of 90 mm.

Radiologic parameters

The ischemic lesion volume was measured using MIPAV software (version 10.0.0., http://mipav.cit.nih.gov) on the initial DWI. Two observers (Y.J.K. and S.H.J.) independently captured the regions with higher signal intensities than the surrounding normal brain tissues using a semi-computerized method, and the lesion volume was automatically calculated by multiplying the sum of the regions in each axial section by the slice thickness. The results from the two observers were averaged.

Statistical analysis

Categorical variables are presented as frequency (percentage) and continuous variables are expressed as median (interquartile range [IQR]). The study population was grouped into tertiles based on PI. To test the trends of variables across the PI tertiles, we conducted a chi-square test for trends for categorical data and correlation analysis for continuous data. Correlations between TCD parameters and admission NIHSS score and between TCD parameters and ischemic lesion volume were assessed using the Pearson correlation test. Multivariable linear regression analysis was performed to identify independent variables associated with admission NIHSS score. Individual variables with p-value <0.05 on univariable analysis were entered into the multivariable analysis, and the results are expressed as B (95% confidence interval [CI]). Mediation analysis was used to evaluate the potential mediating effect of ischemic lesion volume on the relationship between PI and admission NIHSS score. The mediating effect was assessed by Baron and Kenny's 4-step procedure[9], and statistical significance was confirmed using the Sobel test (Supplementary figure). All statistical analyses were conducted using SPSS for Windows (version 23.0; IBM Corp., Armonk, NY, USA), and p-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The median age of the 129 patients enrolled in this study was 68.0 years (IQR, 59.5–74.0), and

87 (67.4%) were male. The median time intervals from symptom onset to hospital arrival and TCD examination were 15.2 hours (IQR, 9.1–24.7) and 52.0 hours (IQR, 33.4–79.8), respectively. The median NIHSS score on admission was 2.0 (IQR, 1.0–4.0), and the median ischemic lesion volume was 0.47 cm^3 (IQR, 0.24–0.79). Among the TCD parameters, the median MFV and PI were 37.0 cm/s (IQR, 29.0–51.0) and 0.94 (IQR, 0.80–1.11), respectively.

The patients' baseline characteristics according to PI tertiles are shown in Table 1. Age (p for trend = 0.004), admission NIHSS score (p for trend = 0.033), ischemic lesion volume (p for trend = 0.010), diastolic blood pressure (p for trend = 0.008), prevalence of diabetes mellitus (p for trend = 0.010), hemoglobin level (p for trend = 0.008], and hematocrit level (p for trend = 0.017) showed significant linear trends from the lowest to the highest PI tertile.

PI and stroke severity

There was a significant correlation between the PI and admission NIHSS score (r = 0.222, p = 0.011) and between the PI and ischemic lesion volume (r = 0.187, p = 0.039; Figure 1). Other TCD parameters, such as MFV, PSV, and EDV, were not associated with admission NIHSS score or ischemic lesion volume. In the univariable linear regression analysis, older age (B, 0.050; 95% CI, 0.004 to 0.095; p = 0.032), lower hematocrit level (B, -0.099; 95% CI, -0.197 to -0.001; p = 0.047), higher C-reactive protein level (B, 0.614; 95% CI, 0.013 to 1.215, p = 0.045), and higher PI (B, 2.879; 95% CI, 0.662 to 5.096; p = 0.011) were

Table 1: Clinical factors according to tertile of pulsatility index

	Tertiles of pulsatility index			
	1st (n=41)	**2nd (n=44)**	**3rd (n=44)**	**p for trend**
Age, years	60.0 (54.0-72.0)	70.0 (61.0-74.8)	70.5 (62.3-75.8)	0.004*
Male	27 (65.9)	28 (63.6)	32 (72.7)	0.492
Admission NIHSS score	2.0 (1.0-3.0)	2.0 (1.0-4.8)	3.0 (1.3-6.0)	0.033*
Ischemic lesion volume, cm^3	0.32 (0.11-0.74)	0.47 (0.23-0.83)	0.58 (0.35-0.72)	0.010*
Systolic BP, mmHg	150.0 (132.5-160.0)	160.0 (140.0-180.0)	160.0 (150.0-180.0)	0.099
Diastolic BP, mmHg	80.0 (80.0-90.0)	100.0 (90.0-100.0)	100.0 (90.0-110.0)	0.008*
Risk factors				
Hypertension	26 (63.4)	32 (72.7)	33 (75.0)	0.247
Diabetes	11 (26.8)	21 (47.7)	26 (59.1)	0.003*
Dyslipidemia	9 (22.0)	8 (18.2)	15 (34.1)	0.188
Smoking	12 (29.3)	10 (22.7)	19 (43.2)	0.111
Prior ischemic stroke	5 (12.2)	8 (18.2)	5 (11.4)	0.896
Prior ischemic heart disease	3 (33.3)	0 (0.0)	6 (66.7)	0.236
Prior medication				
Antithrombotics	9 (28.1)	11 (34.4)	12 (37.5)	0.572
Statins	7 (17.1)	10 (22.7)	13 (29.5)	0.175
Laboratory findings				
Hemoglobin, g/dL	14.4 (13.5-15.8)	13.4 (12.5-14.7)	13.7 (11.8-14.9)	0.008*
Hematocrit, %	42.3 (38.6-44.5)	38.7 (36.7-42.3)	40.3 (34.6-43.1)	0.017*
Platelet count	213.0 (185.0-244.0)	221.0 (188.0-270.0)	216.0 (181.5-262.0)	0.742
Admission glucose, mmol/L	7.80 (5.99-10.93)	7.38 (6.11-10.71)	8.32 (5.83-12.74)	0.507
LDL cholesterol, mmol/L	3.21 (2.73-3.78)	2.86 (2.21-3.68)	2.98 (2.23-3.78)	0.641
PT INR	0.99 (0.97-1.05)	1.03 (0.97-1.07)	0.99 (0.97-1.05)	0.067
C-reactive protein, mg/dL	0.12 (0.06-0.26)	0.15 (0.07-0.45)	0.16 (0.06-0.29)	0.781

Values are number (column %) or median (interquartile range).
*p<0.05.
NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; LDL, low-density lipoprotein; PT INR, prothrombin time international normalized ratio.

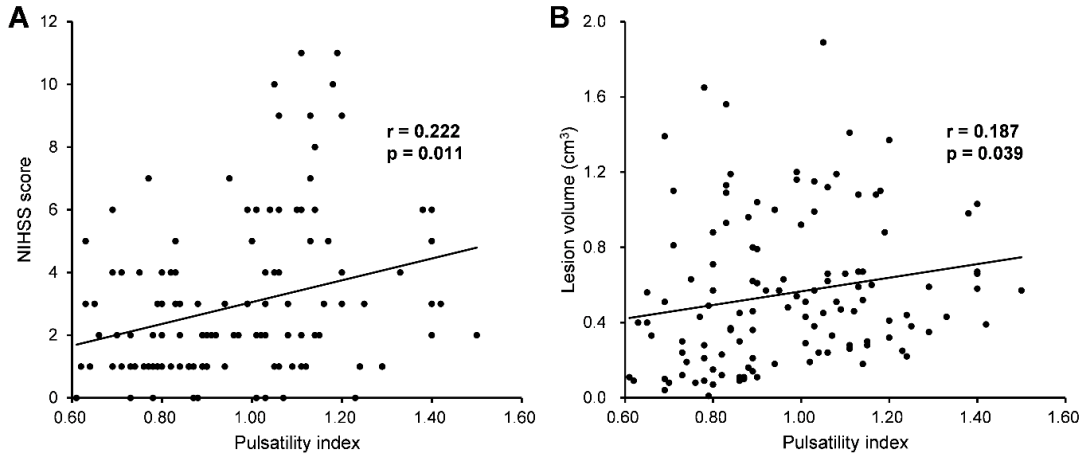

Figure 1. Correlations of pulsatility index with admission NIHSS score (A) and ischemic lesion volume (B). NIHSS, National Institutes of Health Stroke Scale.

associated with an increased admission NIHSS score (Table 2). After adjusting for significant confounders, multivariable analysis revealed that a higher PI was an independent and significant predictor of a higher admission NIHSS score (B, 2.530; 95% CI, 0.195 to 4.866; p = 0.034; Table 2). Mediation analysis showed a complete mediating effect of ischemic lesion volume on the relationship between PI and NIHSS score at admission (Z = 2.012, p = 0.043; Figure 2).

Table 2: Linear regression analysis of the factors associated with initial stroke severity

	Univariable		Multivariable	
	B (95% CI)	**p-value**	**B (95% CI)**	**p-value**
Age	0.050 (0.004 to 0.095)	0.032*	0.020 (-0.029 to 0.070)	0.420
Male	0.103 (-0.894 to 1.099)	0.839		
Onset to arrival	0.001 (-0.042 to 0.044)	0.974		
Risk factors				
Hypertension	-0.204 (-1.228 to 0.820)	0.694		
Diabetes	0.896 (-0.030 to 1.822)	0.058		
Dyslipidemia	-0.789 (-1.861 to 0.284)	0.148		
Smoking	0.078 (-0.925 to 1.081)	0.878		
Prior ischemic stroke	-0.237 (-1.585 to 1.110)	0.728		
Prior ischemic heart disease	-0.458 (-2.290 to 1.373)	0.621		
Prior medication				
Antithrombotics	-0.207 (-1.288 to 0.874)	0.706		
Statins	-0.425 (-1.528 to 0.678)	0.447		
Laboratory findings				
Hemoglobin	-0.249 (-0.504 to 0.006)	0.055		
Hematocrit	-0.099 (-0.197 to -0.001)	0.047*	-0.040 (-0.146 to 0.065)	0.452
Platelet count	0.000 (-0.008 to 0.008)	0.979		
Admission glucose	0.003 (-0.006 to 0.013)	0.479		
LDL cholesterol	-0.002 (-0.014 to 0.011)	0.806		
PT INR	1.172 (-0.191 to 2.536)	0.091		
C-reactive protein	0.614 (0.013 to 1.215)	0.045*	0.549 (-0.070 to 1.167)	0.082
TCD parameters				
Mean flow velocity	0.011 (-0.013 to 0.035)	0.352		
Systolic flow velocity	0.010 (-0.005 to 0.025)	0.195		
Diastolic flow velocity	0.000 (-0.036 to 0.035)	0.987		
Pulsatility index	2.879 (0.662 to 5.096)	0.011*	2.530 (0.195 to 4.866)	0.034*

*p<0.05.
B, standard coefficient; CI, confidence interval; LDL, low-density lipoprotein; PT INR, prothrombin time international normalized ratio.

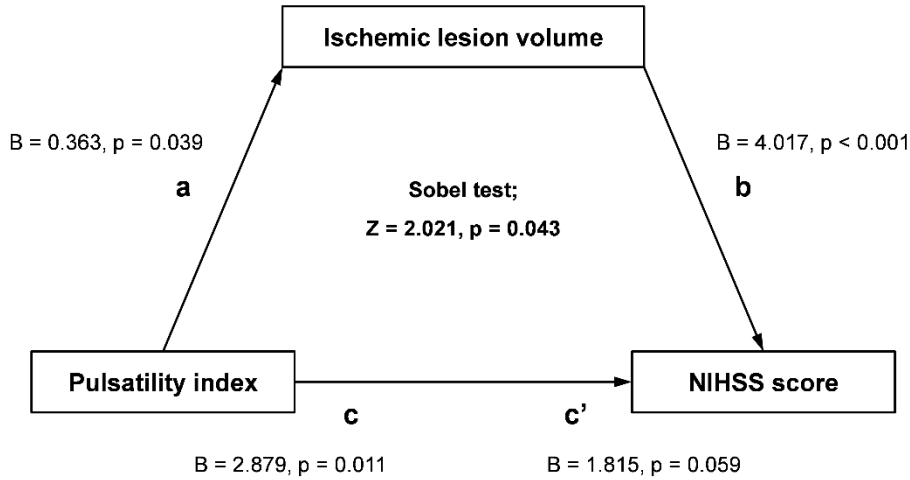

Figure 2. Analysis of the mediating effect of ischemic lesion volume on the association between pulsatility index and admission NIHSS score. NIHSS, National Institutes of Health Stroke Scale.

DISCUSSION

Our study demonstrated an independent positive relationship between PI in the basilar artery and stroke severity in patients with acute unilateral pontine infarction due to small vessel occlusion and showed that ischemic lesion volume was a significant mediator responsible for this association.

PI is strongly affected by arterial stiffness and vascular resistance.[2,3,10,11] Arterial elasticity plays an important role in diminishing the delivery of harmful pulsations to end-organ microcirculation by acting as a reservoir for a portion of the blood during systole. Therefore, the stiffness of the arterial wall can provide high pulsatile pressure to the distal microvasculature[12,13], which in turn causes increased wall stress and hypertrophy of small cerebral arteries.[14,15] These changes contribute to increased vascular resistance and the resultant reduced cerebral blood flow.[16] Although the precise underlying mechanism cannot be drawn from our study, we speculate that a high PI, indicative of increased arterial stiffness and vascular resistance, may be associated with an increased risk of severe stroke by providing insufficient cerebral blood flow toward the distal circulation, including the perforators. Indeed, in our study, ischemic lesion volume was also positively correlated with PI and was a major factor in determining stroke severity. Our findings may be in line with previous observations that an increase in PI is a marker of cerebral small-vessel pathology, including white matter hyperintensity.[10,17,18] Based on accumulating data showing that hypoperfusion plays a role in the pathogenesis of white matter hyperintensity[19,20], our results may strengthen the evidence supporting a deleterious impact of more pulsatile blood flow on the small arteries of the brain.

Several studies have shown that an increased PI on TCD was associated with poorer outcomes in acute ischemic stroke patients.[21,22] However, these studies were conducted to investigate only the correlation of PI values obtained from the MCA with stroke outcome in patients with anterior circulation stroke. Our study is unique because there have been limited data regarding how PI in the basilar artery relates to stroke severity and ischemic lesion volume in patients with acute unilateral pontine infarction. The posterior brain arteries generally have different characteristics compared to the anterior circulation arteries. First, the former has a thinner wall and less elastin than the latter.[23] A decreased amount of elastin is related to an increase in arterial stiffness because elastic fibers are mainly responsible for the reversible extensibility and resilience of arterial walls. Second, the arteries in the posterior circulation have a restricted vasodilatory function according to the change in the flow dynamics because they have fewer adrenergic neurons than the anterior circulation arteries.[24] Vasodilating capability, as assessed by CO_2 reactivity, has been reported to be lower in the posterior circulation arteries than in the anterior circulation arteries.[25] Lastly, the perforators arising from the posterior circulation arteries have a smaller diameter than those of anterior circulation arteries.[26] Given these discrepancies in the histologic and

mechanical properties, an ischemic insult in response to diminished cerebral blood flow may not be consistent between anterior and posterior circulation strokes. Nonetheless, our study suggests that the positive relationship between the PI and stroke severity, which was previously identified in anterior circulation stroke, may be equally applicable to patients with posterior circulation stroke.

There are some limitations to our study that need to be taken into account when interpreting the results. First, it was a single-center retrospective study with a relatively small sample size. Therefore, potential bias may have weakened the generalizability of the results. The small sample size may partly be due to the narrow inclusion criteria. In order to evaluate the direct influence of the pulsatility of blood flow on stroke severity, we sought to exclude potential etiologic factors that might affect stroke severity, such as atheromatous plaque of the basilar artery or embolism from proximal sources. Further, larger prospective studies are needed to confirm the findings of our study. Second, although several variables, including intracranial pressure, cardiac output, and respiration, affect the PI of the cerebral arteries, these factors were not fully considered and adjusted for in our study. Finally, the time point for TCD examination may not be sufficient to reliably demonstrate the hemodynamic status of the cerebral arteries at the time of stroke onset. However, we included only patients who presented within 48 hours of symptom onset. In particular, 82 patients (63.6%) underwent a TCD examination within 3 days of symptom onset and all patients within 5 days, which might have reduced the potential bias caused by the time lag between symptom onset and acquisition of the TCD measures.

In conclusion, our study suggests that increased arterial pulsatility in the basilar artery may be related to more severe clinical symptoms accompanied by larger ischemic lesion volumes in patients with acute unilateral pontine infarction due to small vessel occlusion. Accumulation of more clinical data is warranted to support the findings of our study.

DISCLOSURE

Financial support: This work was supported by clinical research grant from Pusan National University Hospital 2021.

Conflicts of interest: None

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