The Effect of Pulsatility Index on Infarct Volume in Acute Lacunar Stroke

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**Purpose:** Lacunar stroke, in the context of small vessel disease, is a type of cerebral infarction caused by occlusion of a penetrating artery. Pulsatility index (PI) is an easily measurable parameter in Transcranial Doppler ultrasound (TCD) study. PI reflects distal cerebral vascular resistance and has been interpreted as a surrogate marker of small vessel disease. We hypothesized that an increased PI, a marker of small vessel disease, might be associated with a larger infarct volume in acute lacunar stroke.

**Materials and Methods:** This study included 64 patients with acute lacunar stroke who underwent TCD and brain MRI. We evaluated the association between the mean PI value of bilateral middle cerebral arteries and infarct volume on diffusion-weighted MRI using univariate and multivariate linear regression.

**Results:** The mean infarct volume and PI were 482.18±406.40 mm³ and 0.86±0.18, respectively. On univariate linear regression, there was a significant positive association between PI and infarct volume ($p=0.001$). In the multivariate model, a single standard deviation increase of PI (per 0.18) was associated with an increase of 139.05 mm³ in infarct volume (95% confidence interval, 21.25 to 256.85; $p=0.022$).

**Conclusion:** We demonstrated that PI was an independent determinant of infarct volume in acute lacunar stroke. The PI value measured in acute stroke may be a surrogate marker of the extent of ischemic injury.

**Key Words:** Transcranial Doppler, lacunar stroke, small vessel disease, diffusion MRI
with vascular risk factors or pre-existing microangiopathy including hypertension, diabetes mellitus (DM), retinopathy, nephropathy, and white matter disease.8,9

Based on the current understanding of lacunar stroke as a manifestation of small vessel disease, we hypothesized that the PI, a marker of cerebral small vessel disease, might also be associated with the degree of ischemic injury in acute lacunar stroke. To better understand the role of small vessel disease in lacunar stroke, we undertook this study to determine whether the PI value measured in acute lacunar stroke has an influence on the size of infarct volume.

MATERIALS AND METHODS

Study design and subjects

The study candidates were patients admitted for acute lacunar stroke to our hospital between February 2005 and October 2014. Only those patients who completed both diffusion-weighted MRI (DWI) and TCD examination within 7 days from stroke onset were included. Patients with a poor temporal window for TCD and those with cardiac arrhythmia, which could interfere with exact measurements of PI in TCD, were excluded. Acute lacunar stroke was defined as a DWI finding showing focal high signal intensity in the territory of a single perforating artery (in deep gray or white matter of the cerebral hemispheres or brainstem) compatible with clinical presentation. Patients with acute ischemic lesions extending to the cerebral cortex, those with multiple lesions, and those whose lesions were greater than 20 mm in maximum diameter were excluded, as these cases were generally not considered to be caused by the occlusion of a single perforating artery.10 To exclude the potential effects of large artery disease on PI and infarct volume, only those patients who had no significant stenosis on magnetic resonance angiography or CT angiography were included. We also excluded patients with a mean blood flow velocity of the middle cerebral artery (MCA) of >120 cm/sec in TCD, which suggested significant narrowing of the vessel. In addition, patients with potential sources of cardioembolism such as atrial fibrillation and those who received thrombolytic therapy were excluded. In the end, this study included 64 patients with acute lacunar stroke. The Institutional Review Board at CHA Bundang Medical Center approved this study and waived informed consent from the subjects due to the retrospective and observational nature of the study.

Characteristics and risk factors

We collected information regarding sex, age, presence of hypertension, DM, current smoking, and previous stroke. Criteria for the diagnosis of hypertension were the use of antihypertensive medication, a systolic blood pressure (SBP) of ≥140 mm Hg, or a diastolic blood pressure (DBP) of ≥90 mm Hg on repeated measurements. A diagnosis of DM was based on a fasting plasma glucose level of ≥7.0 mmol/L or treatment with oral antidiabetic medication or insulin. Current smokers were defined as those who had smoked within one year. We also collected laboratory findings obtained at admission including white blood cell count, hematocrit, serum creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein (CRP), and homocysteine. On the day of TCD examination, SBP/DBP over brachial artery, and heart rate (HR) were recorded.

TCD examination

TCD studies were performed using a Power M mode transcranial Doppler (PMD-100/150, 2 channels, Spencer Technologies Inc., Seattle, WA, USA) with a 2-MHz probe.11 TCD examination was performed along the full segments of the MCA; the depths of insonation were 45–60 mm for the MCA. Systolic, diastolic, and mean blood flow velocity (SFV, DFV, MFV) were calculated automatically by the TCD device. Values with the highest MFV were selected from several measurements on each side. PI was derived using the formula [PI=(SFV-DFV)/MFV]. We used the mean values of TCD parameters including PI, obtained from the bilateral MCAs, for analysis.

Measurement of infarct volume and Fazekas scale on MRI

Brain MRI including DWI sequence was performed using one of three 1.5-T systems (Sonata, Siemens Medical, Erlangen, Germany; Signa Excite, GE Healthcare, Milwaukee, IL, USA; Signa HDs, GE Healthcare, Milwaukee, IL, USA). Acute ischemic lesions were defined as high-signal intensities on the DWI. Infarct volume was measured using the three-dimensional image analysis software Mango (Multi-Image Analysis GUI, Ver. 3.1.2 for Windows, Research Imaging Institute, San Antonio, TX, USA; http://ric.uthscsa.edu/mango/). For each axial DWI, the grey-scale value of each pixel was measured, and the regions with higher grey-scale values than adjacent normal brain tissue were captured as the region of interest (ROI) using a semi-computerized, intensity-threshold method. Infarct volume (mm³) was calculated as the product of the sum of the ROI on each axial DWI slice multiplied by the slice thickness (5 mm).

Using axial T2-weighted or fluid attenuation inversion recovery MRI, the degree of white matter changes was classified according to the Fazekas scale (0, 1, 2, 3; 0 indicates absent and 3 severe) as an another marker for cerebral small vessel disease.12,13 The two investigators (Y.K. and J.K.) independently determined the MRI-based parameters, infarct volume and Fazekas scale, blind to both clinical and laboratory data. Inter-rater reliability for the Fazekas scale was assessed using kappa statistics, and the kappa value was 0.718. Disagreements on the Fazekas scale were resolved by consensus. The interrater difference of infarct volume measured by the Mango software was evaluated using a paired t-test, and the difference was not significant (p>0.05). For the analyses, the mean of infarct vol-
ume measured by the two investigators was used. Across the three 1.5-T MRI systems, there were no significant differences in terms of infarct volume or Fazekas scale (p>0.05).

**Statistical analysis**
Categorical data are expressed as number (%), and continuous data are expressed as mean±standard deviation (SD) or median (interquartile range). To evaluate the association between infarct volume and PI value, we performed univariate and multivariate linear regression analyses with infarct volume as a continuous, dependent variable. In the regression models, we treated PI as a continuous variable and calculated the coefficient and the 95% confidence interval (CI) per one SD increase in PI. Adjustments were performed for traditional risk factors (sex, age, hypertension, DM, current smoking, previous stroke), homocysteine, CRP, and Fazekas scale based on prior knowledge. We additionally adjusted for the variables with p<0.10 in the univariate analysis for infarct volume. All statistical analyses were performed using the R package for Windows (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value of <0.05 was considered statistically significant.

**RESULTS**
This study included 64 patients with acute lacunar stroke according to the study criteria. Among them, 46 (71.9%) were men, and the mean age was 58.17±10.23 years (Table 1). The mean infarct volume measured on DWI was 482.18±406.40 mm³ (Table 2). The mean PI was 0.86±0.18. On univariate linear regression between PI and infarct volume, PI was significantly associated with infarct volume (p=0.001) (Table 3). Fig. 1 demonstrates the proportional increase of infarct volume with PI. The Supplementary Table 1 (only online) presents the results of univariate analyses of other collected variables with infarct volume. Except for PI, all other parameters of TCD were not significantly associated with infarct volume. To evaluate the independent effect of PI, we conducted multivariate linear regression. Using a multivariate model adjusted for sex, age, hypertension, DM, current smoking, previous stroke, homocysteine, CRP, and Fazekas scale, an increase of PI was significantly associated with an increase of infarct volume (p<

### Table 1. Baseline Characteristics of Study Patients

| Variable                      | n=64 |        |
|-------------------------------|------|--------|
| **Risk factors**              |      |        |
| Sex, male                     | 46   | (71.88)|
| Age, yr                       | 58.17| ±10.23|
| Hypertension                  | 32   | (50.00)|
| Diabetes mellitus             | 24   | (37.50)|
| Current smoking               | 37   | (57.81)|
| Previous stroke               | 10   | (15.62)|
| **Laboratory findings**       |      |        |
| White blood cell count, ×10⁹/L| 7.49 | ±2.46  |
| Hematocrit, %                 | 43.79| ±13.48|
| Glucose, mg/dL                | 144.39| ±63.19|
| Creatinine, mg/dL             | 0.99 | ±0.23  |
| Total cholesterol, mg/dL      | 186.86| ±40.68|
| High-density lipoprotein      | 43.72| ±11.24|
| Low-density lipoprotein       | 113.41| ±28.53|
| Triglyceride, mg/dL           | 171.89| ±131.91|
| Homocysteine, umol/L          | 11.17| ±4.78  |
| C-reactive protein, mg/dL     | 0.28 | ±0.49  |

Values are expressed as number (%), mean±standard deviation.

### Table 2. Findings of Brain MRI and Transcranial Doppler Ultrasound Study

| Variable                        | n=64 |        |
|---------------------------------|------|--------|
| **MRI findings**                |      |        |
| Infarct volume, mm³             | 482.18| ±406.40|
| Acute infarct in anterior cerebral circulation | 46 | (71.88) |
| Fazekas scale                   |      |        |
| 0                               | 5    | (7.81) |
| 1                               | 29   | (45.31)|
| 2                               | 17   | (26.56)|
| 3                               | 13   | (20.31)|
| Time from stroke onset to MRI, hr| 37.15| (17.78; 57.67)|

### Table 3. The Effect of Pulsatility Index on Infarct Volume in Linear Regression Models

| Pulsatility index, per one SD | Coefficient, mm³ | 95% CI | p value |
|-------------------------------|------------------|-------|--------|
| Univariate                    | 159.59           | 64.71 to 254.48 | 0.001 |
| Multivariate                  |                  |       |        |
| Model 1*                      | 241.36           | 132.77 to 349.96| <0.001|
| Model 2*                      | 226.96           | 119.82 to 334.11| <0.001|
| Model 3‡                      | 139.05           | 21.25 to 256.85 | 0.022 |

CI, confidence interval; SD, standard deviation. Data are derived from the linear regression models that have infarct volume (mm³) as a dependent variable. Coefficient and 95% CI are per increase of one SD in pulsatility index (0.18).

*Adjusted for sex, age, †Adjusted for sex, age, hypertension, diabetes mellitus, current smoking, previous stroke, homocysteine, C-reactive protein, and Fazekas scale, ‡Adjusted for variables in Model 2 plus variables with p<0.1 on univariate analysis for infarct volume (low-density lipoprotein cholesterol, lesion in anterior cerebral circulation, time from stroke onset to MRI).
bral small vessel disease. We showed that underlying severe
ment. Therefore, PI is regarded as a surrogate marker for cere-
failure change, which is another established marker of small
ers in acute stroke by themselves. Higher PI may not only
tribute to further vascular injury and progression of atherosclero-
sis in cerebral vasculature. Higher PI signifies increased trans-
mission of pulsatile flow to distal cerebral small vessels, which
would induce stretch, necrosis, calcification, fibrosis, and hyper-
trophy of endothelium and smooth muscle cells in cerebral
ulation. The brain is one of the organs most susceptible
to an excess of pulsatile flow, with a consistently high blood
flow and low resistance.

In lacunar stroke, early hemodynamic factors are crucial in
determining whether the hypoperfused area will be trans-
formed into a permanent infarct. PI is positively associated
with elevation of intracranial pressure, which results in
creased cerebral perfusion pressure. The excessive pulsatile
flow of cerebral circulation is accompanied by the reduction
of total cerebral blood flow. Under normal conditions, increased
pulsatile flow could be compensated for by autoregulation of
the cerebrovascular system. However, as vascular reactivity is
impaired in acute stroke, transmission of the excessive pulsatile
flow may overwhelm the autoregulatory reserve, causing further
brain damage. The increased pulsatile flow pattern is also
associated with unfavorable conditions, including vasospasm,
endothelial dysfunction, insulin resistance, oxidative stress, and
inflammation. Recent studies have suggested that the signifi-
cance of PI is not limited to cerebral circulation only; it also
reflects increased pulsatile blood pressure in systemic circulation
and arterial stiffness. In acute stroke, arterial stiffness is asso-
ciated with progressive neurological deficits, poor functional
outcome, and increased long-term mortality.

This study had several potential limitations. Our results were
obtained from a retrospective study with a small sample size.
As patients who had not completed TCD and those with a poor
temporal window were excluded, the possibility of selection
bias was present. The PI values could have also been affected
by various clinical factors. For example, medication history,
particularly that of antihypertensive agents, could have influ-
enced both PI and brain perfusion. We did not have data on
long-term outcomes including functional outcome, stroke re-
currence, and mortality. Due to the limitation of the cross-sec-
tional design, we could not definitively answer the question of
whether PI is merely a marker of underlying small vessel dis-
ease or also a cause of greater ischemic injury during the acute
phase of stroke. However, the effect of PI on infarct volume was
significant even after adjusting for multiple risk factors includ-
ing CRP, a marker of inflammation, and the degree of white
matter change, which is another established marker of small
vessel disease. There are many potential mechanisms through
which increased pulsatile flow could induce structural and
functional deterioration of cerebral vasculature and impair cerebral perfusion, resulting in brain injury. Therefore, we supposed that excess pulsatile flow, expressed as a high PI value, might aggravate ischemic injury in acute lacunar stroke. Further studies are needed to evaluate the mechanism behind pulsatile flow and consequently PI. Cilostazol, one of the antiplatelet agents frequently used in stroke prevention, can lower PI in flow and consequently PI. Cilostazol, one of the antiplatelet agents frequently used in stroke prevention, can lower PI in flow and consequently PI.

In conclusion, we demonstrated that PI has a significant positive association with infarct volume in acute lacunar stroke. The easily obtainable PI value on non-invasive TCD study may be a surrogate marker of infarct volume in acute stroke. Further studies are needed to explore the role of cerebral pulsatile flow and small vessel disease in acute ischemic injury.

ACKNOWLEDGEMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2014R1A1A1002067).

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