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The Relationship between Changes in Systemic Blood Viscosity and Transcranial Doppler Pulsatility in Lacunar Stroke

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Background: We hypothesized that changes in blood viscosity (BV) would influence cerebral vessel viscosity, which is related to the transcranial Doppler (TCD) pulsatility index (PI). Using serial BV and TCD examinations, we sought to evaluate the relationship between changes in BV and TCD PI in lacunar stroke patients.
Methods: Patients (aged ≥50 years) who developed lacunar stroke within 7 days of symptom onset were enrolled. Laboratory tests and TCD examinations were conducted at admission and 180 (±30) days after the onset of stroke. Patients were categorized into the decreased BV and increased BV groups. Decreased BV suggested that the BV value in the baseline study minus the 180-day study was positive, and vice-versa.
Results: A total of 128 patients who had experienced classic lacunar syndromes were enrolled and 67 (52%) were included in the final analysis. At the end of the 180-day study, changes in systolic BV (SBV) were not associated with PI changes. Regarding diastolic BV (DBV), hematocrit (Hct) adjusted partial correlation analysis showed no significant relationship between changes in DBV and PI (r=0.25, p=0.068). The correlation analysis showed that changes in hemoglobin and Hct were positively associated with SBV and DBV changes (r>0.488, p<0.0001 and r>0.461, p<0.0001), confirming that Hct was the major determinant factor of BV.
Conclusion: This study did not show a relationship between changes in BV and cerebral arterial pulsatility in patients with lacunar stroke. The changes in BV were positively associated with changes in Hct.
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NTRODUCTION

We previously reported that middle cerebral artery (MCA) pulsatility is highly associated with systemic blood viscosity (BV) in acute ischemic stroke within 24 hours of symptom onset.[1] Our findings indicated that transcranial Doppler (TCD) pulsatility index (PI) is a useful non-invasive imaging modality for exploring the viscosity of cerebral vessels. We also showed that prior antithrombotic use was significantly associated with decreased BV in acute ischemic stroke patients.[2] This study demonstrated that prior antithrombotic medication changes the hemorheological profile in the acute phase of ischemic stroke. When using antithrombotics, inhibition of platelet aggregation and enhancement of erythrocyte deformability may be associated with decreased BV.

BV is the measurement of intrinsic blood resistance to flow and is characterized by blood stickiness and thickness.[3-5] Several studies have revealed an associa-

tion between BV and the occurrence of major thromboembolic events.[6,7] High BV increases the risk of thromboembolic events and has an important role in cerebro-cardiovascular diseases.[4,5,8-10] One of the more conspicuous impacts of BV is on microcirculatory tissue perfusion; an increase in BV may lead to a decrease in tissue perfusion.[2] PI measures cerebral vascular resistance and is the reflection of multifactorial, pleiotropic events occurring in the systemic vascular system.[11] The most important factors affecting PI are cerebral flow velocity (FV) and BV.[12] PI increases with old age, presence of diabetes and hypertension, and lacunar stroke.[13,14]

Although BV is the major factor influencing PI, it is unknown whether changes in BV are related to PI changes in patients with ischemic stroke.[12] We hypothesized that changes in BV would influence cerebral vessel viscosity, which is related to TCD PI. Hence, this study was designed to evaluate the relationship between changes in BV and TCD PI in patients with lacunar stroke by using serial BV and TCD examinations.

SUBJECTS AND METHODS

1. Patients

For this study, patients (aged ≥50 years) who developed lacunar stroke within 7 days of symptom onset from January 2019 to December 2019 were enrolled. Patient demographics and clinical information were assessed at admission. Physical examination and systemic investigations were performed for all patients. Each patient underwent brain magnetic resonance imaging and at least one vascular imaging study, such as magnetic resonance angiography or computed tomography angiography. Echocardiography and 24-hour Holter monitoring were performed in selected patients to determine the potential cardiac sources of embolism. Stroke subtypes were classified according to the Trial of ORG 10172 using the Acute Stroke Treatment classification system.[15] During the study, all patients received proper treatment, including anti-hypertensive drugs, anti-diabetes drugs, or statins. The Research Ethics Committee of Inje University Sanggye Paik Hospital approved the present study (IRB No. 2020-07-016-001). Informed consent was waived because the database was accessed only for purposes of analysis; personal information was not used.

2. BV measurement

We used previously published methods of BV measurement.[2] The scanning capillary-tube viscometer (Hemovister, Pharmode Inc., Seoul, Korea) was used to assess whole blood viscosity (WBV). This assesses systolic BV (SBV) and diastolic BV (DBV), which characterize viscosities at high and low shear rates, respectively. In this study, a WBV measured at a shear rate of 300 s^{-1} was selected as the SBV and at 1 s^{-1} as the DBV.[4] Laboratory tests, including BV, hemoglobin (Hb), hematocrit (Hct), and platelet count, were conducted at admission and 180 (±30) days after the onset of stroke. All BV samples were obtained before hydration therapy, and measurements were taken within 24 hours of collection. For the study, patients were categorized into the decreased BV and increased BV groups. Decreased BV suggested that the BV value in the baseline study minus the 180-day study was positive, and vice-versa. If the calculated BV values in patients were zero or discordant between SBV and DBV, they were excluded from the study.

3. Transcranial Doppler

Techniques for the use of TCD have also been published previously.[11,13] Serial TCD examinations were carried out with a Companion III (Nicolet Biomedical, Inc., Madison, Wisconsin, USA) according to the standard operating manual at 7 (±2) and 180 (±30) days after stroke onset. Doppler signals from the MCA were acquired at depths of 56, 58, 60, and 62 mm. Doppler signals from the basilar artery (BA) were obtained at depths of 80, 84, 88, and 92 mm. Gosling's PI was calculated as the difference between the peak systolic and end-diastolic velocities divided by the mean FV (mFV) in each artery. The depth showing the highest mFV was used as a parameter for PI analysis. The relevant artery was classified as MCA or BA for the study.

4. Statistical analysis

Normality was checked using the Kolmogorov–

Smirnov test. Descriptive data were expressed as mean±standard deviation or number (percentage). Univariate analyses of patient characteristics were performed using an independent sample *t* test or the Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables. The patient characteristics among the antiplatelet treatment groups were analyzed using one-way analysis of variance with Tukey's post hoc test for continuous variables. Pearson's and Spearman's correlation coefficients were calculated to evaluate the correlations between changes in BV and PI. Statistical analyses were performed using SPSS version 25.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

We screend 402 patients who had experienced first ischemic stroke within 7 days of symptom onset. The most frequent stroke subtype was lacunar stroke (128, 32%), followed by stroke of undetermined etiology (119, 29%), cardioembolism (76, 19%), large artery atherosclerosis (75, 19%), and stroke with other determined etiology (4, 1%). For this study, 128 patients who had experienced classic lacunar syndromes were enrolled. During the trial, 61 patients (48%) did not follow the study protocol (40 patients refused to undergo BV or TCD measurements and 21 patients were lost to follow-up). As a result, 67 (52%) were subjected to final analysis.

The baseline characteristics of the study population are shown in Table 1. The mean age was 66.1±11.39 years, and 36% of the patients were female. Of these, 67% had a history of hypertension, 25% had a history of diabetes, 40% had a history of dyslipidemia, and 45% were current smokers. An anterior circulation lesion was found in 45% of the patients. The baseline characteristics and the relevant artery FV and PI values did

Table 1. Baseline characteristics of the study population

	Total (n=67)	Decreased-BV (n=44)	Increased-BV (n=23)	*p*-value
Age (years)	66.1±11.39	64.8±11.28	68.6±11.46	0.212
Female	24 (35.8)	16 (36.3)	8 (34.7)	0.898
Hypertension	45 (67.2)	33 (75)	12 (52.2)	0.059
Diabetes mellitus	17 (25.4)	10 (22.7)	7 (30.4)	0.491
Dyslipidemia	27 (40.3)	18 (40.9)	9 (39.1)	0.888
Current smoking	30 (44.8)	18 (40.9)	12 (52.2)	0.735
Stroke in anterior circulation	30 (44.8)	21 (47.7)	9 (39.1)	0.502
Relevant artery flow velocity (cm/sec): MCA				
Peak systolic velocity	80±23.02	87±19.73	85±27.43	0.806
End diastolic velocity	37±12.69	39±15.59	37±12.84	0.577
Mean flow velocity	50±13.45	54±12.61	53±16.21	0.803
Relevant artery flow velocity (cm/sec): BA				
Peak systolic velocity	56±18.83	60±22.02	53±17.25	0.224
End diastolic velocity	24±7.81	25±8.08	22±6.69	0.153
Mean flow velocity	36±11.64	37±12.94	33±9.42	0.216
Relevant artery PI				
MCA	0.89±0.13	0.94±0.15	0.91±0.17	0.522
BA	0.96±0.14	0.96±0.14	0.97±0.15	0.668

Values are presented as number (%) or mean±standard deviation. Decreased-BV suggests the BV value in the baseline study minus the 180-day study is positive, and vice-versa.

BV; blood viscosity, SBV; systolic blood viscosity, DBV; diastolic blood viscosity, MCA; middle cerebral artery, BA; basilar artery, PI; pulsatility index.

not significantly differ between the groups. Table 2 shows the patients' laboratory findings according to BV changes. Hb, Hct, SBV, and DBV were significantly higher in the decreased BV group at baseline, suggesting that Hb and Hct were positively related to BV.

At the end of the 180-day study, aspirin plus clopidogrel were given to 44 patients (66%), clopidogrel alone to 14 (21%), aspirin alone to 4 (6%), and other antiplatelets were to 5 (7%). There were no significant differences in the 180-day study including Hb, Hct, SBV, and DBV between the groups. The changes in SBV were not associated with changes in PI. Hct-adjusted partial correlation analyses also showed no significant relationship between changes in DBV and PI (r=0.25, p=0.068). The changes in BV were significantly related to Hb and Hct changes. Correlation analysis showed that changes in Hb and Hct were positively associated with SBV and DBV changes (r>0.488, p<0.0001 and r>0.461, p<0.0001),

Table 2. Patients' laboratory findings according to the BV changes

	Total (n=67)	Decreased-BV (n=44)	Increased-BV (n=23)	p-value
Baseline study				
Hemoglobin (g/dL)	14.1±1.85	14.5±1.76	13.4±1.81	0.013*
Hematocrit (%)	41.3±4.95	42.4±4.74	39.2±4.73	0.01*
Platelets (10^3/μL)	245±65.84	250±58.59	236±78.48	0.411
SBV (cP)	4.64±0.87	4.91±0.87	4.14±0.61	<0.0001*
DBV (cP)	38.37±9.22	41.34±8.78	32.69±7.26	<0.0001*
Relevant artery PI				
MCA	0.89±0.13	0.94±0.15	0.91±0.17	0.522
BA	0.96±0.14	0.96±0.14	0.97±0.15	0.668
180-day study				
Hemoglobin (g/dL)	13.7±1.62	13.7±1.65	13.8±1.61	0.775
Hematocrit (%)	40.7±4.29	40.6±4.36	40.9±4.27	0.761
Platelets (10^3/μL)	244±55.78	251±56.29	230±53.39	0.15
SBV (cP)	4.52±0.68	4.38±0.59	4.78±0.77	0.022
DBV (cP)	32.15±8.89	30.03±8.02	36.21±9.25	0.006
Relevant artery PI				
MCA	0.87±0.17	0.87±0.17	0.87±0.17	0.926
BA	0.9±0.15	0.9±0.15	0.9±0.16	0.923
Changes in SBV (cP)	0.12±0.83	0.53±0.64	-0.64±0.59	<0.0001*
Changes in DBV (cP)	6.22±9.72	11.31±6.69	-3.52±6.68	<0.0001*
Changes in PI				
MCA	0.06±0.14	0.07±0.11	0.05±0.19	0.546
BA	0.06±0.11	0.06±0.11	0.07±0.13	0.677
Changes in hemoglobin (g/dL)	0.4±1.18	0.9±1.11	-0.5±0.74	<0.0001*
Changes in hematocrit (%)	0.7±3.43	2±3.22	-1.7±2.33	<0.0001*
Changes in platelets (10^3/μL)	0.7±36.56	2±34.43	5±40.58	0.462

Values are presented as mean±standard deviation. Decreased-BV suggests the BV value in the baseline study minus the 180-day study is positive, and vice-versa. The changes in Hemoglobin, Hematocrit, and Platelets were calculated by subtracting the later value from the initial value.

BV; blood viscosity, SBV; systolic blood viscosity, DBV; diastolic blood viscosity, cP; centipoise, MCA; middle cerebral artery, BA; basilar artery. PI; pulsatility index.

*Significant p is marked with.

confirming that Hct was the major determinant factor of BV. Regarding antiplatelet treatment, no differences in BV and PI values changes were observed among the treatment groups.

DISCUSSION

In this study, we evaluated the relationship between changes in BV and TCD PI in lacunar stroke patients using serial BV and TCD examinations. Our study did not show a relationship between changes in BV and cerebral arterial pulsatility in lacunar stroke patients. The changes in BV were positively associated with changes in Hct. Several studies have demonstrated the relationship between BV and ischemic stroke.[3,4,16] BV is elevated in the acute phase of ischemic stroke and gradually improves in the chronic phase.[3,4,17] BV may contribute to the onset of stroke subtypes and may be related to the pathogenesis of thrombus formation.[3] BV and TCD PI share common pathophysiological mechanisms. BV is significantly higher in lacunar or cardioembolic strokes.[3,4,18] TCD PI is generally elevated in lacunar stroke. The most important effect of BV is in the microcirculation, where it contributes extensively to peripheral resistance.[5] Since DBV has a greater impact on the tissue perfusion of small vessels than SBV, DBV more likely influence lacunar stroke. When the blood passes through the stenotic perforating arteries, an elevated DBV can exacerbate the flow disturbance and cause endothelial remodeling and luminal occlusion.[4] This hemorheological change could be associated with thrombus formation in lacunar stroke.[2,3]

BV reflects frictional interactions between blood components and erythrocytes within the systemic vascular system.[2] The changes in Hct were positively associated with BV changes in this study. These results were in concordance with those of previous studies showing that the major determinants of BV are the aggregation and deformability of erythrocytes, Hct, and plasma viscosity.[5] Physicians should be aware that BV was affected by Hct during serial measurements.

The strength of this study was that it incorporated a longitudinal design using serial BV and TCD examinations. Unlike simple cross-sectional studies, our study was used to estimate the serial changes in BV and TCD PI in lacunar stroke patients. There were several limitations to this study. First, the baseline BV and PI were measured at different times. The median time from BV measurement to TCD examination at admission was 2 days. BV is uniform over a short period of time and TCD PI is influenced by several physiological factors.[1] One study demonstrates that BV at admission is significantly higher in patients with lacunar stroke but drops after 2 weeks of normal hydration.[3] Our previous study also shows that PIs decreased in the first 14 days after the lacunar stroke.[11] Second, we presumed that scheduled measurement at 7 (±2) and 180 (±30) days after onset of stroke was acceptable for the study but instructive studies regarding BV and PI changes in ischemic stroke patients are limited. Third, the small sample size and short duration of follow-up limit the generalizability of our findings. Of the 128 patients screened during the trial, only 67 (52%) were enrolled in this study. Finally, BV can be modified by drug therapy such as antiplatelets, anti-hypertensive drugs, or statins. Although no differences in BV and PI changes were observed among the different antiplatelet treatment groups in this study, these limitations should be considered when interpreting our data.

In conclusion, this study did not show a relationship between changes in BV and cerebral arterial pulsatility in lacunar stroke patients. The changes in BV were positively associated with Hct changes. Further studies on long-term follow-up with a large sample size and plasma components such as fibrinogen or high-sensitivity C-reactive protein are essential to assess the effects of BV on cerebral arterial pulsatility.

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

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