Original Article

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Variation in blood viscosity based on the potential cause of stroke of undetermined etiology

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Background: This study investigated potential differences in blood viscosity (BV) among patients with stroke of undetermined etiology, negative evaluation (SUDn), specifically those with potential atherothrombosis (SUDn-AT) and those with possible embolism (SUDn-E).

Methods: This single-center study employed a retrospective observational design. The participants were patients over 20 years old with the SUDn stroke subtype who were admitted within 5 days of symptom onset. These patients were categorized as SUDn-AT or SUDn-E. Patients in the SUDn-AT group had nonsignificant stenosis (<50%) of a major brain artery relevant to their symptoms and exhibited one or more signs of systemic atherosclerosis, including atherosclerosis of at least one major brain artery other than those clinically relevant, coronary artery disease, and/or peripheral artery disease. For the SUDn-E group, the SUDn criteria from the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system were strictly applied.

Results: The final analysis included 153 patients, with 104 (68%) classified as SUDn-E and the remaining 32% as SUDn-AT. Patients in the SUDn-AT group had a higher systolic BV (P=0.012) and diastolic BV (P=0.020) than those in the SUDn-E group. Multivariable logistic regression analysis revealed that age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.13; P=0.003), systolic BV (OR, 3.11; 95% CI, 1.41–6.85; P=0.005), and diastolic BV (OR, 1.08; 95% CI, 1.02–1.14; P=0.009) were associated with SUDn-AT.

Conclusions: Within the TOAST system, two SUDn entities may be distinguishable, with potentially different underlying etiologies: atherothrombosis and embolic stroke of undetermined source.

Keywords: Blood viscosity; Etiology; Stroke

INTRODUCTION

The classification of stroke type is a critical component of its evaluation and treatment. The assessment and treatment of stroke depend heavily on its etiology, underscoring the importance of accurate classification. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system, established in 1993 for the study of low molecular weight heparinoid [1], has become the predominant method for determining the cause of ischemic stroke. Despite the trial's lack of success, the TOAST classification has been employed in numerous studies concerning stroke epidemiology, intervention, risk factors, and prognosis. However, despite its current widespread use, the TOAST system

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has several limitations. These include a high frequency of stroke of undetermined etiology, negative evaluation (SUDn), also known as cryptogenic stroke, as well as inconsistent results across observers [2,3]. Advances in imaging techniques now allow a more accurate diagnosis of strokes and identification of their underlying causes. Concurrently, new therapeutic strategies have been developed. These include medications such as statins or non–vitamin K antagonist oral anticoagulants (NOACs), which are used to prevent further vascular events in patients with systemic atherosclerosis or atrial fibrillation (AF).

The TOAST classification system defines SUDn as stroke for which the cause remains uncertain, even after a thorough evaluation. Patients diagnosed with SUDn should not exhibit significant stenosis (≥50%) of any clinically relevant artery, and no sign of embolism originating from the heart should be evident. Furthermore, even with extensive investigation, no other explanation for the stroke should be identifiable. Within the TOAST classification system, two distinct SUDn entities may be distinguishable: atherothrombosis (AT) and embolic stroke of undetermined source (ESUS). These may differ in their underlying etiology [2,4]. Blood viscosity (BV) is a crucial factor in predicting endothelial shear stress, as it represents the inherent resistance encountered by blood flow. BV refers to the thickness and stickiness of blood, and it plays a key role in determining the frictional force exerted on the blood vessel wall. BV is associated with thromboembolic events, and elevated BV levels are associated with an increased risk of cerebrovascular and cardiovascular disease [5]. Previous studies have suggested that BV levels vary across stroke subtypes [6,7]. For instance, lacunar stroke is associated with higher BV than other subtypes, such as large artery atherosclerosis and cardioembolism [8].

Given the distinct stroke mechanisms associated with AT and ESUS, we hypothesized that BV levels would vary based on the potential cause of stroke within the SUDn group. Consequently, this study was conducted to determine whether differences were present in BV levels between patients with SUDn with possible AT (SUDn-AT) and those with SUDn with possible embolism (SUDn-E).

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (No. 2022-03-011). The requirement for written informed consent was waived due to the retrospective nature of the study.

Patients

This study was carried out at a single center (Inje University Sanggye Paik Hospital, Seoul, Korea), utilizing a retrospective observational design. The participants were patients exhibiting the SUDn stroke subtype, as classified using the TOAST system, between March 2017 and December 2021. The inclusion criteria were as follows: (1) having an age of over 20 years and being admitted within 5 days of stroke onset; (2) exhibiting the SUDn stroke subtype according to the TOAST classification; and (3) displaying a cortical or nonlacunar subcortical lesion on brain computed tomography (CT) or magnetic resonance imaging (MRI). Patients were excluded if they met the following criteria: (1) displayed a hematocrit (Hct) level of less than 30% or greater than 50% at baseline, due to the potential influence of Hct on BV; (2) had received intravenous thrombolysis or intra-arterial thrombectomy during admission; or (3) had taken antithrombotic medication within 5 days of stroke onset.

For the study, patients were categorized into two groups: SUDn-AT and SUDn-E. Those in the SUDn-AT group were required to have nonsignificant stenosis (less than 50%) of a major brain artery relevant to their symptoms. The major brain arteries were identified as the carotid, vertebral, and basilar arteries, along with proximal segments of the anterior, middle, and posterior cerebral arteries. Furthermore, these patients needed to exhibit one or more signs of systemic atherosclerosis, including atherosclerosis of at least one major brain artery other than those clinically relevant, coronary artery disease (CAD), and/or peripheral artery disease (PAD) [2]. For the SUDn-E group, the criteria for SUDn in the TOAST classification system were strictly applied.

During admission, all patients with SUDn underwent a thorough examination. Each patient received a brain CT or MRI scan, along with an angiographic study. Demograph-

ics, medical history, and traditional vascular risk factors were also evaluated. Additionally, measurements were taken for 12-lead electrocardiography, complete blood counts, blood lipid profiles, renal and liver function, and coagulation factors. Except for those who did not provide informed consent, the patients underwent transthoracic echocardiography and 24-hour Holter monitoring.

BV measurement

The methods employed in this study to measure BV have been previously reported [9]. From January 2017 onward, BV measurements at our institution have been taken from consecutive patients with ischemic stroke, considering the potential influence of BV on treatment. Although not obligatory, this practice was adopted to ensure the highest quality of patient care. In the present study, a scanning capillary-tube viscometer (SCTV; Hemovister, Pharmode Inc) was utilized to evaluate whole BV. The SCTV measured both systolic BV (SBV) and diastolic BV (DBV), which represent viscosities at high and low shear rates, respectively. SBV was assessed at a shear rate of 300 seconds^{-1}, while DBV was measured at 1 second^{-1}. BV samples were collected via initial blood sampling prior to hydration therapy in the emergency room or outpatient department, and all measurements were taken within 24 hours of sample collection.

Statistical analysis

Statistical analysis was performed using IBM SPSS ver. 25.0 (IBM Corp), with a two-sided P-value of less than 0.05 considered to indicate statistical significance. Descriptive analyses were expressed as number (percentage) for categorical data and as mean±standard deviation for continuous data. The Kolmogorov-Smirnov test was employed to evaluate normality. Univariate analyses were performed to identify significant factors for the SUDn-AT group. For continuous variables, either the independent samples t-test or the Mann-Whitney U-test was utilized, while the chi-square test was used to analyze categorical variables. Variables that yielded a P-value of <0.05 in the univariate analyses were incorporated into the multivariable logistic regression models. A partial correlation analysis was carried out to ascertain the differences in BV, adjusting for the effects of Hct between the two groups.

RESULTS

A total of 297 patients with the SUDn subtype of stroke, representing 25% of all consecutive patients with ischemic stroke during the study period, were considered for inclusion in the study. However, 144 of these patients (49%), were excluded from the study for various reasons: 18 patients due to the absence of BV measurements, 38 patients due to Hct levels below 30% or above 50%, 14 patients due to undergoing intravenous thrombolysis or intra-arterial treatments, and 93 patients due to prior use of antithrombotic medication. Consequently, 153 patients were selected for the final analysis.

Table 1 presents the baseline characteristics of the enrolled patients. The mean age was 69.6±12.34 years, with women constituting 47.1% of the patient population. Most patients (75.2%) had a history of hypertension, 34.6% had diabetes, 43.8% had dyslipidemia, and 27.5% were current cigarette smokers. Seven patients (4.6%) had a history of CAD, while none of the patients had PAD. The median time from the onset of symptoms to hospital arrival was 18 hours, with 61.3% of patients arriving at the hospital within 24 hours. No significant difference was observed in the time to admission between groups. Of the 153 patients, 104 (68.0%) were classified as SUDn-E and the remaining 32.0% as SUDn-AT. No significant differences were observed in the baseline characteristics between these groups, except for age, history of hypertension, and National Institutes of Health Stroke Scale (NIHSS) score at admission. The SUDn-AT group had a significantly higher age (P=0.001), more frequent history of hypertension (P=0.004), and higher NIHSS score at admission (P=0.007). These findings suggest that advanced age and a history of hypertension are major risk factors for systemic atherosclerosis.

Table 2 displays the laboratory findings from the study population. The SUDn-AT group exhibited higher levels of serum creatinine, plasma glucose at admission, and high-sensitivity C-reactive protein (hs-CRP), suggesting these results as potential risk factors for systemic atherosclerosis. Regarding BV, patients in the SUDn-AT group demonstrated higher SBV (P=0.012) and DBV (P=0.020), indicating an overall pattern of greater BV at admission relative to the SUDn-E group. In the multivariable logistic regression analysis, age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.13; P=0.003), SBV (OR, 3.11; 95% CI,

Table 1. Baseline characteristics of the study population

Characteristic	Total (n=153)	SUDn-E (n=104)	SUDn-AT (n=49)	P-value
Age (yr)	69.6±12.34	67.5±12.66	74.3±10.28	0.001*
Sex				0.984
Male	81 (52.9)	55 (52.9)	26 (53.1)	
Female	72 (47.1)	49 (47.1)	23 (46.9)	
Hypertension	115 (75.2)	71 (68.3)	44 (89.8)	0.004*
Diabetes mellitus	53 (34.6)	32 (30.8)	21 (42.9)	0.143
Dyslipidemia	67 (43.8)	43 (41.3)	24 (49.0)	0.375
Stroke	8 (5.2)	5 (4.8)	3 (6.1)	0.711
Coronary artery disease	7 (4.6)	5 (4.8)	2 (4.1)	0.841
Current smoking	42 (27.5)	32 (30.8)	10 (20.4)	0.180
Statin use	35 (22.9)	26 (25.0)	9 (18.4)	0.362
Time to admission (hr)	30.2±31.35	30.8±32.77	29.4±28.32	0.853
NIHSS score at admission	2.4±2.56	2.0±2.12	3.2±3.19	0.007*
Lesion localization				0.190
Anterior	90 (58.8)	56 (53.8)	34 (69.4)	
Posterior	59 (38.6)	45 (43.3)	14 (28.6)	
Multiple	4 (2.6)	3 (2.9)	1 (2.0)	
Systolic blood pressure (mmHg)	162±28.24	160±29.12	168±24.67	0.053
Diastolic blood pressure (mmHg)	88±17.23	87±17.92	88±15.82	0.705

Values are presented as mean±standard deviation, number (%) or mean±standard deviation.
SUDn, stroke of undetermined etiology, negative evaluation; SUDn-E, SUDn with possible embolism; SUDn-AT, SUDn with possible atherothrombosis; NIHSS, National Institutes of Health Stroke Scale.
*Statistically significant.

Table 2. Laboratory findings of the study population

Variable	Total (n=153)	SUDn-E (n=104)	SUDn-AT (n=49)	P-value
Hemoglobin (g/dL)	13.8±1.60	13.7±1.62	14.1±1.55	0.142
Hematocrit (%)	41.3±4.51	41.0±4.42	42.1±4.64	0.167
White blood cells (10^3/μL)	7.9±2.60	7.7±2.68	8.4±2.39	0.100
Platelets (10^3/μL)	236.1±66.69	237.5±66.93	233.0±66.77	0.708
Blood urea nitrogen (mg/dL)	17.2±5.74	16.9±5.41	17.8±6.39	0.432
Creatine (mg/dL)	0.86±0.28	0.83±0.23	0.93±0.37	0.045*
Random plasma glucose (mg/dL)	154.0±62.80	146.6±51.58	169.8±80.24	0.034*
Total cholesterol (mg/dL)	166.3±39.91	163.5±38.06	172.0±43.32	0.243
LDL cholesterol (mg/dL)	101.1±31.29	98.8±30.76	105.8±32.18	0.206
HDL cholesterol (mg/dL)	44.7±11.21	44.3±10.96	45.6±11.78	0.526
Triglyceride (mg/dL)	110.3±50.55	112.3±52.01	106.0±47.61	0.463
International normalized ratio	0.99±0.06	0.99±0.06	0.99±0.65	0.584
Fasting glucose	103.0±35.67	99.2±30.96	111.4±43.25	0.083
Systolic blood viscosity (cP)	4.53±0.62	4.44±0.55	4.71±0.72	0.012*
Diastolic blood viscosity (cP)	29.01±8.54	27.91±7.83	31.33±9.54	0.020*
hs-CRP (mg/dL)	0.65±1.50	0.41±0.77	1.15±2.35	0.006*

Values are presented as mean±standard deviation.
SUDn, stroke of undetermined etiology, negative evaluation; SUDn-E, SUDn with possible embolism; SUDn-AT, SUDn with possible atherothrombosis; LDL, low-density lipoprotein; HDL, high-density lipoprotein; cP, centipoise; hs-CRP, high-sensitivity C-reactive protein.
*Statistically significant.

1.41–6.85; P=0.005), and DBV (OR, 1.08; 95% CI, 1.02–1.14; P=0.009) were found to be associated with SUDn-AT. Given that Hct is a major determinant of BV, a Hct-adjusted partial correlation analysis was conducted. This analysis revealed a significant association between the SUDn-AT subtype and increases in both SBV (r=0.176, P=0.012) and DBV (r=0.165, P=0.036).

DISCUSSION

In this study, we classified the stroke subtype of SUDn within the TOAST classification system into two groups: SUDn-AT and SUDn-E. We then examined the differences in BV levels between these groups. Our findings indicated that the SUDn-AT group had significantly higher SBV and DBV levels than the SUDn-E group. Additionally, relative to the SUDn-E participants the SUDn-AT group was characterized by older age, a history of hypertension, and higher levels of serum creatinine, plasma glucose at admission, and hs-CRP. The findings suggest that these factors may be associated with the development of systemic atherosclerosis.

AT is likely the most common etiologic mechanism of ischemic stroke. However, it can sometimes be challenging to ascertain whether cerebral arterial stenosis was induced by atherosclerosis or an ESUS. According to the Reduction of Atherothrombosis for Continued Health (REACH) registry, 15.9% of patients with symptomatic AT also had symptomatic polyvascular disease [10]. One in six patients with stroke, CAD, or PAD display symptomatic involvement of one or two additional arterial beds. Consequently, the presence of other major brain arterial stenosis, CAD, and PAD was utilized as supportive evidence for the diagnosis of SUDn-AT in this study. This approach is based on the concept that atherosclerosis is a systemic disease that simultaneously affects multiple vascular beds [2].

In our study, the SUDn-AT group exhibited a higher BV than the SUDn-E group. While one study [11] indicated that higher BV levels are associated with ischemic stroke in patients with AF, no direct comparison has been made of BV measurements among the other stroke subtypes. Results have also differed based on the study design and the enrolled population [9]. Several plausible explanations support our findings of higher BV in the SUDn-AT group. First, the concept of ESUS was developed based on the hypothesis that most strokes in patients with ESUS are caused by numerous cardioembolic events, and that anticoagulation could prevent secondary ischemic events [4]. Importantly, however, two large, randomized NOAC trials have demonstrated that paroxysmal AF appears to be a rare cause of ESUS [4]. In the present study, nonstenotic atherosclerotic plaques, a major contributor to ESUS, were classified as SUDn-AT if they were associated with systemic atherosclerosis. Second, intracranial atherosclerosis (ICAS) is one of the most common causes of stroke, accounting for 30% to 50% of strokes in Asian populations [12]. The proposed stroke mechanisms of ICAS include hypoperfusion distal to the stenotic vessel, artery-to-artery embolism, and branch atheromatous disease [13]. Plaque stability may be more important than the degree of stenosis in ICAS, as artery-to-artery embolism may also occur more frequently [14]. A study investigating recurrent stroke and its mechanisms in patients initially classified as SUD based on the TOAST classification found that recurrent strokes were associated with the presence of stenosis of <50% in the relevant artery or stenosis of ≥50% in a nonrelevant artery. This underscores the importance of atherothrombotic mechanisms in these patients [15]. Endothelial damage, impaired blood flow, and hypercoagulability can trigger thrombus formation [16]. BV constitutes a primary mechanism for thrombus formation, and increased BV is a risk factor for AT [5]. Elevated BV may promote shear-mediated platelet activation; thus, it is prothrombotic and atherogenic, as it increases shear stress. One study [17] revealed that BV, Hct, and fibrinogen concentration were significantly higher in those with stenosis in two or three arteries compared to other patients. Considering the Virchow triad, thromboembolic susceptibility in ICAS may be related to endothelial damage, impaired blood flow, and hyperviscosity due to hemorheological alterations. These changes might be associated with the higher BV observed in the SUDn-AT group.

Our study did have certain limitations. First, the data were collected retrospectively from a single center, which made it impossible to establish a causal relationship between BV levels and the SUDn stroke subtype. Confounding factors may also have been present and not considered. Second, not all patients underwent transcranial Doppler or transesophageal echocardiography. Prior NOAC studies suggest that a patent foramen ovale with high-risk clinical features should not be classified as ESUS. This could suggest the presence of selection bias and may have impacted the va-

lidity of our results. Third, our conclusion was not robustly supported by statistical power due to the small sample size and the absence of age-matched controls. Finally, our findings are applicable only to Korean patients and cannot be generalized. These limitations should be taken into account when interpreting the results of the present study.

In conclusion, the findings revealed that the SUDn-AT group exhibited a higher BV than the SUDn-E group. This suggests that within the TOAST classification system, two distinct SUDn entities could be identifiable: SUDn-AT, associated with systemic atherosclerosis, and SUDn-E, associated with ESUS. These entities may have differing underlying etiologies. The role of BV in the mechanism of stroke requires further elucidation, which should be achieved through additional research involving larger patient populations.

ARTICLE INFORMATION

Ethics statements

This study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (No. 2022-03-011). The requirement for written informed consent was waived due to the retrospective nature of the study.

Conflicts of interest

Sang Won Han is the Associate Editor of *Cardiovascular Prevention and Pharmacotherapy*, but was not involved in the peer reviewer selection, evaluation, or decision process of this article. The authors have no other conflicts of interest.

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Author contributions

Conceptualization: all authors; Data curation: all authors; Formal analysis: JO, SWH; Investigation: SWH, JO; Methodology: all authors; Project administration: all authors; Software: SWH, JO; Supervision: JSB; Validation: SWH, JSB; Visualization: JO; Writing–original draft: JO, JSB; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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