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Citation	Journal of Stroke and Cerebrovascular Diseases, 25(11), 2762-2769 https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.07.031
Issue Date	2016-11
Doc URL	http://hdl.handle.net/2115/67492
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Type	article (author version)
File Information	JStrokeCerebrovascDis25_2762.pdf

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Increased blood viscosity in ischemic stroke patients with small artery occlusion measured by an electromagnetic spinning sphere viscometer

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Cover title

Increased blood viscosity in patients with small artery occlusion

Key words

blood viscosity, ischemic stroke, small artery occlusion, pathogenesis, rheology, dehydration

Abstract

Background and Purpose: High blood viscosity causes blood stagnation and subsequent pathological thrombotic events, resulting in the development of ischemic stroke. We hypothesize that the contribution of blood viscosity may differ among ischemic stroke subtypes based on specific pathological conditions. We tried to verify this hypothesis by measuring blood viscosity in acute ischemic stroke patients using a newly developed electromagnetic spinning sphere (EMS) viscometer. **Methods:** Measurements in acute ischemic stroke patients were performed 4 times during admission and data were compared with those obtained from 100 healthy outpatient volunteers. **Results:** We enrolled 92 patients (cardioembolism [CE]: 25, large-artery atherosclerosis [LAA]: 42, and small artery occlusion [SAO]: 25) in this study. Comparisons of blood viscosity between the ischemic stroke subgroups and control group revealed that blood viscosity at the date of admission was significantly higher in the SAO group (5.37 ± 1.11 mPa·s) than in the control group (4.66 ± 0.72 mPa·s) ($p < 0.01$). Among all subtype groups showing a reduction in blood viscosity after 2 weeks, the SAO group showed the highest and most significant reduction, indicating that SAO patients had the most concentrated blood at the onset. **Conclusions:** Blood viscosity was significantly increased in the SAO group at the date of admission, which indicated the contribution of dehydration to the onset of ischemic stroke. The importance of dehydration needs to be emphasized more in the pathogenesis of SAO. The clinical application of the EMS viscometer is promising for understanding and differentiating the pathogenesis of ischemic stroke. (242 words)

Introduction

Blood viscosity, one of the important rheological parameters, is determined by blood components and varies with the shear rate as a non-Newtonian fluid.^{1,2} The determining factors of blood viscosity are the concentration of blood cells, erythrocyte deformability and aggregation, and the concentration of plasma components. Blood viscosity increases when the concentrations of blood cells and plasma components become elevated and also with the low deformability and high aggregation of erythrocytes. Among these factors, the concentration of blood cells contributes the most to determining blood viscosity.³⁻⁵ A strong correlation has been demonstrated between blood viscosity and the concentration of blood cells.⁵ Shear rate is an important factor regulating blood viscosity with non-Newtonian characteristics in the circulatory system. While blood viscosity increases exponentially with reductions in the shear rate, it decreases and converges to a certain value with elevations in the shear rate, which exhibits shear-thinning behavior.⁶ The important rheological function of blood viscosity is to control resistance to blood flow in combination with the characteristics of vessels (length and radius).⁷ Therefore, blood viscosity measurements have been performed in thrombotic diseases since the 1960s and previous studies have demonstrated that increased blood viscosity is related to cardiovascular events.⁸⁻¹⁰ Furthermore, relationships have been reported between blood viscosity and some cardiovascular risk factors, such as hypertension, dyslipidemia, smoking, and obesity.¹¹⁻¹⁴ An increase in blood viscosity has been identified in the acute phase of ischemic stroke, similar to other thrombotic diseases.¹⁵⁻¹⁹ However, actual

measurements of blood viscosity have not been performed because of the stereotypical belief that blood viscosity increases equally in all ischemic stroke subtypes, which is within expectations and with less clinical value. However, since the measurement of blood viscosity may provide useful information on differential diagnoses, treatments, and the prevention of stroke, it needs to be examined more extensively. Ischemic stroke consists of a number of subtypes with different pathogeneses, and, thus, we hypothesize that the contribution of blood viscosity may differ among ischemic stroke subtypes due to specific pathological conditions.

A newly developed electromagnetic spinning sphere (EMS) viscometer has the ability to measure a small amount of samples quickly and sequentially in a non-contact disposable manner and skips the time-consuming washing process after each sample measurement.²⁰⁻²¹ We previously introduced the measurement of blood viscosity with the EMS viscometer and reported our findings on control volunteers.²² In the present study, we measured blood viscosity in acute ischemic stroke patients and discussed the importance of blood viscosity measurements in terms of differential diagnoses and the treatment of ischemic stroke.

Methods

Patient population and blood sampling

We herein conducted a prospective study with the recruitment phase between June 2014 and August 2015 in a comprehensive stroke center hospital. Patients (≥ 20 years) diagnosed with cardioembolism

(CE), large-artery atherosclerosis (LAA), and small artery occlusion (SAO) were eligible for the study if they were admitted for more than 2 weeks. Ischemic stroke subtypes were determined according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) with the aid of the findings of magnetic resonance imaging or computerized tomographic scans. Measurements were performed 4 times (date of admission, a couple of days after, 1 week after, and 2 weeks after) during admission. As a control group to compare blood viscosity with the stroke subtype groups, we used the 100 healthy outpatient volunteers (male 58.0%, mean age 65.5 ± 14.8 years) recruited in our previous study.²² All participants provided written informed consent prior to inclusion in the study, which was approved by the hospital's Ethics Committee. Blood sampling was performed to measure blood cells and biochemical parameters as a routine clinical examination, and residual EDTA anti-coagulated blood after the completion of blood cell counts was then used in this study.

Measurement of blood viscosity by the EMS viscometer

Blood viscosity was measured using the EMS viscometer (Kyoto Electronics Manufacturing Co., Ltd, Kyoto, Japan) as previously described.²² Briefly, 0.3 ml of a 37°C pre-warmed EDTA anti-coagulated blood sample in a disposable glass tube containing a 2-mm aluminum sphere was set in the EMS viscometer and its viscosity was measured at 37°C in accordance with the following measurement sequence. The measurement sequence was programmed to measure blood viscosity at six different rotational speeds of a driving magnetic field (1000, 800, 640, 500, 400, and 300 rpm)

sequentially in one measurement cycle, and the cycle was set to repeat 5 times at 30-second intervals. The sample was shaken at every interval of the 5 measurement cycles to prevent sedimentation. The shear rate of blood typically ranges between 30 and 110 s⁻¹ under this experimental condition. After the exclusion of outliers (greater than 20 mPs), the mean value of 5 measurements was calculated in order to obtain the representative value of each rotational speed. Blood viscosity at 100s⁻¹ was used as a representative value for comparisons and data analyses.

Statistical analysis

Data are given as the mean $\pm$ standard deviation. Statistical analyses were performed using the commercially available software, Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan). The Kruskal-Wallis test followed by Steel's multiple comparison test was used to compare multiple data sets. A level of $p < 0.05$ was accepted as significant.

Results

We enrolled 92 patients (male 58.7%, mean age 74.4 $\pm$ 11.5), comprising 25 CE, 42 LAA, and 25 SAO in this study. Although no significant difference was observed in the gender ratio between the total patient group and the control group (male 58.0%), the mean age of the total patient group was significantly higher than that of the control group (mean age 65.5 $\pm$ 14.8, $p < 0.01$). No significant difference was noted in the gender ratio or mean age between the CE (male 44.0%, mean age 77.2 $\pm$ 10.2), LAA (male 66.7%, mean age 73.5 $\pm$ 12.7), and SAO (male 60.0%, mean age 73.3 $\pm$ 10.6)

groups, even though the rates of female and aged patients were slightly higher in the CE group. No significant differences were also noted in other demographic characteristics including risk factors and neurological severity, even though there was a tendency for the CE group to have relatively lower Glasgow coma scale scores (Table 1).

Comparisons of blood viscosity between the ischemic stroke subgroups and control group revealed that blood viscosity at the date of admission was significantly higher in the SAO group (5.37 ± 1.11 mPa·s) than in the control group (4.66 ± 0.72 mPa·s) ($p < 0.01$) (Fig.1). Blood viscosity was slightly higher in the CE (4.85 ± 1.09 mPa·s) and LAA (4.95 ± 1.04 mPa·s) groups than in the control group, but with no significant difference (Fig.1). After admission, blood viscosity decreased until after 1 week because of fluid replacement by intravenous infusions and then increased after 2 weeks when intravenous infusions were terminated (Fig.2). The SAO group alone showed significantly higher blood viscosity at the date of admission (5.36 ± 1.02 mPa·s) than after 2 weeks (4.64 ± 0.80 mPa·s) (Fig.2). This result indicates that blood viscosity, which was abnormally increased at the date of admission, returned to normal levels after 2 weeks.

Blood viscosity correlated well with blood cell counts in accordance with exponential approximation fitting in healthy outpatient volunteers in our previous study (Fig.3).²² Therefore, we examined the relationship between blood viscosity and blood cell counts in each stroke subgroup and the control group. When plotting the values of blood viscosity and blood cell counts of individual patients from each stroke subtype group at the date of admission and after 2 weeks on a graph with the exponential

approximation curve from Figure 3, most plots were located higher than the approximation curved line (Fig.4). This result indicates that the blood of patients was more concentrated and/or contained more non-cellular substances, which elevated blood viscosity. When the mean values of blood viscosity and blood cell counts from each stroke subtype group at the date of admission and after 2 weeks were plotting, changes in these values after the hospital treatment were clearly observed (Fig.5). While all subtype groups showed reductions in blood viscosity and blood cell counts after the treatment, those in the SAO group, which had the highest blood viscosity and blood cell count at the date of admission, were the greatest.

Discussion

We are the first to apply the EMS viscometer to the measurement of blood viscosity in acute ischemic stroke patients. The results obtained demonstrated that blood viscosity at the date of admission was significantly higher in the SAO group than in the control group. Since age was significantly higher in the patient group than in the control group, age appears to play a role in the significantly higher blood viscosity observed in the SAO group. However, we previously reported that the elderly had slightly low blood viscosity due to age-related anemia.²² Therefore, high blood viscosity in the SAO group is more likely to depend on the pathophysiological condition of SAO itself, and not on the effects of aging. Among all subtype groups showing reductions in blood viscosity after 2 weeks, the SAO group showed the most significant decreases, indicating that SAO

patients had the most concentrated blood at the onset. Normal hydrated conditions were restored in patients with oral or tube feeding intake after 2 weeks when infusion therapy was terminated; therefore, the difference observed in blood viscosity between the date of admission and after 2 weeks was considered to be mediated by dehydration at the onset, and not by therapeutic hemodilution.

The results of the present study suggest that blood viscosity contributes differently to the onset of ischemic stroke subtypes. SAO appeared to be affected the most by increases in blood viscosity due to dehydration at the onset, while CE was affected the least. This may be related to differences in the pathogenesis of thrombus formation. Flow resistance is proportional to blood viscosity and vessel length, and inversely proportional to the vessel radius of the fourth power.⁷ Accordingly, when blood viscosity increases due to changes in blood composition and concentration, flow resistance markedly increases in narrow vessels such as stenotic perforating arteries. This rheological abnormality may be related to thrombus formation in SAO. On the other hand, thrombus formation in CE may be affected more by blood stagnation due to atrial motion abnormalities than by an increase in blood viscosity.

Increased blood viscosity was previously demonstrated in the acute phase of ischemic stroke.¹⁵⁻¹⁹

Previous studies mostly analyzed blood viscosity in a group combining all ischemic stroke subtypes.

Only one study compared blood viscosity among ischemic stroke subtypes and demonstrated that CE patients had the highest blood viscosity among the subtypes examined, which is in contrast to the results of the present study.¹⁶ Although we have no precise explanation for this discrepancy, differences may exist in patient conditions between the previous and present studies. One possibility

is that post-stroke water intake limitations due to severe neurological symptoms may have contributed to increased blood viscosity in CE patients in the previous study.

Dehydration is commonly regarded as one of the conditions to be avoided in order to prevent ischemic stroke. However, few studies have provided evidence for dehydration at the onset of stroke.

One of the reasons for this may be that no definitive laboratory test or diagnostic criteria are available for dehydration. Although the BUN-to-creatinine ratio, hematocrit, electrolytes, and plasma protein levels are used to evaluate dehydration, they are easily affected by other factors as well as dehydration. Among these laboratory tests, the BUN-to-creatinine ratio has been associated with poor outcomes or stroke-in evolution in acute ischemic stroke patients.²³⁻²⁵ It is also increased not only by dehydration, but also heart failure. A higher BUN-to-creatinine ratio has been associated with the severity of the congestive state, risk of hospitalization, and mortality in heart failure patients.²⁶⁻²⁷ Therefore, severe CE with heart failure may have contributed to the relationship between a high BUN-to-creatinine ratio and poor outcomes or stroke-in evolution reported in previous studies. Although the BUN-to-creatinine ratio may be useful for detecting stroke severity, it may not be an ideal tool for detecting dehydration.

In order to examine and evaluate the values of the above mentioned laboratory test in the preset study, we employed hematocrit and BUN-to-creatinine ratio and compared the values between the three stroke subgroups. Table 2 shows the values at the date of admission and after 2 weeks. Both hematocrit and BUN-to-creatinine ratio were significantly decreased after 2 weeks in the three

subgroups, except for BUN-to-creatinine ratio of the CE group. The decreased changes in these values are likely to be a similar phenomenon of the decreased changes in blood viscosity and blood cell counts (Figure 5), which is depended on dehydration. The values of hematocrit and BUN-to-creatinine ratio were highest in the SAO group (Table 2), suggesting that the SAO group may have the most severe dehydration. BUN-to-creatinine ratio of the CE group was conversely increased after 2 weeks with high standard deviation (Table 2). The cause of this change is probably the existence of several patients who had very high BUN-to-creatinine ratio over 30 due to the progression of cardiac failure. This increased BUN-to-creatinine ratio does not seem to depend on dehydration, since hematocrit was decreased in these patients (Table 2).

The present study is the first to suggest the contribution of dehydration, as represented by an increase in blood viscosity, to the onset of SAO. As described above, since no definitive laboratory test is currently available for dehydration, a potentially effective evaluation for dehydration, as we performed, involves a comparison of blood viscosity between stroke onset and a later time when infusion therapy has been terminated. To the best of our knowledge, no other studies have demonstrated a relationship between dehydration and the onset of SAO among the subtypes of ischemic stroke. However, seasonal differences in the incidence of stroke may support the contribution of dehydration to the onset of SAO. Two studies with large sample sizes (more than 10,000) from Japan separately demonstrated the same findings that SAO was observed more frequently in summer and CE in winter.²⁸⁻²⁹ Since the Japanese summer is sufficiently hot to induce

dehydration and heat stroke,³⁰ dehydration may commonly occur in a large number of individuals, some of whom with stenotic lesions in the perforating artery may develop SAO. A recent review emphasized the importance of increases in blood viscosity due to dehydration in small vessel disease.³¹ Taken together, previous findings and the results of the present study indicate the important of dehydration in the pathogenesis of SAO, but to a lesser extent in the pathogenesis of CE.

The present study has some limitations that need to be considered when interpreting the results obtained. We only examined a small number of Japanese patients, which raises a concern regarding the generalization of data. Furthermore, the control group was not age-matched to the patient group. However, this mismatch did not appear to affect the results obtained for the reason described above. In addition, dehydration cannot be diagnosed at the date of admission from the measurement of blood viscosity. We have to wait to compare blood viscosity between the onset and at a later time when infusion therapy has been terminated. Therefore, increased blood viscosity at the date of admission may be derived from dehydration or another cause such as polycythemia or macroglobulinemia.

Conclusion

The present study demonstrated that blood viscosity at the date of admission was significantly higher in the SAO group than in the control group and in the same group after 2 weeks. Increased blood viscosity at the date of admission may have been mediated by dehydration because patients returned

to normal hydrated conditions after 2 weeks. The importance of dehydration needs to be emphasized in the pathogenesis of SAO. If we correctly understand the pathogenesis of ischemic stroke, we may apply effective approaches to its treatment and/or prevention. The clinical application of the EMS viscometer appears to be promising for understanding and differentiating the pathogenesis of ischemic stroke.

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Figure legends

Figure 1

Comparison of blood viscosity between ischemic stroke subgroups at the date of admission and the control group.

Figure2

Change in blood viscosity during admission in each ischemic stroke subtype; (A) CE, (B) LAA, or (C) SAO. DOA, 2-3D, 1W, and 2W stand for the date of admission, 2-3 days after admission, 1 week after admission, and 2 weeks after admission, respectively.

Figure 3

Relationship between blood viscosity and blood cell counts (RBC + platelet) in 100 healthy outpatient volunteers. A curve line indicates the result of exponential approximation fitting.

Figure 4

Relationship between blood viscosity and blood cell counts in each stroke group at the date of admission and 2 weeks after admission in comparison with that in the control group; (A) CE, (B) LAA, or (C) SAO. Crosses indicate individual patients and a black circle and numbers indicate the mean value of all patients. A curve line indicates the result of exponential approximation fitting. DOA and 2W stand for the date of admission and 2 weeks after admission.

Figure 5

Change in mean values of blood viscosity and the blood cell count in each stroke subtype group from

the date of admission to 2 weeks after. The circle, triangle, and rectangle indicate SAO, LAA, and CE, respectively.

Table 1

Demographic characteristics of patients in total and in ischemic stroke subgroups

Table 2

The values of hematocrit and BUN-to-creatinine ratio in total and in three stroke subgroups at the date of admission and after 2 weeks. Ht, BUN/Cr, DOA, and 2W stand for hematocrit, BUN-to-creatinine ratio, the date of admission, and 2 weeks, respectively. * $p < 0.01$, compared with the value at the date of admission.

Figure.1

Figure.2

A

B

C

Figure.3

Figure.4

A

B

C

Figure.5

Table1

		Total	CE	LAA	SAO
N of patients		92	25	42	25
Age	year	74.4±11.5	77.2±10.2	73.5±12.7	73.3±10.6
Gender, male	N (%)	54(58.7)	11(44.0)	28(66.7)	15(60.0)
Hypertension	N (%)	85(92.4)	21(84)	40(95.2)	24(96)
Dyslipidemia	N (%)	53(57.6)	13(28.5)	24(57.4)	16(64)
Diabetes	N (%)	32(34.8)	9(36)	13(31)	10(40)
Smoking	N (%)	25(27.2)	5(20)	14(33.3)	6(24)
Alcohol	N (%)	28(30.4)	8(32)	14(33.3)	6(24)
Glasgow coma scale	score	14.36±1.63	13.72±2.37	14.43±1.45	14.88±0.33

Table2

		Total	CE	LAA	SAO
N of patients		92	25	42	25
Ht (DOA)	value	40.6±4.5	39.7±5.4	40.3±4.1	41.8±4.0
Ht (2W)	value	37.0±4.7*	36.6±5.4*	36.8±4.6*	37.9±4.3*
BUN/Cr (DOA)	value	19.0±5.4	19.1±5.7	18.5±5.4	19.7±5.3
BUN/Cr (2W)	value	18.1±7.7	22.3±11.3	16.3±5.6*	16.9±4.4*